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Requests for Information Completed - A

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Abciximab
Advice on research on the effects/effectiveness of abciximab (intravenous glycoprotein IIb/IIIa receptor (GPIIb/IIIa) inhibitor). ARIF was asked to appraise available research on the above new drug.

Abdominal Aortic Aneurysm (infrarenal)
What is the effectiveness and cost-effectiveness of EVARs for infrarenal abdominal aortic aneurysms?

Abdominal Aortic Aneurysm
What is the evidence of the effectiveness and cost-effectiveness of fenestrated endovascular repair (f-EVAR) for the treatment of abdominal aortic aneurysm (AAA)?

Abdominal Aortic Aneurysm
What is the effectiveness of fenestrated endovascular stents in patients who have abdominal aneurysms. Has the evidence base changed since ARIF last undertook a search for this question?

Abdominal Aortic Aneurysm
What is the clinical and cost-effectiveness of endovascular aneurysm repair (EVAR) in the management of abdominal aortic aneurysms, with particular reference to higher risk patients deemed unfit for surgery?

Accident and Emergency
Is there any evidence on the effectiveness of general practitioners (GPs) in accident and emergency (A&E) units and are there any additional benefits compared to if he or she was not present on outcomes such as admission rates?

Acne
What is the effectiveness of laser therapy for acne?

Acne Scarring
What is the effectiveness of laser therapy for acne scarring?

Acoustic Neuroma
What is the 'gold standard' investigation of someone presenting with symptoms suggestive of acoustic neuroma?

Acromegaly
In 2007 the West Midlands Health Technology Assessment Collaboration (WMHTAC) completed a systematic review that assessed the clinical and cost effectiveness of Pegvisomant (PEG) for use in patients with acromegaly. ARIF were asked to determine if any new research had been published since the completion of the WMHTAC review and whether this alters any conclusions of the report.

Acromegaly
What is the effectiveness of lanreotide and octreotide in the treatment of acromegaly?

Acromegaly
What is the effectiveness of pegvisomant (Somavert) in the treatment of patients with acromegaly whose disease is not controlled by surgery and subsequent medical therapy?

Acupuncture
Requestor had been approached with proposals for use of acupuncture in primary care for relief of and

wide range of conditions e.g. pain, allergic conditions, nausea in pregnancy, stress, menstrual disorders and polysymptomatic relief for terminal illness. For which of these indications is there evidence of effectiveness?

Acupuncture (Laser)
What is the effectiveness of laser acupuncture in patients with chronic pain, relative to other forms of pain relief?

Acute Coronary Syndrome
What is the clinical and cost-effectiveness of early aggressive lipid lowering therapy using very high dose statins (80mg/day) for patients with acute coronary syndrome, patients with crescendo angina, and patients undergoing revascularisation?

Acute Ischaemic Stroke
What is known about the effects and effectiveness of tissue plasminogen activator (rt-PA) for acute ischaemic stroke?

Acute Myocardial Infarction
What evidence is there on the effectiveness of media campaigns and other interventions which aim to reduce patient delay factors in pain to needle time in acute myocardial infarction?

Acyclovir
What is the evidence that treatment of adult chicken pox with acyclovir helps prevent complications and is cost effective?

Adalimumab
To advise on the relative effectiveness of Adalimumab compared to escalating the dose of Infliximab in patients with severe Crohn's disease

Adefovir Dipivoxil
What is the effectiveness of adefovir dipivoxil for the treatment of patients with lamivudine-resistant chronic HBV?

Adolescents
The National Institute for Health and Clinical Effectiveness (NICE) as part of the wider programme of work on smoking and the NHS in England and Wales, commissioned a report from ARIF and the West Midlands Health Technology Assessment Collaboration, to identify the best evidence on the clinical and cost-effectiveness of NRT

Aetiology
Does mental health well-being (as opposed to mental illness) affect physical health?

Age-Related Macular Degeneration (AMD)
Rapid assessment of implantable intraocular lens systems for age-related macular degeneration (AMD)

Age-Related Macular Degeneration (AMD/ARMD)
Is photodynamic therapy an effective treatment for wet age-related macular degeneration with predominantly classic CNV?

Age-Related Macular Degeneration (AMD/ARMD)
Is photodynamic therapy an effective treatment for wet age-related macular degeneration with occult CNV?

AIDS/HIV
What is the evidence base of clinical guidelines on the use of antiretroviral agents, e.g. zidovudine and protease inhibitors, particularly their use in combination? ARIF was asked to contribute to a West Midlands working group on HIV/AIDS care whose aim in December 1996 was to decide the priorities for expenditure in the forthcoming financial year.

Alcoholism
What is the long-term effectiveness of interventions aimed at reducing alcohol consumption/promoting abstinence amongst heavy/alcohol dependent drinkers, with specific reference to reducing mortality?

Alcohol Awareness
What is the effectiveness of theatre/drama aimed at young people (12-18 year olds) as an intervention to improve alcohol awareness/ability to make safe, sensible choices?

Alcohol Consumption
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to reducing alcohol consumption?

Alcohol Counselling
What is the effectiveness of brief interventions including alcohol counselling services in reducing the frequency and severity of domestic violence?

Alcohol Dependence
What is the effectiveness of naltrexone in alcohol dependent patients?

Alcohol Dependent Drinkers
What is the clinical and cost-effectiveness of providing incentives to motivate reduced alcohol consumption?

Alcohol Dependency
What is the clinical and cost-effectiveness of community-based versus inpatient alcohol detoxification regiments for alcohol dependent patients?

Alcohol - Dependent Drinkers
What is the long-term effectiveness of interventions aimed at reducing alcohol consumption/promoting abstinence amongst heavy/alcohol dependent drinkers, with specific reference to reducing mortality?

Alcohol - Non-Dependent Drinkers
What is the long-term effectiveness of interventions aimed at reducing alcohol consumption/promoting abstinence amongst heavy/alcohol dependent drinkers, with specific reference to reducing mortality?

Alcohol - Promoting Abstinence
What is the long-term effectiveness of interventions aimed at reducing alcohol consumption/promoting abstinence amongst heavy/alcohol dependent drinkers, with specific reference to reducing mortality?

Alcohol - Reducing Consumption
What is the long-term effectiveness of interventions aimed at reducing alcohol consumption/promoting abstinence amongst heavy/alcohol dependent drinkers, with specific reference to reducing mortality?

Alcohol Withdrawal Symptoms
What is the clinical and cost-effectiveness of community-based versus inpatient alcohol detoxification regiments for alcohol dependent patients?

Alemtuzumab
What is the effectiveness of Alemtuzumab in the treatment of chronic lymphocytic leukaemia?

Allergies
What is the strength of the research evidence for the diagnosis and treatment of multiple allergies by provocation-neutralisation techniques (the Miller techniques) and controlled environments?

Allogeneic Stem Cell Transplantation (reduced intensity)
What is the evidence of effectiveness of reduced intensity allogeneic stem cell transplantation in patients with metastatic renal cell carcinoma. Does it extend survival, improve quality of life, and what are the side effects?

Alpha Agonists
What treatments have been shown to be effective in the treatment of the common cold?

Alzheimer's Disease
What is the evidence on the effects/effectiveness of donepezil (Aricept)?

Alzheimer's Disease

Is there any new evidence of benefits for people with Alzheimer's Disease, from treatment with Donepezil, since the West Midlands Regional Anti-Dementia Drugs Working Party Recommendations and the establishment of the AD2000 trial? What are the current indications for treatment with Donepezil?

Alzheimer's Disease

What is the effectiveness of galantamine in the treatment of Alzheimer's disease (AD)?

Amniocentesis

What is the most effective and cost-effective way of screening for Down's syndrome in older women (>35 years).

Aneurysm

What is the clinical and cost-effectiveness of endovascular aneurysm repair (EVAR) in the management of abdominal aortic aneurysms, with particular reference to higher risk patients deemed unfit for surgery?

Angina

What are the implications of implementing the recommendation from the North of England Guideline Development Group (BMJ 1996; 312: 827-832) that all patients with angina should have an exercise ECG test?

Angina

What are the effects/effectiveness of CABG and other interventional cardiological procedures i.e. PTCA, specifically in relationship to prioritisation of those procedures?

Angina

What is the effectiveness of cardiac rehabilitation particularly in respect to: mortality, tackling depression, return to work and ensuring continued access to GP for medication?

Angina

Has anyone designed and evaluated alternative approaches to cardiac rehabilitation which overcome access issues by ethnic minority groups or low income groups?

Angina Chronic Refractory

To find information regarding the clinical effectiveness of treatment of enhanced external counterpulsation (EECP) in patients with angina which cannot be relieved by conventional treatment.

Angiotensin II Receptor Antagonists

What is the relative effectiveness of the different angiotensin II receptor antagonists (AIIRAs) in lowering blood pressure?

Anorexia Nervosa

How does the effectiveness of in-patient treatment compare to (intensive) out-patient treatment for patients with severe or moderate anorexia nervosa, and what type of out-patient treatment is most effective?

Anterior Cruciate Ligament (ACL) Tears of Knee

What are the effects and effectiveness of surgical repair of acute tears of the anterior cruciate ligament (particular emphasis on incomplete tears where there is little instability of the knee)?

Anthroposophical Medicine

What is the evidence on effectiveness of anthroposophical medicine in the treatment of chronic fatigue syndrome (CFS)?

Antibiotics

What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Antibiotics

What is the evidence on effectiveness of antibiotic regimes in the treatment of pelvic inflammatory disease (PID)?

Antibiotics

Interventions to improve prescribing practice of antibiotics in primary care and ambulatory/community settings with the aim of reducing inappropriate prescribing.

Antibiotic Associated Diarrhoea

Are probiotics, particularly Saccharomyces boulardii, effective in reducing antibiotic associated diarrhoea?

Anticholinergics

What treatments have been shown to be effective in the treatment of the common cold?

Anti-Coagulation Clinics

Siting and staffing of anti-coagulation clinics; what is the variation in effectiveness and cost effectiveness?The specific question posed by the requester, a GP, was: Should we continue to provide an in-practice, nurse run anti-coagulation clinic?

Antihistamines

What treatments have been shown to be effective in the treatment of the common cold?

Antihistamine and Decongestants

What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Antimicrobials

Interventions to improve prescribing practice of antibiotics in primary care and ambulatory/community settings with the aim of reducing inappropriate prescribing.

Antimicrobial Drugs

What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Antiretroviral Agents (Combination Therapy)

What is the evidence base of clinical guidelines on the use of antiretroviral agents e.g. zidovudine and protease inhibitors, particularly their use in combination? ARIF was asked to contribute to a West Midlands working group on HIV/AIDS care whose aim in December 1996 was to decide the priorities for expenditure in the forthcoming financial year.

Anti-vascular Endothelial Growth Factor Agents

What is the quantity and quality of the evidence regarding ranibizumab (Lucentis) and bevacizumab (Avastin) in the treatment of eye conditions (excluding age-related macular degeneration), thought to be related to vascular endothelial growth factor?

Anti VEGF

What is the quantity and quality of the evidence regarding ranibizumab (Lucentis) and bevacizumab (Avastin) in the treatment of eye conditions (excluding age-related macular degeneration), thought to be related to vascular endothelial growth factor?

Arthroscopic Surgery

What is the clinical effectiveness and cost-effectiveness of arthroscopic treatment for young people (of working age) with hip impingement (femoro-acetabular impingement) and/or hip pain and what group(s) of patients may be expected to be benefit from it?

Aspirin

ARIF were asked to look at the evidence base to assess the effectiveness and safety for the combination of antiplatelet therapy (aspirin and clopidogrel) plus warfarin (an anticoagulant) in patients receiving a stent for coronary disease, particularly in relation to how patients are monitored.

Assisted Ventilation

What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in

infants?

Atenolol
What is the quality of a recent systematic review (Carlberg et al, 2004) assessing the effect of atenolol on cardiovascular morbidity and mortality in hypertensive patients?

Attachment Disorder
What is the evidence on the effectiveness/cost effectiveness of dyadic developmental psychotherapy in the treatment of children with attachment disorders and particularly the effect on adoption rates amongst 'looked after' children?

Attention Deficit Hyperactivity Disorder
What is the benefit of continuing treatment with Ritalin in adulthood for patients who have been treated with Ritalin (as children) for ADHD?

Audiological Screening
What is the strength of the evidence that screening adults with Downs Syndrome for hearing impairment is of benefit and is cost-effective?

Autoinflation
What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Automated Peritoneal Dialysis
Are there any recognised criteria for the use of automated peritoneal dialysis and is it a cost-effective form of treatment for end stage renal failure?

Autism
What is the extent of the association between autism and chronic gastrointestinal disease?

Autism
What is the effectiveness of gluten-free diets for autistic children?

Autism
What is the evidence on the effectiveness of sensory integrated therapy provided by occupational therapists to children with autism? In particular, is there any evidence for the most effective number of sessions or length of treatment?

Autologous Stem Cell Transplant
What is the effectiveness of autologous stem cell transplantation for systemic sclerosis?

Automated Implantable Cardioverter Defibrillators
What is known about the effectiveness and cost-effectiveness of automatic implantable cardioverter defibrillators (ICD) in the management of ventricular arrhythmias?

Avastin
What is the quantity and quality of the evidence regarding ranibizumab (Lucentis) and bevacizumab (Avastin) in the treatment of eye conditions (excluding age-related macular degeneration), thought to be related to vascular endothelial growth factor?

Awareness Campaigns
Do awareness campaigns targeted at the public or GPs which are aimed at reducing delays to diagnostic and specialised health care services, improve survival for cancer?

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Requests for Information Completed - B

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Baclofen (Continuous Intrathecal)
What is the effectiveness of intrathecal baclofen for treating patients with severe spasticity/mobility problems?

Baclofen (Continuous Intrathecal)
What is the effectiveness of intrathecal baclofen for treating children with severe spasticity/mobility problems caused by cerebral palsy?

Baclofen (Continuous Intrathecal)
In 2003 ARIF investigated the role of intrathecal baclofen in the treatment of spasticity for any cause and spasticity due to cerebral palsy in children. We were asked to update this request in 2006.

B-cell Lymphocytic Leukaemia
What is the effectiveness of Alemtuzumab in the treatment of chronic lymphocytic leukaemia?

Behcet's Disease
What is the clinical effectiveness of mycophenolate mofetil for patients with Behcet's disease who are intolerant of immunosuppresive treatment with methotrexate, cyclosporine and azathioprine?

Benign Prostatic Hypertrophy or Hyperplasia
What is the effectiveness and cost-effectiveness of Gyrus PKVP versus standard therapy, unipolar TURP, for benign prostatic hypertrophy?

Benign Prostatic Hypertrophy or Hyperplasia
What is the effectiveness of PVP using the green-light (KTP) laser?

Benign Prostatic Obstruction or Enlargement
What is the effectiveness and cost-effectiveness of Gyrus PKVP versus standard therapy, unipolar TURP, for benign prostatic hypertrophy?

Benign Prostatic Obstruction or Enlargement
What is the effectiveness of PVP using the green-light (KTP) laser?

Beraprost
Critical Appraisal of "Goal-oriented treatment and combination therapy for pulmonary arterial hypertension" Hoeper MM et al. - in relation to assessment of study design and interpretation of the results particularly regarding the effectiveness of dual therapy relative to monotherapy.

Betablocker
What is the quality of a recent systematic review (Carlberg et al, 2004) assessing the effect of atenolol on cardiovascular morbidity and mortality in hypertensive patients?

Bevacizumab
What is the quantity and quality of the evidence regarding ranibizumab (Lucentis) and bevacizumab (Avastin) in the treatment of eye conditions (excluding age-related macular degeneration), thought to be related to vascular endothelial growth factor?

Bilateral Subthalamic Stimulation
What is the effectiveness and cost-effectiveness of bilateral subthalamic stimulation in patients with

Parkinson's disease, compared to standard medical treatment or no treatment in patients who have failed medical management?

Bipolar Electrosurgical Transurethral Resection of the Prostate (TURP)
What is the effectiveness and cost-effectiveness of Gyrus PKVP versus standard therapy, unipolar TURP, for benign prostatic hypertrophy?

Bisphosphonates
What is the effectiveness of bisphosphonates for cancer patients (particularly those with breast cancer, prostate cancer and myeloma) with, or at risk of developing, bone metastases?

Biventricular Pacing
What is the effectiveness of biventricular pacing in patients with severe heart failure who have not responded to other treatment?

Blood Pressure Lowering
What is the relative effectiveness of the different angiotensin II receptor antagonists (AIIRAs) in lowering blood pressure?

The Bobath Method
How effective is the Bobath method as a therapy for children with cerebral palsy?

Bone Anchored Hearing Aids (Bilateral)
What is the clinical and cost-effectiveness of bilateral bone anchored hearing aids (BAHAs) in comparison with unilateral bone anchored hearing aids?

Bone Densitometry
What is the contribution of bone densitometry in the prediction of osteoporosis fracture and diagnosing osteoporosis? In particular, how does it help identify populations at risk of osteoporosis?

Bosentan
What is the effectiveness of bosentan for the treatment of pulmonary hypertension?

Bosentan
Critical Appraisal of "Goal-oriented treatment and combination therapy for pulmonary arterial hypertension" Hoeper MM et al. - in relation to assessment of study design and interpretation of the results particularly regarding the effectiveness of dual therapy relative to monotherapy.

Botulinum Toxin type A (BTX-A)
Is BTX-A a safe and effective treatment for the relief of limb spasticity in cerebral palsy?

Brachytherapy (High Dose Rate)
What is the effectiveness of high dose rate brachytherapy using temporarily inserted isotopes in combination with external beam radiotherapy (EBRT) versus EBRT alone in localised prostate cancer?

Brachytherapy (Low Dose Rate)
What is the effectiveness of low dose rate brachytherapy using inserted iodine or palladium isotopes compared to other common methods of treatment such as radical prostatectomy or external beam radiotherapy (EBRT)?

Brain Natriuretic Peptide
What is the accuracy of pro-Brain Natriuretic Peptide (proBNP) in the diagnosis of heart failure?

Brain Tumours (Glioblastoma)
What is the effectiveness of temozolomide in addition to surgery and radiotherapy for newly diagnosed glioblastoma multiforme?

Brain Tumour
What is the effectiveness of Gliadel wafer implants in the treatment of recurrent glioblastoma multiforme (GBM)?

Breakspear Hospital

ARIF has received many requests concerning the evidence on effectiveness of the services by the Breakspear Hospital.

Breast Cancer

Evidence on effectiveness of herceptin in small size tumours (equal to or less than 0.5cm) and lymphovascular invasion HER-2 positive early-stage breast cancer.

Breast Cancer (early stage; HER2-positive)

What is the quality of two recently published articles reporting the results of three randomised controlled trials assessing the effectiveness of trastuzumab (Herceptin) in the treatment of HER2-positive, early-stage breast cancer?

Breast Cancer

What is the evidence base of the proposals made for the West Midlands Familial Cancer Initiative, particularly those concerning screening of individuals with a positive family history of breast cancer?

Breast Cancer (Advanced)

Is docetaxel effective in the management of patients with advanced breast cancer?

Breastfeeding

The National Institute for Health and Clinical Effectiveness (NICE) as part of the wider programme of work on smoking and the NHS in England and Wales, commissioned a report from ARIF and the West Midlands Health Technology Assessment Collaboration, to identify the best evidence on the clinical and cost-effectiveness of NRT

Brief Interventions

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to reducing alcohol consumption?

Brief Interventions

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to diet?

Brief Interventions

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to increasing physical activity?

Brief Interventions

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to the prevention of falls amongst older people?

Brief Interventions

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to advice on delaying the time of first intercourse?

Brief Interventions

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to the prevention/reduction of illicit drug use amongst young people?

Brief Interventions

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to safe sex?

Brief Interventions

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to smoking

cessation?

Bronchiolitis - Antibiotics
What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Bronchiolitis - Assisted Ventilation
What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Bronchiolitis - Bronchodilators
What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Bronchiolitis - Continuous Negative Extrathoracic Pressure (CNEP)
What is the evidence base for the treatment of infants with bronchiolitis with Continuous Negative Extrathoracic Pressure (CNEP) ventilation?

Bronchiolitis - Immunoglobulin
What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Bronchiolitis - Ribavirin
What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Bronchiolitis - Steroids
What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Bronchodilators
What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

BTX-A (Botulinum Toxin type A)
Is BTX-A a safe and effective treatment for the relief of limb spasticity in cerebral palsy?

Buccal Nitrates
What is the effectiveness and cost effectiveness of using buccal nitrates in primary care, in the management of patients with heart failure after a myocardial infarction?

Buprenorphine
Is there any evidence on the effectiveness of buprenorphine in the management of detoxification for opiate addiction?

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Requests for Information Completed - C

C1 Esterase Inhibitor Concentrate
What is the evidence for using C1 Esterase Inhibitor Concentrate as a long-term prophylaxis in patients with severe Herediatry Angioedema (HAE)?

Cancer
What evidence is there that clinical nurse specialists are effective, particularly in the care of cancer patients?

Cancer
Do awareness campaigns targeted at the public or GPs which are aimed at reducing delays to diagnostic and specialised health care services, improve survival for cancer?

Cancer
ARIF were asked if vaccinations for influenza and pneumococcal disease improve survival for patients with cancer who have had systemic therapy (chemotherapy, hormonal therapy or radiotherapy).

Cancer
Is there firm outcome evidence to support strategies and campaigns to improve uptake of the 3 UK cancer screening programmes (breast, cervical, bowel), and if so what is the cost to save an additional life based on this evidence?

Cancer
To assess the feasibility of cancer chemotherapy being delivered to patients in the community.

Cancer, Bone Metastases
What is the effectiveness of bisphosphonates for cancer patients (particularly those with breast cancer, prostate cancer and myeloma) with, or at risk of developing, bone metastases?

Cancer Pain
What interventions should a pain clinic be offering?

Candidal Hypersensitivity
ARIF has received many requests concerning the effectiveness of provocation-neutralisation therapy.

CAPD (Continuous Ambulatory Peritoneal Dialysis)
What is the evidence on the effectiveness of different methods of renal replacement therapy, other than renal transplant?

Carbon Monoxide Poisoning
What is the evidence for hyperbaric oxygen in the management of patients with acute carbon monoxide poisoning?

Cardiac Arrest
Is the LUCAS device effective/cost-effective particularly in the context of an ambulance service?

Cardiac Arrhythmias
What is known about the effectiveness and cost-effectiveness of automatic implantable cardioverter defibrillators (ICD) in the management of ventricular arrhythmias?

Cardiac Disease
Is cardiac rehabilitation an effective and cost-effective service?

Cardiac Disease
Is there any evidence on the role of risk stratification, and in particular by exercise tests, for cardiac rehabilitation?

Cardiac Rehabilitation
Is cardiac rehabilitation an effective and cost-effective service?

Cardiac Rehabilitation
Is there any evidence on the role of risk stratification, and in particular by exercise tests, for cardiac rehabilitation?

Cardiac Rehabilitation
What is the effectiveness of cardiac rehabilitation particularly in respect to: mortality, tackling depression, return to work and ensuring continued access to GP for medication?

Cardiac Rehabilitation, Access, Uptake
Has anyone designed and evaluated alternative approaches to cardiac rehabilitation which overcome access issues by ethnic minority groups or low income groups?

Cardiovascular Disease
Is there a reduction in cardiovascular mortality, morbidity and risk in patients with kidney failure and hyperphosphataemia taking non-metal containing phosphate binders (sevelamer and lanthanum) compared to patients taking calcium-containing phosphate binders (calcium acetate and calcium carbonate)?

Cardiovascular Disease
The National Institute for Health and Clinical Effectiveness (NICE) as part of the wider programme of work on smoking and the NHS in England and Wales, commissioned a report from ARIF and the West Midlands Health Technology Assessment Collaboration, to identify the best evidence on the clinical and cost-effectiveness of NRT

Cardiovascular Disease
ARIF were asked to look at the evidence base to assess the effectiveness and safety for the combination of antiplatelet therapy (aspirin and clopidogrel) plus warfarin (an anticoagulant) in patients receiving a stent for coronary disease, particularly in relation to how patients are monitored.

Carmustine Implants
What is the effectiveness of Gliadel wafer implants in the treatment of recurrent glioblastoma multiforme (GBM)?

Carpal Tunnel Syndrome
What is the usefulness of electrodiagnostic techniques as a prognostic tool in pre-surgical assessment of patients with carpal tunnel syndrome?

Ceramic Joint Implants
What is the evidence of effectiveness of ceramic joint implants in the treatment of metatarsophalangeal joint disease?

Cerebral Palsy
Does conductive education for the treatment of cerebral palsy achieve better long term results than conventional treatment?

Cerebral Palsy
How effective is the Bobath method as a therapy for children with cerebral palsy?

Cerebral Palsy
Is BTX-A a safe and effective treatment for the relief of limb spasticity in cerebral palsy?

Cerebral Palsy

What is the effectiveness of continuous intrathecal baclofen for treating children with severe spasticity/mobility problems caused by cerebral palsy?

Cerebral Palsy

ARIF was asked to assess the effectiveness of targeted training therapy in the treatment of patients with Cerebral Palsy

Ceredase/Cerezyme

What is the evidence of effectiveness and cost effectiveness of Ceredase (Alglucerase) or Cerezyme (Imighicerase) in the treatment of Gaucher's disease?

Cervical Cancer

ARIF were asked to investigate the impact of changing referral practice in cervical screening, both on the individual regarding patient benefit and on the service regarding cost and impact on service provision, for women presenting with mild dyskaryosis.

Cervical Screening

What evidence is there on the effects/effectiveness of 3 year and 5 year screening intervals for cervical cancer?

Cervical Screening

ARIF were asked to investigate the impact of changing referral practice in cervical screening, both on the individual regarding patient benefit and on the service regarding cost and impact on service provision, for women presenting with mild dyskaryosis.

Chelation Therapy

Is chelation therapy effective for the treatment of peripheral vascular disease?

Chemotherapy

To assess the feasibility of cancer chemotherapy being delivered to patients in the community.

Chest Pain Assessment

To gain an understanding of the current knowledge base regarding chest pain presentations to both primary and secondary care services.

Chest Pain Services

To gain an understanding of the current knowledge base regarding chest pain presentations to both primary and secondary care services.

Chest Wall Diseases

Evidence on clinical and cost-effectiveness of non-invasive ventilation in patients with neuromuscular and chest wall diseases.

Chest Wall Disorders

What is the effectiveness of nocturnal mechanical ventilation in relieving symptoms of hypoventilation in patients with neuromuscular and chest wall disorders?

Chicken Pox

What is the evidence that treatment of adult chicken pox with acyclovir helps prevent complications and is cost effective?

Child Behaviour

What is the evidence on the effectiveness of fish oil supplements on school aged children's behaviour and educational attainment?

Child Health

Assessment of the effectiveness of health visitor activities in the NHS

Childhood Cancer - Treatment Effects on Fertility

What is the impact of childhood cancer treatment on women of reproductive age and what possible strategies would address their needs (with specific reference to reproductive function)?

Children
What is the clinical effectiveness of DermaSilk therapeutic clothing for children with severe dermatitis?

Children with Conduct Disorders
The effect of parent education programmes on the behaviour and mental health of children with conduct disorders and their parents.

Chlorambucil
What is the effectiveness of Alemtuzumab in the treatment of chronic lymphocytic leukaemia?

Choroidal Neovascularisation (CNC)
Is photodynamic therapy an effective treatment for pathological myopia?

Chronic Fatigue Syndrome
ARIF has received many requests concerning the evidence on effectiveness of the services by the Breakspear Hospital.

Chronic Fatigue Syndrome
ARIF has received several requests concerning the effectiveness of EPD.

Chronic Fatigue Syndrome
ARIF has received many requests concerning the effectiveness of provocation-neutralisation therapy.

Chronic Fatigue Syndrome (ME)
What is the evidence on the effects/effectiveness of treatments of chronic fatigue syndrome?

Chronic Fatigue Syndrome (ME)
What is the evidence on effectiveness of anthroposophical medicine in the treatment of chronic fatigue syndrome?

Chronic Fatigue Syndrome (ME)
What is the effectiveness of enzyme potentiated desensitisation (EPD) for chronic fatigue syndrome?

Chronic Graft-Versus-Host Disease (cGVHD)
ARIF were asked to evaluate the effectiveness and safety of Extracorporeal Photochemotherapy (ECP) in children who have steroid refractory chronic graft-versus-host disease (cGVHD)

Chronic Lymphocytic Leukaemia
What is the effectiveness of Alemtuzumab in the treatment of chronic lymphocytic leukaemia?

Chronic Neuropathic Pain
What is the effectiveness of spinal cord stimulation for chronic neuropathic pain, particularly in "failed" back surgery syndrome and complex regional pain syndrome?

Chronic Obstructive Airways Disease
(Chronic Obstructive Pulmonary Disease)
What is the evidence for respiratory rehabilitation for those with chronic obstructive pulmonary/airways disease?

Chronic Obstructive Pulmonary Disease (COPD)
What is the evidence to advocate the use of spirometry and oximeters to improve and manage symptoms of patients with chronic obstructive pulmonary disease (COPD) who are treated in primary care?

Chronic Obstructive Pulmonary Disease
When is domiciliary oxygen effective?

Chronic Obstructive Pulmonary Disease
What is the effectiveness of spirometry and screening for chronic obstructive pulmonary disease (COPD) in primary versus secondary care?

Chronic Obstructive Pulmonary Disease

What is the effectiveness of non-invasive positive pressure ventilation for patients with stable hypercapnic chronic obstructive pulmonary disease in a domiciliary environment?

Chronic Pain (Breast and Back)
What is the effectiveness of PENS in reducing back and breast pain?

Chronic Pain
What interventions should a pain clinic be offering?

Chronic Pain
What is the evidence on the effectiveness of spinal cord stimulation in the management of chronic pain?

Chronic Pain
What is the effectiveness of intraspinal drug delivery in the management of chronic pain?

Chronic Pain
What is the effectiveness of residential pain management programmes (PMPs) for patients with severe chronic pain that has not responded to other therapies?

Chronic Pain
What is the effectiveness of laser acupuncture in patients with chronic pain, relative to other forms of pain relief?

Chronic Renal Failure
What is the evidence on the effectiveness of early referral to specialist renal services for people with chronic renal failure?

Chronic Renal Failure
What is the evidence on the effectiveness of different methods of renal replacement therapy, other than renal transplant?

Chronic Sinusitis
What is the most effective diagnostic test for chronic sinusitis?

Chronic Tonsillitis
Evidence for the effectiveness of tonsillectomy for chronic tonsillitis and chronic pharyngitis in children and adults.

Chronic Wounds
What is the clinical and cost-effectiveness of vacuum assisted wound closure (VAC) therapy for wound management?

Clinical Nurse Specialists
What evidence is there that clinical nurse specialists are effective, particularly in the care of cancer patients?

Clinical Psychology (Clinical Psychologists)
Is there any evidence on the effectiveness of clinical psychology in general and whether clinical psychologists are more effective than other professionals such as counsellors in certain conditions?

Clopidogrel
ARIF were asked to look at the evidence base to assess the effectiveness and safety for the combination of antiplatelet therapy (aspirin and clopidogrel) plus warfarin (an anticoagulant) in patients receiving a stent for coronary disease, particularly in relation to how patients are monitored.

Clothing - Therapeutic
What is the clinical effectiveness of DermaSilk therapeutic clothing for children with severe dermatitis?

Cognitive Behavioural Therapy and Other Treatments
What is the evidence on the effects/effectiveness of treatments of chronic fatigue syndrome?

Cognitive Behavioural Therapy
The effectiveness of cognitive behavioural therapy (CBT) in treating depression in non-white communities, particularly South Asian/Pakistani women

Colorectal Cancer
What is the evidence base of the proposals made for the West Midlands Familial Cancer Initiative, particularly those concerning screening of individuals with a positive family history of colorectal cancer?

Colposcopy
ARIF were asked to investigate the impact of changing referral practice in cervical screening, both on the individual regarding patient benefit and on the service regarding cost and impact on service provision, for women presenting with mild dyskaryosis.

Combination of NRTs
The National Institute for Health and Clinical Effectiveness (NICE) as part of the wider programme of work on smoking and the NHS in England and Wales, commissioned a report from ARIF and the West Midlands Health Technology Assessment Collaboration, to identify the best evidence on the clinical and cost-effectiveness of NRT

Combined use of Aspirin, Clopidogrel and Warfarin
ARIF were asked to look at the evidence base to assess the effectiveness and safety for the combination of antiplatelet therapy (aspirin and clopidogrel) plus warfarin (an anticoagulant) in patients receiving a stent for coronary disease, particularly in relation to how patients are monitored.

Common Cold - Alpha Agonists
What treatments have been shown to be effective in the treatment of the common cold?

Common Cold - Anticholinergics
What treatments have been shown to be effective in the treatment of the common cold?

Common Cold - Antihistamines
What treatments have been shown to be effective in the treatment of the common cold?

Common Cold - Echinacea
What treatments have been shown to be effective in the treatment of the common cold?

Common Cold - NSAIDs
What treatments have been shown to be effective in the treatment of the common cold?

Common Cold - "Over-the-Counter" Remedies
What treatments have been shown to be effective in the treatment of the common cold?

Common Cold - Steam Inhalation
What treatments have been shown to be effective in the treatment of the common cold?

Common Cold - Vitamin C
What treatments have been shown to be effective in the treatment of the common cold?

Common Cold - Zinc
What treatments have been shown to be effective in the treatment of the common cold?

Communication Disorders in Pre-School Children
Community Trusts are seeking an effective screening tool for communication disorder in children as part of the pre-school child health surveillance programme. The local Trust was particularly interested in WILSTAAR and CHAT. Are these tools effective?

Community-based Alcohol Detoxification
What is the clinical and cost-effectiveness of community-based versus inpatient alcohol detoxification regiments for alcohol dependent patients?

Community Chemotherapy
To assess the feasibility of cancer chemotherapy being delivered to patients in the community.

Community Development Programmes
Are Community Development Programmes an effective way of empowering communities?

Community Health Teams
Is there any evidence that the provision of a community health team for older people with physical health problems and frailty would benefit service users?

Community Hospitals
Is there any evidence on the effectiveness of community hospitals within the UK for the delivery of services such as rehabilitation, GP beds, and nurse run clinics for chronic conditions such as diabetes and epilepsy?

Complex Regional Pain Syndrome
What is the effectiveness of spinal cord stimulation for chronic neuropathic pain, particularly in "failed" back surgery syndrome and complex regional pain syndrome?

Conduct Disorders
The effect of parent education programmes on the behaviour and mental health of children with conduct disorders and their parents.

Conductive Education
Does conductive education for the treatment of cerebral palsy achieve better long term results than conventional treatment?

Conductive Education
How effective is conductive education in the rehabilitation of patients with Parkinson's disease?

Conductive Hearing Loss
What is the clinical and cost-effectiveness of bilateral bone anchored hearing aids (BAHAs) in comparison with unilateral bone anchored hearing aids?

Continuous Hyperfractionated Accelerated Radiotherapy (CHART)
What is the effectiveness of Continuous Hyperfractionated Accelerated Radiotherapy (CHART)?

Continuous Negative Extrathoracic Pressure (CNEP)
What is the evidence base for the treatment of infants with bronchiolitis with Continuous Negative Extrathoracic Pressure (CNEP) ventilation?

Continuous Positive Airways Pressure (CPAP)
What is the effectiveness of continuous positive airways pressure for obstructive sleep apnoea?

Corneal Disease
What is the effectiveness of osteo-odonto-keratoprosthesis in the management of severe corneal disease?

Coronary Artery Bypass Grafting
What are the effects/effectiveness of CABG and other interventional cardiological procedures i.e. PTCA, specifically in relationship to prioritisation of those procedures?

Coronary Heart Disease
What is the effectiveness of cardiac rehabilitation particularly in respect to: mortality, tackling depression, return to work and ensuring continued access to GP for medication?

Coronary Heart Disease
Has anyone designed and evaluated alternative approaches to cardiac rehabilitation which overcome access issues by ethnic minority groups or low income groups?

Counselling
What is the effectiveness of counselling services in general and in the primary care setting in particular?

Counselling
What is the effectiveness of counselling for the victims of domestic violence?

Crime
What is the effectiveness of improved street lighting on reduction in crime?

Crime
What is the effectiveness of face-to-face restorative justice on repeat offending and victim satisfaction?

Critical Appraisal
What is the effectiveness of teaching critical appraisal to health care professionals and consumers on health care practice and the use of facilities and interventions?

Crohn's Disease
To advise on the relative effectiveness of Adalimumab compared to escalating the dose of Infliximab in patients with severe Crohn's disease

Cyclo-oxygenase-2 (COX-2) Inhibitors
Is naproxen associated with reduced numbers of fatal and non-fatal ischaemic heart disease events relative to no use of naproxen?

Cystic Fibrosis
What is the evidence base of a proposal to introduce regionwide neonate screening for cystic fibrosis using immunoreactive trypsin?

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Requests for Information Completed - D

Day Hospitals

What is the evidence on the effectiveness/cost-effectiveness of day hospitals in the treatment of people with mental illness in comparison with other NHS or social services models of provision?

Day Hospitals

What is the evidence on the effectiveness/cost-effectiveness of day hospitals in the treatment of the elderly in comparison with other NHS or social services models of provision?

Deafness

What is the clinical and cost-effectiveness of bilateral bone anchored hearing aids (BAHAs) in comparison with unilateral bone anchored hearing aids?

D-Dimer Test

In the diagnosis of deep venous thrombosis and pulmonary embolism, what is the effectiveness and cost effectiveness of undertaking serum D-Dimer tests and, based on the result, progressing to ultrasound or V/Q scan for the final diagnosis?

Deep Brain Stimulation

What are the effects of: (a) thermocoagulation (pallidotomy) (b) deep brain stimulation in the treatment of movement disorders, especially Parkinson's Disease?

Deep Brain Stimulation

What is the effectiveness of deep brain stimulation for dystonia?

Deep Brain Stimulation

What is the effectiveness and cost-effectiveness of bilateral subthalamic stimulation in patients with Parkinson's disease, compared to standard medical treatment or no treatment in patients who have failed medical management?

Deep Vein Thrombosis

What evidence is there that low molecular weight heparin for the treatment of deep vein thrombosis/venous thromboembolism can safely and be successfully used in a community setting?

Deep Venous Thrombosis

How effective and cost-effective is LMWH relative to other treatments, particularly unfractionated heparin, in the prevention of deep venous thrombosis (DVT)?

Deep Venous Thrombosis

How effective are foot pumps and other physical devices for preventing thromboembolism following elective hip and knee surgery?

Deep Venous Thrombosis (DVT)

In the diagnosis of deep venous thrombosis and pulmonary embolism, what is the effectiveness and cost effectiveness of undertaking serum D-Dimer tests and, based on the result, progressing to ultrasound or V/Q scan for the final diagnosis?

Dementia

Is there evidence indicating the best diagnostic tool for identifying mild cognitive impairment in patients presenting with subjective cognitive impairment?

Dementia

ARIF were asked to investigate the literature on models of care which can have a positive impact on mental health outcomes in persons over 65 years, particularly outcomes relating to dementia and/or depression.

Dementia

What is the evidence concerning treatment of the elderly mentally infirm, in particular with regard to dementia?

Dementia

What is the evidence on the effects/effectiveness of donepezil (Aricept)?

Dementia

Is there any evidence that memory clinics are more effective than routine OPD appointments in the management of people with dementia?

Dental Care

What is the effectiveness and cost-effectiveness of providing dental care by people from professions complimentary to dentistry (PCD's)?

Depression

What is the evidence that increased physical activity improves depression in adults?

Depression

The effectiveness of cognitive behavioural therapy (CBT) in treating depression in non-white communities, particularly South Asian/Pakistani women

Depression

Can depression be prevented in adults?

Depression

ARIF were asked to investigate the literature on models of care which can have a positive impact on mental health outcomes in persons over 65 years, particularly outcomes relating to dementia and/or depression.

Depression in Children and Adolescents

Can depression be prevented in children and adolescents?

Deprived Communities

To gain an understanding of the current knowledge base regarding chest pain presentations to both primary and secondary care services.

Dermasilk

What is the clinical effectiveness of DermaSilk therapeutic clothing for children with severe dermatitis?

Dermatitis - Severe

What is the clinical effectiveness of DermaSilk therapeutic clothing for children with severe dermatitis?

Detoxification

Is there any evidence on the effectiveness of dextropopoxyphene in the management of detoxification for opiate addiction?

Detoxification

Is there any evidence on the effectiveness of buprenorphine in the management of detoxification for opiate addiction?

Detoxification - Alcohol

What is the clinical and cost-effectiveness of community-based versus inpatient alcohol detoxification regiments for alcohol dependent patients?

Dextropopoxyphene

Is there any evidence on the effectiveness of dextropopoxyphene in the management of detoxification for opiate addiction?

Diabetes Mellitus
What is the evidence that population registers for diabetes at a district level are effective in improving patient care and disease outcomes?

Diabetes (Type 2)
Is there evidence that pioglitazone (a glitazone) is a more effective second line therapy than newer drugs e.g. Incretin enhancers (DPP-4 inhibitors) and Incretin mimics (GLP-1 analogues) in controlling HbA1c in adults with type 2 diabetes?

Diabetic Eye Disease
What are the effects/effectiveness of alternative arrangements for the screening (or early diagnosis) of diabetic retinopathy?

Dialysis
What is the effectiveness of sevelamer (Renagel®) for the treatment of hyperphosphataemia in patients on haemodialysis?

Diarrhoea (Antibiotic Associated)
Are probiotics, particularly Saccharomyces boulardii, effective in reducing antibiotic associated diarrhoea?

Diet
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to diet?

Dietary Change
Is dietician advice and dietary change for symptomatic gallstones effective in reducing or abolishing symptoms and in eliminating the need for surgery?

Dietician Advice
Is dietician advice and dietary change for symptomatic gallstones effective in reducing or abolishing symptoms and in eliminating the need for surgery?

Diphosphonates
A policy for treating osteoporosis is to be developed, therefore: Which patients should be treated with diphosphonates for verified osteoporosis and what role does bone densitometry have in assessment?

Docetaxel (Taxotere)
Is docetaxel effective in the management of patients with advanced breast cancer?

Domestic Violence
What is the effectiveness of brief interventions including alcohol counselling services in reducing the frequency and severity of domestic violence?

Domestic Violence
How effective is routine screening for domestic violence by healthcare professionals?

Domestic Violence
What is the effectiveness of counselling for the victims of domestic violence?

Domiciliary Oxygen
When is domiciliary oxygen effective?

Donepezil
What is the evidence on the effects/effectiveness of donepezil (Aricept)?

Donepezil
Is there any new evidence of benefits for people with Alzheimer's Disease, from treatment with Donepezil, since the West Midlands Regional Anti-Dementia Drugs Working Party Recommendations

and the establishment of the AD2000 trial? What are the current indications for treatment with Donepezil?

Doppler Ultrasound Scanning
Is there any evidence on the effectiveness and safety of Doppler scanning for the detection of foetal abnormalities?

Down's Syndrome
What is the strength of the evidence that screening adults with Downs Syndrome for hearing impairment is of benefit and is cost-effective?

Down's Syndrome
What is the most effective and cost-effective way of screening for Down's syndrome in older women (>35 years).

Drama Techniques
What is the effectiveness of drama techniques for imparting health promotion messages and bringing about changes in behaviour?

Drama Techniques
What is the effectiveness of theatre/drama aimed at young people (12-18 year olds) as an intervention to improve alcohol awareness/ability to make safe, sensible choices?

Drotrecogin alfa (activated)
What is the effectiveness of drotrecogin alfa (activated) in the treatment of patients with severe sepsis?

Drug Therapy combined with Psychological Interventions
Is there any research evidence on the effects/effectiveness of combined psychological and conventional medical care (pharmacotherapy) to improve outcomes in severe mental illness?

DVT
Does inactivity when in a cramped seating position (such as during long-haul air travel) increase the risk of the development of DVT in airline passengers? Is there evidence that interventions such as the use of compression stockings, hydration, exercise and aspirin prevent DVT?

Dyadic Developmental Psychotherapy
What is the evidence on the effectiveness/cost effectiveness of dyadic developmental psychotherapy in the treatment of children with attachment disorders and particularly the effect on adoption rates amongst 'looked after' children?

Dyspepsia - Upper Gastrointestinal Symptoms
Is there any information which will assist with the development of local policies and processes for the investigation and referral of patients with upper GI symptoms, outside those for urgent cancer referrals?

Dystonia
What is the effectiveness of deep brain stimulation for dystonia?

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Early Prostate Cancer

What is the effectiveness of high dose rate brachytherapy using temporarily inserted isotopes in combination with external beam radiotherapy (EBRT) versus EBRT alone in localised prostate cancer?

Early Prostate Cancer

What is the effectiveness of low dose rate brachytherapy using inserted iodine or palladium isotopes compared to other common methods of treatment such as radical prostatectomy or external beam radiotherapy (EBRT)?

Early Prostate Cancer

Evidence on the effectiveness of brachytherapy uses comparisons with existing standard treatments like EBRT and radical prostatectomy. Following on from this, what is the evidence for the effectiveness of these standard treatments themselves?

Early Referral

What is the evidence on the effectiveness of early referral to specialist renal services for people with chronic renal failure?

Early Detection and Treatment

What is the effectiveness of the early detection and treatment of severe mental illness in children and adolescents?

Eating Disorders

How does the effectiveness of in-patient treatment compare to (intensive) out-patient treatment for patients with severe or moderate anorexia nervosa, and what type of out-patient treatment is most effective?

Eating Disorders

Can eating disorders be prevented?

Echinacea

What treatments have been shown to be effective in the treatment of the common cold?

Echocardiography

Is GP open access to echocardiography for the diagnosis of heart failure (LVF - Left Ventricular Failure) likely to be effective in maximising the proven benefits of ACE inhibition?

Elderly Health Promotion, Disease Prevention and Rehabilitation

What are the effects/effectiveness of interventions to promote health, prevent disease and rehabilitate older patients?

Elderly Mentally Infirm

What is the evidence concerning treatment of the elderly mentally infirm, in particular with regard to dementia?

Elderly Patients

What is the evidence on the effectiveness/cost-effectiveness of day hospitals in the treatment of the elderly in comparison with other NHS or social services models of provision?

Elderly Physically Frail People

Is there any evidence that the provision of a community health team for older people with physical health problems and frailty would benefit service users?

Electrodiagnostic Techniques

What is the usefulness of electrodiagnostic techniques as a prognostic tool in pre-surgical assessment of patients with carpal tunnel syndrome?

EMDR (Eye Movement Desensitisation and Reprocessing)

What is the effectiveness of EMDR in the management of post traumatic stress disorder (PTSD) arising from sexual abuse?

Emergency Admissions

What research evidence is there on the reasons for and interventions to reduce rising numbers of emergency admissions? ARIF was asked to help assist in the commission of further research by the West Midlands Department of R&D, by identifying whether there were any systematic reviews on this topic.

Emphysema

What are the effects/effectiveness of lung reduction surgery in severe emphysema?

Endoscopic Laser Foraminoplasty

What is the evidence base for Endoscopic Laser Foraminoplasty?

End Stage Renal Failure

What is the evidence around cost-effectiveness of GP led renal centres versus hospital based or other models?

Endoscopy

What would be the evidence base to inform the development of guidelines for a local open access endoscopy service to diagnose gastrointestinal problems?

Endovascular Laser Therapy

What is the effectiveness of Endovascular Laser Therapy (EVLT) on healing venous leg ulcers, compared to other treatments (such as other surgical procedures) or conservative management (such as bandaging)?

Endovascular Stents (EVAR)

What is the effectiveness and cost-effectiveness of EVARs for infrarenal abdominal aortic aneurysms?

Endovascular Stents (EVAR)

What is the clinical and cost-effectiveness of endovascular aneurysm repair (EVAR) in the management of abdominal aortic aneurysms, with particular reference to higher risk patients deemed unfit for surgery?

Enhanced External Counterpulsation

To find information regarding the clinical effectiveness of treatment of enhanced external counterpulsation (EECP) in patients with angina which cannot be relieved by conventional treatment.

Enzyme Potentiated Desensitisation (EPD)

ARIF has received several requests concerning the effectiveness of EPD.

Enzyme Potentiated Desensitisation (EPD)

What is the effectiveness of enzyme potentiated desensitisation (EPD) for treating patients with severe allergies?

Enzyme Potentiated Desensitisation (EPD)

What is the effectiveness of enzyme potentiated desensitisation (EPD) for chronic fatigue syndrome?

Epilepsy

Do specialist epilepsy clinics offer advantages over general neurology clinics?

Epilepsy
How effective is vagal nerve stimulation for intractable epilepsy?

Erosive Oesophagitis
What is the evidence that esomeprazole is more effective and cost-effective than omeprazole or lansoprazole for peptic ulcer disease in adults?

Essential Fatty Acids (n-3 series)
What is the evidence on the effectiveness of fish oil supplements on school aged children's behaviour and educational attainment?

Esomeprazole
What is the evidence that esomeprazole is more effective and cost-effective than omeprazole or lansoprazole for peptic ulcer disease in adults?

Excess Winter Deaths
Are there any interventions or strategies that have been successful in reducing excess winter deaths?

Exercise
What is the evidence that increased physical activity improves depression in adults?

Exercise
Is there any evidence that participants in exercise referral schemes sustain increased levels of physical activity?

Exercise
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to increasing physical activity?

Exercise ECG
What are the implications of implementing the recommendation from the North of England Guideline Development Group (BMJ 1996; 312: 827-832) that all patients with angina should have an exercise ECG test?

Exercise Referral Schemes
Is there any evidence that participants in exercise referral schemes sustain increased levels of physical activity?

Exercise Testing
Is there any evidence on the role of risk stratification, and in particular by exercise tests, for cardiac rehabilitation?

External Beam Radiotherapy
What is the effectiveness of high dose rate brachytherapy using temporarily inserted isotopes in combination with external beam radiotherapy (EBRT) versus EBRT alone in localised prostate cancer?

External Beam Radiotherapy (EBRT)
Evidence on the effectiveness of brachytherapy uses comparisons with existing standard treatments like EBRT and radical prostatectomy. Following on from this, what is the evidence for the effectiveness of these standard treatments themselves?

Extracorporeal Photochemotherapy (ECP)
ARIF were asked to evaluate the effectiveness and safety of Extracorporeal Photochemotherapy (ECP) in children who have steroid refractory chronic graft-versus-host disease (cGVHD)

Eye Conditions
What is the quantity and quality of the evidence regarding ranibizumab (Lucentis) and bevacizumab (Avastin) in the treatment of eye conditions (excluding age-related macular degeneration), thought to be related to vascular endothelial growth factor?

Eye Movement Desensitisation and Reprocessing (EMDR)
What is the effectiveness of EMDR in the management of post traumatic stress disorder (PTSD) arising

from sexual abuse?

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Fabry's Disease
What is the effectiveness of a-galactosidase A in the treatment of Fabry's Disease?

Facial Blushing
What is the effectiveness of sympathectomy for facial blushing?

Facilitating Introduction
What is the effectiveness of facilitating the introduction of gay men into the gay community on reducing risk-taking behaviour and HIV/AIDS infection or transmission?

"Failed" Back Surgery Syndrome
What is the effectiveness of spinal cord stimulation for chronic neuropathic pain, particularly in "failed" back surgery syndrome and complex regional pain syndrome?

Falls in Older People
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to the prevention of falls amongst older people?

Female Urinary Incontinence
What is the effectiveness and cost effectiveness of tension free vaginal tape compared to standard vaginal hysterectomy or colposuspension for female urinary incontinence?

Femoro-acetabular Impingement
What is the clinical effectiveness and cost-effectiveness of arthroscopic treatment for young people (of working age) with hip impingement (femoro-acetabular impingement) and/or hip pain and what group(s) of patients may be expected to be benefit from it?

Fenestrated Endovascular Repair
What is the evidence of the effectiveness and cost-effectiveness of fenestrated endovascular repair (f-EVAR) for the treatment of abdominal aortic aneurysm (AAA)?

Fenestrated Endovascular Stents (EVAR)
What is the effectiveness of fenestrated endovascular stents in patients who have abdominal aneurysms. Has the evidence base changed since ARIF last undertook a search for this question?

Fertility Preservation
What is the impact of childhood cancer treatment on women of reproductive age and what possible strategies would address their needs (with specific reference to reproductive function)?

Fibroids
What is the effectiveness of uterine arterial embolisation (UAE) in the treatment uterine fibroids?

Financial Incentives
What is the effectiveness and cost-effectiveness of providing financial incentive schemes to motivate increasing levels of physical exercise?

First Intercourse Amongst Adolescents
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in

primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to advice on delaying the time of first intercourse?

Fish Oil Supplements

What is the evidence on the effectiveness of fish oil supplements on school aged children's behaviour and educational attainment?

Flu Vaccination

ARIF were asked if vaccinations for influenza and pneumococcal disease improve survival for patients with cancer who have had systemic therapy (chemotherapy, hormonal therapy or radiotherapy).

Flying

Does inactivity when in a cramped seating position (such as during long-haul air travel) increase the risk of the development of DVT in airline passengers? Is there evidence that interventions such as the use of compression stockings, hydration, exercise and aspirin prevent DVT?

Follicle Stimulating Hormone

What is the effectiveness of recombinant follicle stimulating hormone (rFSH) compared to human-derived urinary follicle stimulating hormone (uFSH) in assisted conception in infertile women?

Forefoot Disease

What is the evidence of effectiveness of ceramic joint implants in the treatment of metatarsophalangeal joint disease?

Formaldehyde Poisoning

ARIF has received several requests concerning the effectiveness of EPD.

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a - Galactosidase A
What is the effectiveness of a-galactosidase A in the treatment of Fabry's Disease?

Galantamine
What is the effectiveness of galantamine in the treatment of Alzheimer's disease (AD)?

Gallstones -Stymptomatic
Is dietician advice and dietary change for symptomatic gallstones effective in reducing or abolishing symptoms and in eliminating the need for surgery?

Gastric Banding
What is the evidence that gastric bypass is better than gastric banding in reducing obesity related to co-morbidities?

Gastric Bypass
What is the evidence that gastric bypass is better than gastric banding in reducing obesity related to co-morbidities?

Gastrointestinal Disease
What would be the evidence base to inform the development of guidelines for a local open access endoscopy service to diagnose gastrointestinal problems?

Gastrointestinal Disease
What is the extent of the association between autism and chronic gastrointestinal disease?

Gastrointestinal Infections
What is the evidence on the effectiveness of interventions to prevent or reduce transmission of gastrointestinal and respiratory infections in schools in young children?

Gastrointestinal Stromal Tumours
What is the effectiveness of imatinib (Glivec®) in the treatment of patients with gastrointestinal stromal tumours?

Gastroplasty
Is banded gastroplasty a safe, effective and cost effective treatment for morbid obesity?

Gay Men
What is the effectiveness of facilitating the introduction of gay men into the gay community on reducing risk-taking behaviour and HIV/AIDS infection or transmission?

Gaucher's Disease
What is the evidence of effectiveness and cost effectiveness of Ceredase (Alglucerase) or Cerezyme (Imiglucerase) in the treatment of Gaucher's disease?

Gender Reassignment Surgery
Which groups are most likely to benefit from surgery for male and female gender reorientation and who should carry out the procedure?

General Management

Is there any evidence on the effectiveness of different interventions for cancer of the oesophagus?

General Practitioners
Is there any evidence on the effectiveness of general practitioners (GPs) in accident and emergency (A&E) units and are there any additional benefits compared to if he or she was not present on outcomes such as admission rates?

Genital Warts
What is the effectiveness of imiquimod in the treatment of genital warts?

Gliadel Wafer
What is the effectiveness of Gliadel wafer implants in the treatment of recurrent glioblastoma multiforme (GBM)?

Glioblastoma Multiforme (GBM)
What is the effectiveness of Gliadel wafer implants in the treatment of recurrent glioblastoma multiforme (GBM)?

Glue Ear - Antihistamine and Decongestants
What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Glue Ear - Antimicrobial Drugs
What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Glue Ear - Autoinflation
What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Glue Ear - Mucolytic Agents
What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Glue Ear - Prevention
What interventions are effective for the prevention of glue ear (otitis media with effusion)?

Glue Ear - Steroids
What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Gluten Free Diets
What is the effectiveness of gluten-free diets for autistic children?

GP (or General Practitioner), Haemodialysis, Renal Services
What is the evidence around cost-effectiveness of GP led renal centres versus hospital based or other models?

Guidelines, Policies, Treatment
Is there any information which will assist with the development of local policies and processes for the investigation and referral of patients with upper GI symptoms, outside those for urgent cancer referrals?

Gulf War Syndrome
ARIF has received several requests concerning the effectiveness of EPD.

Gulf War Syndrome
What is the effectiveness of enzyme potentiated desensitisation (EPD) for treating patients with severe allergies?

Green-Light Laser
What is the effectiveness of PVP using the green-light (KTP) laser?

Growth Hormone

In 2007 the West Midlands Health Technology Assessment Collaboration (WMHTAC) completed a systematic review that assessed the clinical and cost effectiveness of Pegvisomant (PEG) for use in patients with acromegaly. ARIF were asked to determine if any new research had been published since the completion of the WMHTAC review and whether this alters any conclusions of the report.

Growth Hormone

What is the effectiveness/cost effectiveness of growth hormone treatment of growth hormone deficient adults?

Growth Hormone Deficiency

What is the effectiveness/cost effectiveness of growth hormone treatment of growth hormone deficient adults?

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Requests for Information Completed - H

Haemodialysis
What is the evidence on the effectiveness of different methods of renal replacement therapy, other than renal transplant?

Haemodialysis
Is there a reduction in cardiovascular mortality, morbidity and risk in patients with kidney failure and hyperphosphataemia taking non-metal containing phosphate binders (sevelamer and lanthanum) compared to patients taking calcium-containing phosphate binders (calcium acetate and calcium carbonate)?

Haemophilia A
What are the effects/effectiveness of rFVIII in individuals with Haemophilia A, relative to existing plasma derived FVIII (pdFVIII) preparations?

Haemophilia A
What are the effects/effectiveness of continuous versus intermittent FVIII in treatment of Haemophilia A - including the effect of different prophylactic dosage regimes?

Haemorrhagic Disease of the Newborn (HDNB)
What is the evidence for the effectiveness and safety of giving vitamin K to newborns to prevent Haemorrhagic Disease of the Newborn (HDNB), and what is the best means of administration?

Haemorrhoids
What is the effectiveness of the stapling technique versus conventional surgery for grade III haemorrhoids not suitable for non-resective surgery?

Health Behaviour
What evidence is there on the effectiveness of media campaigns and other interventions which aim to reduce patient delay factors in pain to needle time in acute myocardial infarction?

Health Checks
What is the evidence base for asking GPs to carry out health checks on new immigrants, in particular full blood count, Malaria blood film and stool microbiology?

Health Promotion
Are Community Development Programmes an effective way of empowering communities?

Health Promotion
What is the effectiveness of drama techniques for imparting health promotion messages and bringing about changes in behaviour?

Health Promotion
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to reducing alcohol consumption?

Health Promotion
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to diet?

Health Promotion
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to increasing physical activity?

Health Promotion
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to the prevention of falls amongst older people?

Health Promotion
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to advice on delaying the time of first intercourse?

Health Promotion
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to the prevention/reduction of illicit drug use amongst young people?

Health Promotion
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to safe sex?

Health Promotion
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to smoking cessation?

Health Promotion
What is the validity, reliability and effectiveness of health risk appraisal tools, particularly in the workplace setting and in people with chronic diseases?

Health Promotion
Do awareness campaigns targeted at the public or GPs which are aimed at reducing delays to diagnostic and specialised health care services, improve survival for cancer?

Health Visitors (UK)
Assessment of the effectiveness of health visitor activities in the NHS

Healthy Lifestyle - Children
What is the effectiveness of the MEND programme in treating overweight children?

Health Risk Assessment
What is the validity, reliability and effectiveness of health risk appraisal tools, particularly in the workplace setting and in people with chronic diseases?

Heart Failure
What is the accuracy of pro-Brain Natriuretic Peptide (proBNP) in the diagnosis of heart failure?

Heart Failure (LVF) ACE Inhibitors
Is GP open access to echocardiography for the diagnosis of heart failure (LVF - Left Ventricular Failure) likely to be effective in maximising the proven benefits of ACE inhibition?

Heart Failure After Myocardial Infarction
What is the effectiveness and cost effectiveness of using buccal nitrates in primary care, in the management of patients with heart failure after a myocardial infarction?

Heavy Drinkers
What is the clinical and cost-effectiveness of providing incentives to motivate reduced alcohol

consumption?

Hepatitis B
What is the effectiveness of lamivudine in the treatment of chronic hepatitis B?

Hepatitis B
What is the effectiveness of adefovir dipivoxil for the treatment of patients with lamivudine-resistant chronic HBV?

Herceptin
Evidence on effectiveness of herceptin in small size tumours (equal to or less than 0.5cm) and lymphovascular invasion HER-2 positive early-stage breast cancer.

Herceptin
What is the quality of two recently published articles reporting the results of three randomised controlled trials assessing the effectiveness of trastuzumab (Herceptin) in the treatment of HER2-positive, early-stage breast cancer?

Herediatry Angioedema (HAE)
What is the evidence for using C1 Esterase Inhibitor Concentrate as a long-term prophylaxis in patients with severe Herediatry Angioedema (HAE)?

Hernia
To assess the clinical and cost-effectiveness of surgical inguinal hernia repair versus watchful waiting in asymptomatic or minimally symptomatic men.

Hernia Repair
Should laparoscopic treatment of inguinal hernias be purchased in the light of the evidence on its effectiveness?

Hernia Repair
What is the relative effectiveness of partially absorbable mesh in comparison with non-absorbable mesh in the repair of inguinal hernias?

Hip Impingement
What is the clinical effectiveness and cost-effectiveness of arthroscopic treatment for young people (of working age) with hip impingement (femoro-acetabular impingement) and/or hip pain and what group(s) of patients may be expected to be benefit from it?

Hip Replacement
Which clinical measurement tools that measure referral threshold for hip replacement are evidence based and of these, which are the best?

Hirsutism
What is the effectiveness of laser therapy for unwanted hair?

HIV Discordant Couples
What is the evidence of effectiveness of sperm washing in reducing the risk of HIV transmission in couples where the man is HIV+ve and the woman HIV-ve?

Home Births
What is the comparative safety of home births compared to hospital births for women classified as being of low obstetric risk?

Hormone Replacement Therapy
A policy for treating osteoporosis is to be developed, therefore: Is there a defined group of women who should received prolonged Hormone Replacement Therapy (HRT) and what role does bone density scanning have in assessing these women?

Housing Clearances
What is the health impact of housing clearances, and in particular the psychological and physical health impact on those people who have been rehoused following housing clearance?

Human Givens Approach REWIND Technique
What is the effectiveness of the Human Givens approach applied to mental health care?

Hyaluronic Acid Viscosupplements
What is the effectiveness the hyaluronic acid viscosupplements (Synvisc® (Hylan G-F20) and Hyalgan®) in the treatment of osteoarthritis of the knee?

Hydrotherapy
What are the effects/effectiveness of hydrotherapy?

Hyperbaric Oxygen
What is the effectiveness of hyperbaric oxygen for the prevention and treatment of osteoradionecrosis?

Hyperbaric Oxygen Therapy
What is the evidence for hyperbaric oxygen in the management of patients with acute carbon monoxide poisoning?

Hyperphenylalaninaemia
An opinion on the evidence base (reporting of trials and peer reviewed publications) with regard to the use of sapropterin dihydrochloride in phenylketonuria.

Hyperphosphataemia
What is the effectiveness of sevelamer (Renagel®) for the treatment of hyperphosphataemia in patients on haemodialysis?

Hypertension
What is the quality of a recent systematic review (Carlberg et al, 2004) assessing the effect of atenolol on cardiovascular morbidity and mortality in hypertensive patients?

Hysterectomy
Which clinical measurement tools that measure referral threshold for hysterectomy are evidence based and of these, which are the best?

Hysterectomy and Sub-Total Hysterectomy
For non-malignant cases, which produces the best outcomes; hysterectomy or sub-total hysterectomy?

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Requests for Information - I

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Idiopathic Sub-Foveal Choroidal Neovascularisation
What is the effectiveness of photodynamic therapy for idiopathic sub-foveal choroidal neovascularisation?

a - L - iduronidase
What is the evidence on the effectiveness of the recombinant enzyme replacement laronidase in the treatment of the lysosomal storage disorder mucopolysaccharidosis type 1 (MPS 1)?

Illicit Drug Use
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to the prevention/reduction of illicit drug use amongst young people?

Iloprost
Critical Appraisal of "Goal-oriented treatment and combination therapy for pulmonary arterial hypertension" Hoeper MM et al. - in relation to assessment of study design and interpretation of the results particularly regarding the effectiveness of dual therapy relative to monotherapy.

Imatinib
What is the effectiveness of imatinib (Glivec®) in the treatment of patients with gastrointestinal stromal tumours?

Imiquimod
What is the effectiveness of imiquimod in the treatment of genital warts?

Immigration
What is the evidence base for asking GPs to carry out health checks on new immigrants, in particular full blood count, Malaria blood film and stool microbiology?

Immunodeficiency - Primary
What is the effectiveness and cost-effectiveness of immunoglobulin replacement therapy for common variable immunodeficiency (CVID)?

Immunoglobulin
What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Immunoglobulin Replacement Therapy
What is the effectiveness and cost-effectiveness of immunoglobulin replacement therapy for common variable immunodeficiency (CVID)?

Immunoreactive Trypsin
What is the evidence base of a proposal to introduce regionwide neonate screening for cystic fibrosis using immunoreactive trypsin?

Impacted Cancellous Allografts and Cement
What is the strength of evidence in favour of this technique over existing total hip revision in terms of quality and cost effectiveness? Is there any information whether these should be carried out at tertiary centres? Is there a minimal level of activity/experience of operator needed to ensure good quality

surgery?

Implantable Intraocular Lens Systems
Rapid assessment of implantable intraocular lens systems for age-related macular degeneration (AMD)

Impotence
What is the research evidence on the epidemiology, diagnosis and treatment of male impotence?

Incentives
What is the clinical and cost-effectiveness of providing incentives to motivate smokers to quit?

Incentives
What is the clinical and cost-effectiveness of providing incentives to motivate reduced alcohol consumption?

Incentives - Rewards (Smoking Cessation)
What is the evidence for a) the effectiveness of incentives for smoking cessation in pregnancy and b) the use of SMS texting for motivational purposes; to support a smoking cessation programme?

Incontinence
What is the cost effectiveness of peri-urethral collagen injections in the treatment of stress incontinence? Are there short or long term complications that need to be considered?

Infant Mortality Rates (IMR)
Suggest an approach to devise an evidence based strategy to reduce high rates of perinatal and infant mortality. The main role of ARIF in this request was to assist and facilitate a worker from the commissioning authority in question, identify interventions which had been demonstrated to have an effect on perinatal and infant mortality.

Infertile Women
What is the effectiveness of recombinant follicle stimulating hormone (rFSH) compared to human-derived urinary follicle stimulating hormone (uFSH) in assisted conception in infertile women?

Infertility
Are there any reviews on IVF and GIFT that have been produced since the 1992 Effective Health Care Bulletin, The Management of Subfertility? (Leeds: School of Public Health, University of Leeds, 1992. pp24. No 3)

Infertility
What is the evidence for the effectiveness of intra-cytoplasmic sperm injection for assisted conception?

Infertility after Childhood Cancer Treatment
What is the impact of childhood cancer treatment on women of reproductive age and what possible strategies would address their needs (with specific reference to reproductive function)?

Influenza
What are the effects/effectiveness of different policies on the use of influenza vaccination?

Influenza
Is there any evidence that annual vaccination of health care workers against influenza has health benefits for individuals, patients or organisations?

Influenza Vaccination
ARIF were asked if vaccinations for influenza and pneumococcal disease improve survival for patients with cancer who have had systemic therapy (chemotherapy, hormonal therapy or radiotherapy).

Influenza Vaccinations, Home Heating and Insulation, Keeping Warm
Are there any interventions or strategies that have been successful in reducing excess winter deaths?

Inguinal Hernia
To assess the clinical and cost-effectiveness of surgical inguinal hernia repair versus watchful waiting in asymptomatic or minimally symptomatic men.

Inguinal Hernias
What is the relative effectiveness of partially absorbable mesh in comparison with non-absorbable mesh in the repair of inguinal hernias?

Inguinal Hernia Repair
Should laparoscopic treatment of inguinal hernias be purchased in the light of the evidence on its effectiveness?

Inpatient Alcohol Detoxification
What is the clinical and cost-effectiveness of community-based versus inpatient alcohol detoxification regiments for alcohol dependent patients?

In-patient Treatment
How does the effectiveness of in-patient treatment compare to (intensive) out-patient treatment for patients with severe or moderate anorexia nervosa, and what type of out-patient treatment is most effective?

Integrated Care Pathways
Are Integrated Care Pathways (ICPs) effective and cost effective, particularly in terms of getting research evidence into practice?

Intensive Lipid Lowering Therapy
What is the clinical and cost-effectiveness of early aggressive lipid lowering therapy using very high dose statins (80mg/day) for patients with acute coronary syndrome, patients with crescendo angina, and patients undergoing revascularisation?

Intractable Pain
What interventions should a pain clinic be offering?

Intra-Cytoplasmic Sperm Injection
What is the evidence for the effectiveness of intra-cytoplasmic sperm injection for assisted conception?

Intraspinal Drug Delivery
What is the effectiveness of intraspinal drug delivery in the management of chronic pain?

Intravenous Gammaglobulin
What is the evidence that intravenous gammaglobulin prevents the formation of coronary artery aneurysms in children with Kawasaki Disease?

Intravenous Immunoglobulin
What is the effectiveness of intravenous immunoglobulin (IVIG) in the treatment of neurological movement disorders of probable autoimmune origin following infection, given the presence of antibasal ganglia antibodies (ABGAs)?

Iodine-125
What is the effectiveness of low dose rate brachytherapy using inserted iodine or palladium isotopes compared to other common methods of treatment such as radical prostatectomy or external beam radiotherapy (EBRT)?

Iridium
What is the effectiveness of high dose rate brachytherapy using temporarily inserted isotopes in combination with external beam radiotherapy (EBRT) versus EBRT alone in localised prostate cancer?

Irlen Lenses, Coloured Lenses, Tinted Lenses
What is the evidence for Irlen syndrome and if it exists, what evidence is there for the advised therapy?

Irlen Syndrome, Scotopic Sensitivity
What is the evidence for Irlen syndrome and if it exists, what evidence is there for the advised therapy?

Ischaemic Heart Disease
What are the effects/effectiveness of CABG and other interventional cardiological procedures i.e.

PTCA, specifically in relationship to prioritisation of those procedures?

Ischaemic Heart Disease

Advice on research on the effects/effectiveness of abciximab (intravenous glycoprotein IIb/IIIa receptor (GPIIb/IIIa) inhibitor). ARIF was asked to appraise available research on the above new drug.

Ischaemic Heart Disease

Is naproxen associated with reduced numbers of fatal and non-fatal ischaemic heart disease events relative to no use of naproxen?

Isolated Limb Infusion

To compare the clinical effectiveness of isolated limb perfusion in the treatment of melanoma.

Isolated Limb Perfusion

To compare the clinical effectiveness of isolated limb perfusion in the treatment of melanoma.

IVF/GIFT

Are there any reviews on IVF and GIFT that have been produced since the 1992 Effective Health Care Bulletin, The Management of Subfertility? (Leeds: School of Public Health, University of Leeds, 1992. pp24. No 3)

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Joint Replacement Surgery
How effective is simultaneous bilateral joint replacement surgery?

Joint Surgery
Surgery in Obese Patients: What is the evidence that obesity impacts adveraely on patients who have surgery, particularly joint surgery? - If there is poor outcome, what interventions have been shown to reduce BMI prior to surgery? - Are there any trials which have investigate the effect of weight reduction prior to surgery?

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Requests for Information Completed - K

[Kawasaki Disease]
What is the evidence that intravenous gammaglobulin prevents the formation of coronary artery aneurysms in children with Kawasaki Disease?

[Kidney, Dialysis]
Is there a reduction in cardiovascular mortality, morbidity and risk in patients with kidney failure and hyperphosphataemia taking non-metal containing phosphate binders (sevelamer and lanthanum) compared to patients taking calcium-containing phosphate binders (calcium acetate and calcium carbonate)?

[Kidney, Liver and Lung Cancer]
Is there data to support the use of Radiofrequency Ablation of the kidney, liver and lung as an alternative to surgical resection?

[Knee]
What is the effectiveness the hyaluronic acid viscosupplements (Synvisc® (Hylan G-F20) and Hyalgan®) in the treatment of osteoarthritis of the knee?

[Knee Replacement]
Which clinical measurement tools that measure referral threshold for knee replacement are evidence based and of these, which are the best?

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Lamivudine
What is the effectiveness of lamivudine in the treatment of chronic hepatitis B?

Lamivudine-resistant hepatitis-B
What is the effectiveness of adefovir dipivoxil for the treatment of patients with lamivudine-resistant chronic HBV?

Lanreotide
What is the effectiveness of lanreotide and octreotide in the treatment of acromegaly?

Lansoprazole
What is the evidence that esomeprazole is more effective and cost-effective than omeprazole or lansoprazole for peptic ulcer disease in adults?

Lanthanum
Is there a reduction in cardiovascular mortality, morbidity and risk in patients with kidney failure and hyperphosphataemia taking non-metal containing phosphate binders (sevelamer and lanthanum) compared to patients taking calcium-containing phosphate binders (calcium acetate and calcium carbonate)?

Laparoscopic
Should laparoscopic treatment of inguinal hernias be purchased in the light of the evidence on its effectiveness?

Laronidase
What is the evidence on the effectiveness of the recombinant enzyme replacement laronidase in the treatment of the lysosomal storage disorder mucopolysaccharidosis type 1 (MPS 1)?

Laser Acupuncture
What is the effectiveness of laser acupuncture in patients with chronic pain, relative to other forms of pain relief?

Laser Therapy
What is the effectiveness of laser therapy for acne?

Laser Therapy
What is the effectiveness of laser therapy for acne scarring?

Laser Therapy
What is the effectiveness of laser therapy for port wine stains?

Laser Therapy (intralesion)
What is the effectiveness of laser therapy for port wine stains and other subcutaneous vascular disorders (haemangioma and arterio-venous malformations)?

Laser Therapy
What is the effectiveness of laser therapy for unwanted hair?

Learning Disabilities

What is the effectiveness of regular health checks in the primary care setting for people with learning disability?

Learning Disability

Is there evidence of any health promotion interventions that ameliorate the effects of learning disabilities?

Leukaemia, Chronic Lymphocytic

What is the effectiveness of Alemtuzumab in the treatment of chronic lymphocytic leukaemia?

Lifecheck

What is the validity, reliability and effectiveness of health risk appraisal tools, particularly in the workplace setting and in people with chronic diseases?

Limb Spasticity

Is BTX-A a safe and effective treatment for the relief of limb spasticity in cerebral palsy?

Link Worker

Research bids have been received to fund "link workers". Is there any research on the effects and effectiveness of these?

Liver Cancer

Is there data to support the use of Radiofrequency Ablation of the kidney, liver and lung as an alternative to surgical resection?

Localised Prostate Cancer

What is the effectiveness of high dose rate brachytherapy using temporarily inserted isotopes in combination with external beam radiotherapy (EBRT) versus EBRT alone in localised prostate cancer?

Localised Prostate Cancer

What is the effectiveness of low dose rate brachytherapy using inserted iodine or palladium isotopes compared to other common methods of treatment such as radical prostatectomy or external beam radiotherapy (EBRT)?

Localised Prostate Cancer

Evidence on the effectiveness of brachytherapy uses comparisons with existing standard treatments like EBRT and radical prostatectomy. Following on from this, what is the evidence for the effectiveness of these standard treatments themselves?

'Looked After' Children

What is the evidence on the effectiveness/cost effectiveness of dyadic developmental psychotherapy in the treatment of children with attachment disorders and particularly the effect on adoption rates amongst 'looked after' children?

Low Birth Weight Babies (Poor Foetal Growth)

Is there any evidence on the effectiveness and safety of Doppler scanning for the detection of foetal abnormalities?

Low Molecular Weight Heparin

What evidence is there that low molecular weight heparin for the treatment of deep vein thrombosis/venous thromboembolism can safely and be successfully used in a community setting?

Low Molecular Weight Heparin

How effective and cost-effective is LMWH relative to other treatments, particularly unfractionated heparin, in the management of unstable angina?

Low Molecular Weight Heparin

How effective and cost-effective is LMWH relative to other treatments, particularly unfractionated heparin, in the prevention of deep venous thrombosis (DVT)?

Low Molecular Weight Heparin

What is the effectiveness and cost-effectiveness of LMWH relative to other interventions for the

treatment of existing thromboembolic disease?

Low Molecular Weight Heparin
What is known about the relative effectiveness and cost-effectiveness of different LMWH products in the prevention of deep venous thrombosis in orthopaedics; the management of unstable angina; and the treatment of existing thromboembolic disease?

Low Obstetric Risk Women
What is the comparative safety of home births compared to hospital births for women classified as being of low obstetric risk?

LUCAS Device
Is the LUCAS device effective/cost-effective particularly in the context of an ambulance service?

Lucentis
What is the quantity and quality of the evidence regarding ranibizumab (Lucentis) and bevacizumab (Avastin) in the treatment of eye conditions (excluding age-related macular degeneration), thought to be related to vascular endothelial growth factor?

Lumbar Disc Prolapse
What is the evidence base for Endoscopic Laser Foraminoplasty?

Lung Cancer
Is there data to support the use of Radiofrequency Ablation of the kidney, liver and lung as an alternative to surgical resection?

Lung Cancer - Non-Small Cell
Is there evidence that lung cancer mortality could be substantially reduced by carrying out more surgery?

Lung Cancer (Non-Small Cell Lung Cancer)
What is the effectiveness of Continuous Hyperfractionated Accelerated Radiotherapy (CHART)?

Lung Reduction Surgery
What are the effects/effectiveness of lung reduction surgery in severe emphysema?

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Major Trauma
Is there any review evidence relating to the most effective delivery of care to patients who have suffered severe trauma?

Male Menopause
Is there any evidence as to the effects of testosterone supplementation in middle aged males suffering "andropausal symptoms?"

Management of Unstable Angina
What is known about the relative effectiveness and cost-effectiveness of different LMWH products in the prevention of deep venous thrombosis in orthopaedics; the management of unstable angina; and the treatment of existing thromboembolic disease?

Mass Media
What is the evidence on the effectiveness of marketing/publicity/media campaigns aimed at reducing alcohol use amongst young people (aged 16-25 years)?

Measurement Tool
Which clinical measurement tools that measure referral threshold for hip replacement are evidence based and of these, which are the best?

Measurement Tool
Which clinical measurement tools that measure referral threshold for hysterectomy are evidence based and of these, which are the best?

Measurement Tool
Which clinical measurement tools that measure referral threshold for knee replacement are evidence based and of these, which are the best?

Measurement Tool
Which clinical measurement tools that measure referral threshold for meniscectomy are evidence based and of these, which are the best?

Measurement Tools
Is there any systematically reviewed evidence on the valdity, reliability and responsiveness of clinical measurement tools for monitoring outcomes of hand surgery? Does the evidence from these reviews show how the Disabilities of Arm, Shoulder and Hand (DASH) questionnaire compares with other questionnaires for monitoring outcomes of hand surgery?

Media Campaigns
What evidence is there on the effectiveness of media campaigns and other interventions which aim to reduce patient delay factors in pain to needle time in acute myocardial infarction?

Melanoma
To compare the clinical effectiveness of isolated limb perfusion in the treatment of melanoma.

Memory Clinics
Is there any evidence that memory clinics are more effective than routine OPD appointments in the management of people with dementia?

MEND
What is the effectiveness of the MEND programme in treating overweight and obese children?

Meniscectomy
Which clinical measurement tools that measure referral threshold for meniscectomy are evidence based and of these, which are the best?

Men Who Have Sex With Men
What is the effectiveness of peer education interventions aimed at influencing sexual risk-taking behaviour in men who have sex with men?

Menopause
What treatments have been shown to be effective to treat symptoms of the menopause?

Menorrhagia
What research exists on uterine thermal balloon therapy for women with menorrhagia?

Mental Health
ARIF were asked to investigate the literature on models of care which can have a positive impact on mental health outcomes in persons over 65 years, particularly outcomes relating to dementia and/or depression.

Mental Health
What is the effectiveness of counselling services in general and in the primary care setting in particular?

Mental Health
Is there any evidence on the effectiveness of clinical psychology in general and whether clinical psychologists are more effective than other professionals such as counsellors in certain conditions?

Mental Health
Does mental health well-being (as opposed to mental illness) affect physical health?

Mental Health Planning - Older People
ARIF were asked to investigate the literature on models of care which can have a positive impact on mental health outcomes in persons over 65 years, particularly outcomes relating to dementia and/or depression.

Mental Health Problems
What is the effectiveness of the Human Givens approach applied to mental health care?

Mental Illness
What is the effectiveness of the early detection and treatment of severe mental illness in children and adolescents?

Mental Illness
What is the effectiveness of interventions provided by physiotherapists in the treatment of the symptoms of mental illness?

Mental Illness
What is the evidence on the effectiveness/cost-effectiveness of day hospitals in the treatment of people with mental illness in comparison with other NHS or social services models of provision?

Mental Illness
Can mental illness be prevented?

Mental Illness
What validated tools are there to help assess the general functioning of in-patients with mental illness, to follow progress while inpatients and compare discharge with admission state?

Monitoring

Is there any systematically reviewed evidence on the valdity, reliability and responsiveness of clinical measurement tools for monitoring outcomes of hand surgery? Does the evidence from these reviews show how the Disabilities of Arm, Shoulder and Hand (DASH) questionnaire compares with other questionnaires for monitoring outcomes of hand surgery?

Mentoring Programmes

What is the effectiveness of mentoring programmes in reducing teenage pregnancy amongst vulnerable groups?

Mesh (partially absorbable or non-absorbable)

What is the relative effectiveness of partially absorbable mesh in comparison with non-absorbable mesh in the repair of inguinal hernias?

Metal-to-Metal Resurfacing

Metal-to-metal hip resurfacing has been suggested as an alternative to performing a standard total hip replacement in selected cases, usually in younger patients. The procedure is intended to prevent future need for revisions. What is the evidence for the effectiveness and safety of this procedure?

Metastatic Renal Cell Carcinoma

What is the evidence of effectiveness of reduced intensity allogeneic stem cell transplantation in patients with metastatic renal cell carcinoma. Does it extend survival, improve quality of life, and what are the side effects?

Metatarsophalangeal Joint Disease

What is the evidence of effectiveness of ceramic joint implants in the treatment of metatarsophalangeal joint disease?

Metastatic Renal Cell Cancer (RCC)

What is the effectiveness of sorafenib for metastatic renal cell cancer?

Methicillin-resistant Staphylococcus Aureus (MRSA)

Are there any reviews of evidence on the effects/effectiveness of ozone solution for treatment of methicillin-resistant staphylococcus aureus (MRSA)

Miglustat

What is the evidence on the effectiveness of Miglustat for the treatment of Niemann-Pick disease?

Migraine, Chronic

What is the effectiveness of occipital nerve stimulation (ONS) for someone with migraine?

Mild Cognitive Impairment

Is there evidence indicating the best diagnostic tool for identifying mild cognitive impairment in patients presenting with subjective cognitive impairment?

Mild Dyskaryosis

ARIF were asked to investigate the impact of changing referral practice in cervical screening, both on the individual regarding patient benefit and on the service regarding cost and impact on service provision, for women presenting with mild dyskaryosis.

Miller Technique

ARIF has received many requests concerning the effectiveness of provocation-neutralisation therapy.

Monoclonal Antibody Therapy

What is known about the effectiveness of monoclonal antibody therapy for the treatment of patients with relapsed lymphoma? What is the evidence for the effectiveness of this treatment compared to standard chemotherapy?

Morbid Obesity

Is banded gastroplasty a safe, effective and cost effective treatment for morbid obesity?

MRI

Is there any good evidence about the effectiveness and cost effectiveness of MRI diagnostic scanning?

Is there any evidence about when it is of value and when it is not?

MRI for the Diagnosis of Knee Disorders

Is GP open access to MRI for the diagnosis of knee disorders cost effective for the selection of patients to be referred for specialist opinion and care?

MRI for the Diagnosis of Cause of Low Back Pain

Should GPs have open access to MRI, and should they use it in unselected patients with low back pain that remains unresolved after 6 weeks of conservative management with physiotherapy/exercise etc? Used in this way, does MRI offer a cost effective way of selecting patients for referral to surgeons and reasurring others that there is no serious disease?

Mucolytic Agents

What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Mucopolysaccharidosis Type 1

What is the evidence on the effectiveness of the recombinant enzyme replacement laronidase in the treatment of the lysosomal storage disorder mucopolysaccharidosis type 1 (MPS 1)?

Multiple Allergies

What is the effectiveness of enzyme potentiated desensitisation (EPD) for treating patients with severe allergies?

Multiple Allergy Syndrome

ARIF has received many requests concerning the evidence on effectiveness of the services by the Breakspear Hospital.

Multiple Allergy Syndrome

ARIF has received many requests concerning the effectiveness of provocation-neutralisation therapy.

Multiple Chemical Sensitivity

ARIF has received many requests concerning the evidence on effectiveness of the services by the Breakspear Hospital.

Multiple Chemical Sensitivity

ARIF has received several requests concerning the effectiveness of EPD.

Multiple Chemical Sensitivity

ARIF has received many requests concerning the effectiveness of provocation-neutralisation therapy.

Multiple Sclerosis (MS)

Is there any evidence to support the effectiveness of a central multidisciplinary team designated to directly meet the needs of people with multiple sclerosis throughout the country?

Myalgic Encephalopathy (ME)

What is the evidence on the effects/effectiveness of treatments of chronic fatigue syndrome?

Mycophenolate Mofetil

What is the clinical effectiveness of mycophenolate mofetil for patients with Behcet's disease who are intolerant of immunosuppresive treatment with methotrexate, cyclosporine and azathioprine?

Myocardial Infarction

What are the effects/effectiveness of CABG and other interventional cardiological procedures i.e. PTCA, specifically in relationship to prioritisation of those procedures?

Myocardial Infarction

What is the effectiveness of cardiac rehabilitation particularly in respect to: mortality, tackling depression, return to work and ensuring continued access to GP for medication?

Myocardial Infarction

Has anyone designed and evaluated alternative approaches to cardiac rehabilitation which overcome

access issues by ethnic minority groups or low income groups?

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Requests for Information Completed - N

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Naltrexone
What is the effectiveness of naltrexone in alcohol dependent patients?

Naproxen
Is naproxen associated with reduced numbers of fatal and non-fatal ischaemic heart disease events relative to no use of naproxen?

Neuralgia
What interventions should a pain clinic be offering?

Neurological Movement Disorders
What is the effectiveness of intravenous immunoglobulin (IVIG) in the treatment of neurological movement disorders of probable autoimmune origin following infection, given the presence of antibasal ganglia antibodies (ABGAs)?

Neuromuscular Diseases
Evidence on clinical and cost-effectiveness of non-invasive ventilation in patients with neuromuscular and chest wall diseases.

Neuromuscular Disorders
What is the effectiveness of nocturnal mechanical ventilation in relieving symptoms of hypoventilation in patients with neuromuscular and chest wall disorders?

Nicotine Replacement Therapy (NRT)
The National Institute for Health and Clinical Effectiveness (NICE) as part of the wider programme of work on smoking and the NHS in England and Wales, commissioned a report from ARIF and the West Midlands Health Technology Assessment Collaboration, to identify the best evidence on the clinical and cost-effectiveness of NRT

Niemann-Pick Disease
What is the evidence on the effectiveness of Miglustat for the treatment of Niemann-Pick disease?

Nocturnal Mechanical Ventilation
What is the effectiveness of nocturnal mechanical ventilation in relieving symptoms of hypoventilation in patients with neuromuscular and chest wall disorders?

Non-invasive Positive Pressure Ventilation
What is the effectiveness of non-invasive positive pressure ventilation for patients with stable hypercapnic chronic obstructive pulmonary disease in a domiciliary environment?

Non-Invasive Ventilation
Evidence on clinical and cost-effectiveness of non-invasive ventilation in patients with neuromuscular and chest wall diseases.

Nonmyeoblative Stem Cell Transplantation
What is the evidence of effectiveness of reduced intensity allogeneic stem cell transplantation in patients with metastatic renal cell carcinoma. Does it extend survival, improve quality of life, and what are the side effects?

NRT with Bupropion

The National Institute for Health and Clinical Effectiveness (NICE) as part of the wider programme of work on smoking and the NHS in England and Wales, commissioned a report from ARIF and the West Midlands Health Technology Assessment Collaboration, to identify the best evidence on the clinical and cost-effectiveness of NRT

NSAIDs

What treatments have been shown to be effective in the treatment of the common cold?

Nurse Practitioners

What is known about the effects of nurse practitioners and what are the implications for commissioned research on this topic?

Nurse Triage

What is the evidence for the safety and effectiveness of a nurse triage service within the primary care setting?

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Obesity
What is the evidence that gastric bypass is better than gastric banding in reducing obesity related to co-morbidities?

Obesity
Surgery in Obese Patients: What is the evidence that obesity impacts adveraely on patients who have surgery, particularly joint surgery? - If there is poor outcome, what interventions have been shown to reduce BMI prior to surgery? - Are there any trials which have investigate the effect of weight reduction prior to surgery?

Obesity - Children
What is the effectiveness of the MEND programme in treating overweight children?

Obstetric Units
What is the evidence to support a decision about whether funding for maternity services should be directed at general practitioner or consultant led obstetric units?

Occipital Nerve Stimulation
What is the effectiveness of occipital nerve stimulation (ONS) for someone with migraine?

Octreotide
What is the effectiveness of lanreotide and octreotide in the treatment of acromegaly?

Oesophageal Cancer
Is there any evidence on the effectiveness of different interventions for cancer of the oesophagus?

Omeprazole
What is the evidence that esomeprazole is more effective and cost-effective than omeprazole or lansoprazole for peptic ulcer disease in adults?

Oncology
What are the current and future prospects of the use of Positron Emission Tomography (PET) in oncology?

Opiate Addiction
Is there any evidence on the effectiveness of buprenorphine in the management of detoxification for opiate addiction?

Opiate Addiction
Is there any evidence on the effectiveness of dextropopoxyphene in the management of detoxification for opiate addiction?

Opioid Antagonists
What is the effectiveness of naltrexone in alcohol dependent patients?

Oseltamivir (Tamiflu)
Does Oseltamivir reduce mortality in an influenza pandemic situation?

Osteoarthritis
What is the effectiveness the hyaluronic acid viscosupplements (Synvisc® (Hylan G-F20) and

Hyalgan®) in the treatment of osteoarthritis of the knee?

Osteo-odonto-keratoprosthesis

What is the effectiveness of osteo-odonto-keratoprosthesis in the management of severe corneal disease?

Osteoporosis

What is the contribution of bone densitometry in the prediction of osteoporosis fracture and diagnosing osteoporosis? In particular, how does it help identify populations at risk of osteoporosis?

Osteoporosis

A policy for treating osteoporosis is to be developed, therefore: is there a defined group of women who should received prolonged Hormone Replacement Therapy (HRT) and what role does bone density scanning have in assessing these women?

Osteoporosis

A policy for treating osteoporosis is to be developed, therefore: Which patients should be treated with diphosphonates for verified osteoporosis and what role does bone densitometry have in assessment?

Osteoradionecrosis

What is the effectiveness of hyperbaric oxygen for the prevention and treatment of osteoradionecrosis?

Out of Hours Service (type and location)

During 2004 and 2005 ARIF has been approached twice on the effectiveness of different ways of delivering out-of-hours primary care. The most recent request considered the particular merits of co-location with a hospital accident and emergency department.

Outcome

Is there any systematically reviewed evidence on the valdity, reliability and responsiveness of clinical measurement tools for monitoring outcomes of hand surgery? Does the evidence from these reviews show how the Disabilities of Arm, Shoulder and Hand (DASH) questionnaire compares with other questionnaires for monitoring outcomes of hand surgery?

Outcomes Measurement Tools

What validated tools are there to help assess the general functioning of in-patients with mental illness, to follow progress while inpatients and compare discharge with admission state?

Out-patients - any Clinical Speciality

What is the effectiveness of telephone as opposed to face-to-face follow-up of out-patients, particularly with regard to reduction of workload and patient experience?

Out-patient Treatment

How does the effectiveness of in-patient treatment compare to (intensive) out-patient treatment for patients with severe or moderate anorexia nervosa, and what type of out-patient treatment is most effective?

Ovarian Cancer

What is the evidence base of the proposals made for the West Midlands Familial Cancer Initiative, particularly those concerning screening of individuals with a positive family history of ovarian cancer?

"Over-the-Counter" Remedies

What treatments have been shown to be effective in the treatment of the common cold?

Overweight - Children

What is the effectiveness of the MEND programme in treating overweight children?

Oximeters

What is the evidence to advocate the use of spirometry and oximeters to improve and manage symptoms of patients with chronic obstructive pulmonary disease (COPD) who are treated in primary care?

Ozone Solution

Are there any reviews of evidence on the effects/effectiveness of ozone solution for treatment of methicillin-resistant staphyloccus aureus (MRSA)?

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Pain
What is the effectiveness of residential pain management programmes (PMPs) for patients with severe chronic pain that has not responded to other therapies?

Pain
What is the effectiveness of PENS in reducing back and breast pain?

Pain
What is the clinical effectiveness and cost-effectiveness of arthroscopic treatment for young people (of working age) with hip impingement (femoro-acetabular impingement) and/or hip pain and what group(s) of patients may be expected to be benefit from it?

Pain (Chronic)
What is the effectiveness of laser acupuncture in patients with chronic pain, relative to other forms of pain relief?

Pain Management
What interventions are effective for the treatment of pain associated with Post-Polio Syndrome?

Palivizumab
What is the evidence of effectiveness of palivizumab in preventing respiratory syncytial virus infection in infants?

Palladium-103
What is the effectiveness of low dose rate brachytherapy using inserted iodine or palladium isotopes compared to other common methods of treatment such as radical prostatectomy or external beam radiotherapy (EBRT)?

Pallidotomy
What are the effects of: (a) thermocoagulation (pallidotomy) (b) deep brain stimulation in the treatment of movement disorders, especially Parkinson's Disease?

PANDAS
What is the effectiveness of intravenous immunoglobulin (IVIG) in the treatment of neurological movement disorders of probable autoimmune origin following infection, given the presence of antibasal ganglia antibodies (ABGAs)?

Pandemic Influenza
Does Oseltamivir reduce mortality in an influenza pandemic situation?

Parent Education Programmes
The effect of parent education programmes on the behaviour and mental health of children with conduct disorders and their parents.

Parkinson's Disease
What are the effects of: (a) thermocoagulation (pallidotomy) (b) deep brain stimulation in the treatment of movement disorders, especially Parkinson's Disease?

Parkinson's Disease

What is the effectiveness and cost-effectiveness of bilateral subthalamic stimulation in patients with Parkinson's disease, compared to standard medical treatment or no treatment in patients who have failed medical management?

Parkinson's Disease

How effective is conductive education in the rehabilitation of patients with Parkinson's disease?

Partner Notification

ARIF were asked to search and appraise systematic reviews on the effectiveness of different methods of partner notification in people with sexually transmitted infections (STIs) who present either to primary care or to more specialist service providers such as genitourinary medicine (GUM) clinics.

Pathological Myopia

Is photodynamic therapy an effective treatment for pathological myopia?

PCTA (Angioplasty)

Advice on research on the effects/effectiveness of abciximab (intravenous glycoprotein llb/iiia receptor (GPllb/iiia) inhibitor)

Peer Education

What is the effectiveness of peer education interventions aimed at influencing sexual risk-taking behaviour in men who have sex with men?

Peer Led Programmes

Do peer support programmes in school-aged children impact on a range of health and social behaviours, such as smoking, drug taking, safe sex, bullying, educational achievement and criminality?

Peer Support Programmes

Do peer support programmes in school-aged children impact on a range of health and social behaviours, such as smoking, drug taking, safe sex, bullying, educational achievement and criminality?

Pegvisomant

In 2007 the West Midlands Health Technology Assessment Collaboration (WMHTAC) completed a systematic review that assessed the clinical and cost effectiveness of Pegvisomant (PEG) for use in patients with acromegaly. ARIF were asked to determine if any new research had been published since the completion of the WMHTAC review and whether this alters any conclusions of the report.

Pegvisomant

What is the effectiveness of pegvisomant (Somavert) in the treatment of patients with acromegaly whose disease is not controlled by surgery and subsequent medical therapy?

Pelvic Inflammatory Disease

What is the evidence on effectiveness of antibiotic regimes in the treatment of pelvic inflammatory disease (PID)?

Peptic Ulcer

What is the evidence that esomeprazole is more effective and cost-effective than omeprazole or lansoprazole for peptic ulcer disease in adults?

Percuatneous Coronary Intervention (PCI)

ARIF were asked to look at the evidence base to assess the effectiveness and safety for the combination of antiplatelet therapy (aspirin and clopidogrel) plus warfarin (an anticoagulant) in patients receiving a stent for coronary disease, particularly in relation to how patients are monitored.

Percutaneous Electrical Stimulation (PENS)

What is the effectiveness of PENS in reducing back and breast pain?

Perinatal Mortality Rates (PMR)

Suggest an approach to devise an evidence based strategy to reduce high rates of perinatal and infant mortality. The main role of ARIF in this request was to assist and facilitate a worker from the commissioning authority in question, identify interventions which had been demonstrated to have an effect on perinatal and infant mortality.

Peripheral Vascular Disease
Is chelation therapy effective for the treatment of peripheral vascular disease?

Peri-Urethral Injection
What is the cost effectiveness of peri-urethral collagen injections in the treatment of stress incontinence? Are there short or long term complications that need to be considered?

Persistent Severe Depression
Aim - to identify the efficacy of vagal nerve stimulation for treatment of severe depression and enduring depression.

Personality Disorder
What is known about the effectiveness of treating people with severe personality disorders in therapeutic communities?

PET (Positron Emission Tomography) Scanning
What are the current and future prospects of the use of Positron Emission Tomography (PET) in oncology?

PET-CT Scanner
What is the accuracy, effectiveness and cost-effectiveness of the combined PET-CT scanner?

Phenylketonuria (PKU)
To critically appraise the review by Waisbren SE et al to determine whether the level of phenylalanine (PHe) in the blood is a reliable measure of neurotoxicity in patients with phenylketonuria (PKU)

Phenylketonuria
An opinion on the evidence base (reporting of trials and peer reviewed publications) with regard to the use of sapropterin dihydrochloride in phenylketonuria.

Phosphate Binders (Calcium Carbonate, Calcium Acetate, Sevelamer, Lanthanum)
Is there a reduction in cardiovascular mortality, morbidity and risk in patients with kidney failure and hyperphosphataemia taking non-metal containing phosphate binders (sevelamer and lanthanum) compared to patients taking calcium-containing phosphate binders (calcium acetate and calcium carbonate)?

Photodynamic Therapy
Is photodynamic therapy an effective treatment for wet age-related macular degeneration with predominantly classic CNV?

Photodynamic Therapy
Is photodynamic therapy an effective treatment for wet age-related macular degeneration with occult CNV?

Photodynamic Therapy
What is the effectiveness of photodynamic therapy for idiopathic sub-foveal choroidal neovascularisation?

Photodynamic Therapy
Is photodynamic therapy an effective treatment for pathological myopia?

Photokinetic Vaporisation of the Prostate (PKVP)
What is the effectiveness and cost-effectiveness of Gyrus PKVP versus standard therapy, unipolar TURP, for benign prostatic hypertrophy?

Photopheresis
ARIF were asked to evaluate the effectiveness and safety of Extracorporeal Photochemotherapy (ECP) in children who have steroid refractory chronic graft-versus-host disease (cGVHD)

Photoselective Vaporisation of the Prostate (PVP)
What is the effectiveness of PVP using the green-light (KTP) laser?

Physical Activity
What is the evidence that increased physical activity improves depression in adults?

Physical Activity
What is the effectiveness and cost-effectiveness of providing financial incentive schemes to motivate increasing levels of physical activity?

Physical Activity
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to increasing physical activity?

Physical Health
Does mental health well-being (as opposed to mental illness) affect physical health?

Physical Prophylaxis
How effective are foot pumps and other physical devices for preventing thromboembolism following elective hip and knee surgery?

Physiotherapy
What is the effectiveness of interventions provided by physiotherapists in the treatment of the symptoms of mental illness?

Pioglitazone
Is there evidence that pioglitazone (a glitazone) is a more effective second line therapy than newer drugs e.g. Incretin enhancers (DPP-4 inhibitors) and Incretin mimics (GLP-1 analogues) in controlling HbA1c in adults with type 2 diabetes?

Pneumococcal Vaccination
ARIF were asked if vaccinations for influenza and pneumococcal disease improve survival for patients with cancer who have had systemic therapy (chemotherapy, hormonal therapy or radiotherapy).

Population Registers
What is the evidence that population registers for diabetes at a district level are effective in improving patient care and disease outcomes?

Port Wine Stains
What is the evidence on the use of pulsed dye lasers to relieve the psychological effects of port wine stains in children and adults?

Port Wine Stain
What is the effectiveness of laser therapy for port wine stains?

Port Wine Stain
What is the effectiveness of laser therapy for port wine stains and other subcutaneous vascular disorders (haemangioma and arterio-venous malformations)?

Positron Emission Tomography
What are the current and future prospects of the use of Positron Emission Tomography (PET) in oncology?

Post-natal Depression
What is the evidence that increased physical activity improves depression in adults?

Post-natal Depression
Can postnatal depression be prevented?

Post-chemotherapy Fatigue
ARIF has received many requests concerning the effectiveness of provocation-neutralisation therapy.

Post-Polio Syndrome
What interventions are effective for the treatment of pain associated with Post-Polio Syndrome?

Post Traumatic Stress Disorder
What is the effectiveness of EMDR in the management of post traumatic stress disorder (PTSD) arising from sexual abuse?

Post Traumatic Stress Disorder
What is the effectiveness of the Human Givens approach applied to mental health care?

Potassium-titanyl-phosphate (KTP) Laser
What is the effectiveness of PVP using the green-light (KTP) laser?

Pregnancy
What is the evidence for a) the effectiveness of incentives for smoking cessation in pregnancy and b) the use of SMS texting for motivational purposes; to support a smoking cessation programme?

Pregnancy
The National Institute for Health and Clinical Effectiveness (NICE) as part of the wider programme of work on smoking and the NHS in England and Wales, commissioned a report from ARIF and the West Midlands Health Technology Assessment Collaboration, to identify the best evidence on the clinical and cost-effectiveness of NRT

Pre-Operative Smoking Cessation
What is the effectiveness of pre-operative smoking cessation interventions?

Prescribing
Interventions to improve prescribing practice of antibiotics in primary care and ambulatory/community settings with the aim of reducing inappropriate prescribing.

Prescribing Budgets
What is the effectiveness of manoeuvres to manage prescribing budgets in PCTs?

Pre-surgical Assessment
What is the usefulness of electrodiagnostic techniques as a prognostic tool in pre-surgical assessment of patients with carpal tunnel syndrome?

Prevention
Can depression be prevented in children and adolescents?

Prevention
Can eating disorders be prevented?

Prevention
Can mental illness be prevented?

Prevention
Can postnatal depression be prevented?

Prevention of Depression in Adults
Can depression be prevented in adults?

Prevention and Treatment of Thromboembolic Disease
What is known about the relative effectiveness and cost-effectiveness of different LMWH products in the prevention of deep venous thrombosis in orthopaedics; the management of unstable angina; and the treatment of existing thromboembolic disease?

Prevention of Glue Ear
What interventions are effective for the prevention of glue ear (otitis media with effusion)

Prevention of Influenza
Is there any evidence that annual vaccination of health care workers against influenza has health benefits for individuals, patients or organisations?

Primary Care
What is the evidence for the safety and effectiveness of a nurse triage service within the primary care setting?

Primary Care
During 2004 and 2005 ARIF has been approached twice on the effectiveness of different ways of delivering out-of-hours primary care. The most recent request considered the particular merits of co-location with a hospital accident and emergency department.

Primary Care
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to reducing alcohol consumption?

Primary Care
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to diet?

Primary Care
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to increasing physical activity?

Primary Care
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to the prevention of falls amongst older people?

Primary Care
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to advice on delaying the time of first intercourse?

Primary Care
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to the prevention/reduction of illicit drug use amongst young people?

Primary Care
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to safe sex?

Primary Care
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to smoking cessation?

Probiotics
Are probiotics, particularly Saccharomyces boulardii, effective in reducing antibiotic associated diarrhoea?

pro-Brain Natriuretic Peptide
What is the accuracy of pro-Brain Natriuretic Peptide (proBNP) in the diagnosis of heart failure?

Professions Complimentary to Dentistry
What is the effectiveness and cost-effectiveness of providing dental care by people from professions complimentary to dentistry (PCD's)?

Prophylactic versus Intermittent FVIII
What are the effects/effectiveness of continuous versus intermittent FVIII in treatment of Haemophilia A - including the effect of different prophylactic dosage regimes?

Prostatism

What is the effectiveness and cost-effectiveness of Gyrus PKVP versus standard therapy, unipolar TURP, for benign prostatic hypertrophy?

Prostatism

What is the effectiveness of PVP using the green-light (KTP) laser?

Prostate Specific Antigen (PSA) to Detect Prostate Cancer

What are the effects/effectiveness of PSA testing to detect prostate cancer in those with "prostatic symptoms"?

Prostatism (symptoms referable to the prostate)

What are the effects/effectiveness of PSA testing to detect prostate cancer in those with "prostatic symptoms"?

Protein C (Recombinant Human Activated)

What is the effectiveness of drotrecogin alfa (activated) in the treatment of patients with severe sepsis?

Provocation-neutralisation Technique

ARIF has received many requests concerning the effectiveness of provocation-neutralisation therapy.

Psychiatric Disorders

What is the evidence on the effectiveness/cost-effectiveness of day hospitals in the treatment of people with mental illness in comparison with other NHS or social services models of provision?

Psychological and Physical Health Impact

What is the health impact of housing clearances, and in particular the psychological and physical health impact on those people who have been rehoused following housing clearance?

Psychological Interventions combined with Drug Therapy

Is there any research evidence on the effects/effectiveness of combined psychological and conventional medical care (pharmacotherapy) to improve outcomes in severe mental illness?

PTCA (Angioplasty)

Advice on research on the effects/effectiveness of abciximab (intravenous glycoprotein IIb/IIIa receptor (GPIIb/IIIa) inhibitor). ARIF was asked to appraise available research on the above new drug.

Pulmonary Embolism (PE)

In the diagnosis of deep venous thrombosis and pulmonary embolism, what is the effectiveness and cost effectiveness of undertaking serum D-Dimer tests and, based on the result, progressing to ultrasound or V/Q scan for the final diagnosis.

Pulmonary Arterial Hypertension

Critical Appraisal of "Goal-oriented treatment and combination therapy for pulmonary arterial hypertension" Hoeper MM et al. - in relation to assessment of study design and interpretation of the results particularly regarding the effectiveness of dual therapy relative to monotherapy.

Pulmonary Hypertension

What is the effectiveness of bosentan for the treatment of pulmonary hypertension?

Pulmonary Rehabilitation (Respiratory Rehabilitation)

What is the evidence for respiratory rehabilitation for those with chronic obstructive pulmonary/airways disease?

Pulse Dye Laser Treatment

What is the evidence on the use of pulsed dye lasers to relieve the psychological effects of port wine stains in children and adults?

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'Quit and Win'
What is the clinical and cost-effectiveness of providing incentives to motivate smokers to quit?

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Requests for Information Completed - R

Radical Prostatectomy

Evidence on the effectiveness of brachytherapy uses comparisons with existing standard treatments like EBRT and radical prostatectomy. Following on from this, what is the evidence for the effectiveness of these standard treatments themselves?

Radiofrequency Ablation

Is there data to support the use of Radiofrequency Ablation of the kidney, liver and lung as an alternative to surgical resection?

Ranibizumab

What is the quantity and quality of the evidence regarding ranibizumab (Lucentis) and bevacizumab (Avastin) in the treatment of eye conditions (excluding age-related macular degeneration), thought to be related to vascular endothelial growth factor?

Recombinant Factor VIII (rFVIII)

What the effects/effectiveness of rFVIII in individuals with Haemophilia A, relative to existing plasma derived FVIII (pdFVIII) preparations?

Recombinant Tissue Plasminogen Activator (rt-PA)

What is known about the effects and effectiveness of tissue plasminogen activator (rt-PA) for acute ischaemic stroke?

Referral

Which clinical measurement tools that measure referral threshold for hip replacement are evidence based and of these, which are the best?

Referral

Which clinical measurement tools that measure referral threshold for hysterectomy are evidence based and of these, which are the best?

Referral

Which clinical measurement tools that measure referral threshold for knee replacement are evidence based and of these, which are the best?

Referral

Which clinical measurement tools that measure referral threshold for meniscectomy are evidence based and of these, which are the best?

Rehabilitation

How effective is conductive education in the rehabilitation of patients with Parkinson's disease?

Rehousing

What is the health impact of housing clearances, and in particular the psychological and physical health impact on those people who have been rehoused following housing clearance?

Relapsed Non-Hodgkin's Lymphoma

What is known about the effectiveness of monoclonal antibody therapy for the treatment of patients with relapsed lymphoma? What is the evidence for the effectiveness of this treatment compared to standard chemotherapy?

Renal Artery Stenosis
Is stenting for renal artery stenosis an effective procedure especially in terms of life years gained and how many patients are likely to be suitable?

Renal Failure
Are there any recognised criteria for the use of automated peritoneal dialysis and is it a cost-effective form of treatment for end stage renal failure?

Reproductive Function, Preservation
What is the impact of childhood cancer treatment on women of reproductive age and what possible strategies would address their needs (with specific reference to reproductive function)?

Residential Pain Management
What is the effectiveness of residential pain management programmes (PMPs) for patients with severe chronic pain that has not responded to other therapies?

Resource Allocation
What is the effectiveness of manoeuvres to manage prescribing budgets in PCTs?

Respiratory Infections
What is the evidence on the effectiveness of interventions to prevent or reduce transmission of gastrointestinal and respiratory infections in schools in young children?

Respiratory Syncytial Virus
What is the evidence of effectiveness of palivizumab in preventing respiratory syncytial virus infection in infants?

Restorative Justice
What is the effectiveness of face-to-face restorative justice on repeat offending and victim satisfaction?

Revision Total Hip Arthroplasty
What is the strength of evidence in favour of this technique over existing total hip revision in terms of quality and cost effectiveness? Is there any information whether these should be carried out at tertiary centres? Is there a minimal level of activity/experience of operator needed to ensure good quality surgery?

Ribavirin
What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Risk Stratification
Is there any evidence on the role of risk stratification, and in particular by exercise tests, for cardiac rehabilitation?

Ritalin
What is the benefit of continuing treatment with Ritalin in adulthood for patients who have been treated with Ritalin (as children) for ADHD?

Rituximab
What is known about the effectiveness of monoclonal antibody therapy for the treatment of patients with relapsed lymphoma? What is the evidence for the effectiveness of this treatment compared to standard chemotherapy?

Rituximab
What is the effectiveness of rituximab for SLE?

Road Accidents
What is the effectiveness of traffic calming schemes in reducing road accidents?

Routine Health Checks - Primary Care
What is the effectiveness of regular health checks in the primary care setting for people with learning

disability?

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Safe Sex
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to safe sex?

Sapropterin dihydrochloride
An opinion on the evidence base (reporting of trials and peer reviewed publications) with regard to the use of sapropterin dihydrochloride in phenylketonuria.

Schizophrenia
Request from GRIP Committee to assist in the development of a GRIPKIT advising on evidence based purchasing of services for care of patients suffering schizophrenia.

School Age Children
School health services generally focus on physical health. Is there any evidence to support a different model encompassing social and mental health and development?

School Aged-Children
What is the effectiveness of theatre/drama aimed at young people (12-18 year olds) as an intervention to improve alcohol awareness/ability to make safe, sensible choices?

School Aged-Children
Do peer support programmes in school-aged children impact on a range of health and social behaviours, such as smoking, drug taking, safe sex, bullying, educational achievement and criminality?

School Children
What is the evidence on the effectiveness of interventions to prevent or reduce transmission of gastrointestinal and respiratory infections in schools in young children?

School Health Services
School health services generally focus on physical health. Is there any evidence to support a different model encompassing social and mental health and development?

Screening
What is the most effective and cost-effective way of screening for Down's syndrome in older women (>35 years).

Screening by Colonoscopy in those with Family History
What is the evidence base of the proposals made for the West Midlands Familial Cancer Initiative, particularly those concerning screening of individuals with a positive family history of colorectal cancer?

Screening in those with Family History
What is the evidence base of the proposals made for the West Midlands Familial Cancer Initiative, particularly those concerning screening of individuals with a positive family history of ovarian cancer?

Screening in those with Family History
What is the evidence base of the proposals made for the West Midlands Familial Cancer Initiative, particularly those concerning screening of individuals with a positive family history of breast cancer?

Screening Programme

What are the effects/effectiveness of alternative arrangements for the screening (or early diagnosis) of diabetic retinopathy?

Screening Tests

Is there evidence indicating the best diagnostic tool for identifying mild cognitive impairment in patients presenting with subjective cognitive impairment?

Screening Tools (WILSTAAR, CHAT)

Community Trusts are seeking an effective screening tool for communication disorder in children as part of the pre-school child health surveillance programme. The local Trust was particularly interested in WILSTAAR and CHAT. Are these tools effective?

Sensory Integration Therapy

What is the evidence on the effectiveness of sensory integrated therapy provided by occupational therapists to children with autism? In particular, is there any evidence for the most effective number of sessions or length of treatment?

Sepsis (Severe)

What is the effectiveness of drotrecogin alfa (activated) in the treatment of patients with severe sepsis?

Service Delivery

Is there any evidence to support the effectiveness of a central multidisciplinary team designated to directly meet the needs of people with multiple sclerosis throughout the country?

Sevelamer

What is the effectiveness of sevelamer (Renagel®) for the treatment of hyperphosphataemia in patients on haemodialysis?

Sevelamer

Is there a reduction in cardiovascular mortality, morbidity and risk in patients with kidney failure and hyperphosphataemia taking non-metal containing phosphate binders (sevelamer and lanthanum) compared to patients taking calcium-containing phosphate binders (calcium acetate and calcium carbonate)?

Severe Heart Failure

What is the effectiveness of biventricular pacing in patients with severe heart failure who have not responded to other treatment?

Severe Mental Illness

Is there any research evidence on the effects/effectiveness of combined psychological and conventional medical care (pharmacotherapy) to improve outcomes in severe mental illness?

Sexual Behaviour

What is the effectiveness of interventions designed to change sexual behaviour in preventing subsequent recurrent or new sexually transmitted infections?

Sexually Transmitted Diseases (STDs)

ARIF were asked to search and appraise systematic reviews on the effectiveness of different methods of partner notification in people with sexually transmitted infections (STIs) who present either to primary care or to more specialist service providers such as genitourinary medicine (GUM) clinics.

Sexually Transmitted Infections

What is the effectiveness of interventions designed to change sexual behaviour in preventing subsequent recurrent or new sexually transmitted infections?

Sexually Transmitted Infections (STIs)

ARIF were asked to search and appraise systematic reviews on the effectiveness of different methods of partner notification in people with sexually transmitted infections (STIs) who present either to primary care or to more specialist service providers such as genitourinary medicine (GUM) clinics.

Sildenafil

Critical Appraisal of "Goal-oriented treatment and combination therapy for pulmonary arterial hypertension" Hoeper MM et al. - in relation to assessment of study design and interpretation of the results particularly regarding the effectiveness of dual therapy relative to monotherapy.

Skin Cancer
To compare the clinical effectiveness of isolated limb perfusion in the treatment of melanoma.

Skin Cancers
What are the health effects of sunbeds, sunlamps, sun tanning equipment and solaria?

Sleep Apnoea
What are the effects/effectiveness of surgery for the treatment of obstructive sleep apnoea/hypoapnoea (OSA)?

Sleep Apnoea
What is the effectiveness of continuous positive airways pressure for obstructive sleep apnoea?

Smokers
What is the clinical and cost-effectiveness of providing incentives to motivate smokers to quit?

Smoking
What is the effectiveness of pre-operative smoking cessation interventions?

Smoking Cessation
What is the clinical and cost-effectiveness of providing incentives to motivate smokers to quit?

Smoking Cessation
What is the evidence for a) the effectiveness of incentives for smoking cessation in pregnancy and b) the use of SMS texting for motivational purposes; to support a smoking cessation programme?

Smoking Cessation
What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to smoking cessation?

Smoking Cessation (pre-operative)
What is the effectiveness of pre-operative smoking cessation interventions?

Social Behaviours
Do peer support programmes in school-aged children impact on a range of health and social behaviours, such as smoking, drug taking, safe sex, bullying, educational achievement and criminality?

Sorafenib
What is the effectiveness of sorafenib for metastatic renal cell cancer?

South Asian Communities
To gain an understanding of the current knowledge base regarding chest pain presentations to both primary and secondary care services.

Spasticity - Any Cause
In 2003 ARIF investigated the role of intrathecal baclofen in the treatment of spasticity for any cause and spasticity due to cerebral palsy in children. We were asked to update this request in 2006.

Spasticity
What is the effectiveness of intrathecal baclofen for treating patients with severe spasticity/mobility problems?

Spasticity of Cerebral Origin
What is the effectiveness of intrathecal baclofen for treating children with severe spasticity / mobility problems caused by cerebralpalsy?

Special Educational Needs

What evidence is there that speech therapy for children of school age who have special education needs is effective?

Specialist Epilepsy Clinics

Do specialist epilepsy clinics offer advantages over general neurology clinics?

Speech and Language Therapy

Community Trusts are seeking an effective screening tool for communication disorder in children as part of the pre-school child health surveillance programme. The local Trust was particularly interested in WILSTAAR and CHAT. Are these tools effective?

Speech Therapy

What evidence is there that speech therapy for children of school age who have special education needs is effective?

Sperm Washing

What is the evidence of effectiveness of sperm washing in reducing the risk of HIV transmission in couples where the man is HIV+ve and the woman HIV-ve?

Spinal Cord Stimulation

What is the evidence on the effectiveness of spinal cord stimulation in the management of chronic pain?

Spinal Cord Stimulation

What is the effectiveness of spinal cord stimulation for chronic neuropathic pain, particularly in "failed" back surgery syndrome and complex regional pain syndrome?

Spirometry

What is the evidence to advocate the use of spirometry and oximeters to improve and manage symptoms of patients with chronic obstructive pulmonary disease (COPD) who are treated in primary care?

Spirometry

What is the effectiveness of spirometry and screening for chronic obstructive pulmonary disease (COPD) in primary versus secondary care?

Stapling Haemorrhoidectomy

What is the effectiveness of the stapling technique versus conventional surgery for grade III haemorrhoids not suitable for non-resective surgery?

Statins

What is the clinical and cost-effectiveness of early aggressive lipid lowering therapy using very high dose statins (80mg/day) for patients with acute coronary syndrome, patients with crescendo angina, and patients undergoing revascularisation?

Steam Inhalation

What treatments have been shown to be effective in the treatment of the common cold?

Stem Cell Transplant

What is the effectiveness of autologous stem cell transplantation for systemic sclerosis?

Stents

ARIF were asked to look at the evidence base to assess the effectiveness and safety for the combination of antiplatelet therapy (aspirin and clopidogrel) plus warfarin (an anticoagulant) in patients receiving a stent for coronary disease, particularly in relation to how patients are monitored.

Stents with Percutaneous Transluminal Renal Artery Angioplasty (PTRA)

Is stenting for renal artery stenosis an effective procedure especially in terms of life years gained and how many patients are likely to be suitable?

Sterilisation Reversal - Female

What is the evidence for the effectiveness of female sterilization reversal?

Sterilisation Reversal - Male
Is vasectomy reversal of proven effectiveness with regard to patency and fertility?

Steroids - Glue Ear
What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Steroids - Severe Bronchiolitis
What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Strategies to Improve Uptake of Cancer Screening
Is there firm outcome evidence to support strategies and campaigns to improve uptake of the 3 UK cancer screening programmes (breast, cervical, bowel), and if so what is the cost to save an additional life based on this evidence?

Street Lighting
What is the effectiveness of improved street lighting on reduction in crime?

Stroke
Request from GRIP committee to assist in the development of a GRIPKIT advising on evidence based purchasing of services for care of patients suffering stroke.

Sub-foveal Predominantly Classic Choroidal Neovascularisation (CNV)
Is photodynamic therapy an effective treatment for wet age-related macular degeneration with predominantly classic CNV?

Sub-foveal Occult Choroidal Neovascularisation (CNV)
Is photodynamic therapy an effective treatment for wet age-related macular degeneration with occult CNV?

Subjective Cognitive Impairment
Is there evidence indicating the best diagnostic tool for identifying mild cognitive impairment in patients presenting with subjective cognitive impairment?

Sudden Infant Death Syndrome
What is the evidence underpinning guidance on the prevention of sudden infant death syndrome?

Sunbeds
What are the health effects of sunbeds, sunlamps, sun tanning equipment and solaria?

Surgery
To assess the clinical and cost-effectiveness of surgical inguinal hernia repair versus watchful waiting in asymptomatic or minimally symptomatic men.

Surgery
What are the effects/effectiveness of surgery for the treatment of obstructive sleep apnoea/hypoapnoea (OSA)?

Surgery
What is the effectiveness of surgery for CEAP Class 2 varicose veins with significant symptoms?

Surgery
What is the effectiveness and cost-effectiveness of bilateral subthalamic stimulation in patients with Parkinson's disease, compared to standard medical treatment or no treatment in patients who have failed medical management?

Surgery - Repair and Augmented Repair
What are the effects and effectiveness of surgical repair of acute tears of the anterior cruciate ligament (particular emphasis on incomplete tears where there is little instability of the knee)?

Survivors of Childhood Cancer

What is the impact of childhood cancer treatment on women of reproductive age and what possible strategies would address their needs (with specific reference to reproductive function)?

Sydenham's Chorea

What is the effectiveness of intravenous immunoglobulin (IVIG) in the treatment of neurological movement disorders of probable autoimmune origin following infection, given the presence of antibasal ganglia antibodies (ABGAs)?

Sympathectomy

What is the effectiveness of sympathectomy for facial blushing?

Systemic Lupus Erythematosus (SLE)

What is the effectiveness of rituximab for SLE?

Systemic Sclerosis

What is the effectiveness of autologous stem cell transplantation for systemic sclerosis?

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Requests for Information Completed - T

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Targeted Training Therapy

ARIF was asked to assess the effectiveness of targeted training therapy in the treatment of patients with Cerebral Palsy

Teaching Critical Appraisal

What is the effectiveness of teaching critical appraisal to health care professionals and consumers on health care practice and the use of facilities and interventions?

Teaching Hospitals

What are the effects of teaching hospital status on patient outcomes? In particular, is there any research looking at the effect of any given hospital changing from a non-teaching hospital to a teaching hospital?

Teenage Pregnancy

What is the effectiveness of mentoring programmes in reducing teenage pregnancy amongst vulnerable groups?

Telemedicine (Video-links)

What is the evidence that telemedicine is useful in improving quality of care and in what circumstances is it useful?

Telepathology

What evidence is there on the effectiveness of telepathology?

Telephone Follow-Up

What is the effectiveness of telephone as opposed to face-to-face follow-up of out-patients, particularly with regard to reduction of workload and patient experience?

Temozolomide

What is the effectiveness of temozolomide in addition to surgery and radiotherapy for newly diagnosed glioblastoma multiforme?

Tempero-mandibular Joint Replacements

What is the effectiveness of Tempero-mandibular Joint (TMJ) replacements (eg Christiensen joint replacement system) in conditions causing severe degeneration and scarring (fibrosis)?

Tension Free Vaginal Tape (TVT)

What is the effectiveness and cost effectiveness of tension free vaginal tape compared to standard vaginal hysterectomy or colposuspension for female urinary incontinence?

Testosterone Replacement Therapy

Is there any evidence as to the effects of testosterone supplementation in middle aged males suffering "andropausal symptoms?"

Text Messaging

What is the evidence for a) the effectiveness of incentives for smoking cessation in pregnancy and b) the use of SMS texting for motivational purposes; to support a smoking cessation programme?

Theatre/Drama Techniques

What is the effectiveness of theatre/drama aimed at young people (12-18 year olds) as an intervention to improve alcohol awareness/ability to make safe, sensible choices?

Therapeutic Communities

What is known about the effectiveness of treating people with severe personality disorders in therapeutic communities?

Tonsillectomy

Evidence for the effectiveness of tonsillectomy for chronic tonsillitis and chronic pharyngitis in children and adults.

Topical Negative Pressure Vacuum Assisted Wound Closure Therapy

What is the clinical and cost-effectiveness of vacuum assisted wound closure (VAC) therapy for wound management?

Total Hip Replacement

Metal-to-metal hip resurfacing has been suggested as an alternative to performing a standard total hip replacement in selected cases, usually in younger patients. The procedure is intended to prevent future need for revisions. What is the evidence for the effectiveness and safety of this procedure?

Traffic Calming

What is the effectiveness of traffic calming schemes in reducing road accidents?

Trastuzumab

Evidence on effectiveness of herceptin in small size tumours (equal to or less than 0.5cm) and lymphovascular invasion HER-2 positive early-stage breast cancer.

Trastuzamab

What is the quality of two recently published articles reporting the results of three randomised controlled trials assessing the effectiveness of trastuzumab (Herceptin) in the treatment of HER2-positive, early-stage breast cancer?

Trauma Centres

Is there any review evidence relating to the most effective delivery of care to patients who have suffered severe trauma?

Treatment of Thromboembolic Disease

What is the effectiveness and cost-effectiveness of LMWH relative to other interventions for the treatment of existing thromboembolic disease?

Treatment of Thromboemcolic Disease

What is known about the relative effectiveness and cost-effectiveness of different LMWH products in the prevention of deep vein thrombosis in orthopaedics; the management of unstable angina; and the treatment of existing thromboembolic disease?

Triage

Is there any evidence on the effectiveness of general practitioners (GPs) in accident and emergency (A&E) units and are there any additional benefits compared to if he or she was not present on outcomes such as admission rates?

Triple Test

What is the most effective and cost-effective way of screening for Down's syndrome in older women (>35 years).

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Requests for Information Completed - U

UK Health Visitors
Assessment of the effectiveness of health visitor activities in the NHS

Ulcers (Diabetic/Pressure)
What is the clinical and cost-effectiveness of vacuum assisted wound closure (VAC) therapy for wound management?

Unstable Angina
How effective and cost-effective is LMWH relative to other treatments, particularly unfractionated heparin, in the management of unstable angina?

Unstable Angina
What is the clinical and cost-effectiveness of early aggressive lipid lowering therapy using very high dose statins (80mg/day) for patients with acute coronary syndrome, patients with crescendo angina, and patients undergoing revascularisation?

Unwanted Hair
What is the effectiveness of laser therapy for unwanted hair?

Uterine Artery Embolisation
What is the effectiveness and cost-effectiveness of uterine artery embolisation for uterine fibroids?

Uterine Fibroids
What is the effectiveness and cost-effectiveness of uterine artery embolisation for uterine fibroids?

Uterine Thermal Balloon Ablation
What research exists on uterine thermal balloon therapy for women with menorrhagia?

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Vaccination
What are the effects/effectiveness of different policies on the use of influenza vaccination?

Vaccination of Health Care Workers
Is there any evidence that annual vaccination of health care workers against influenza has health benefits for individuals, patients or organisations?

Vaccuum Assisted Wound Closure
What is the clinical and cost-effectiveness of vacuum assisted wound closure (VAC) therapy for wound management?

Vagal Nerve Stimulation
How effective is vagal nerve stimulation for intractable epilepsy?

Vagal Nerve Stimulation
Aim - to identify the efficacy of vagal nerve stimulation for treatment of severe depression and enduring depression.

Varicose Veins
What is the effectiveness of surgery for CEAP Class 2 varicose veins with significant symptoms?

Various Cancers
What is the accuracy, effectiveness and cost-effectiveness of the combined PET-CT scanner?

Vasectomy Reversal
Is vasectomy reversal of proven effectiveness with regard to patency and fertility?

Vascular Endothelial Growth Factor
What is the quantity and quality of the evidence regarding ranibizumab (Lucentis) and bevacizumab (Avastin) in the treatment of eye conditions (excluding age-related macular degeneration), thought to be related to vascular endothelial growth factor?

VEGF
What is the quantity and quality of the evidence regarding ranibizumab (Lucentis) and bevacizumab (Avastin) in the treatment of eye conditions (excluding age-related macular degeneration), thought to be related to vascular endothelial growth factor?

Venous Leg Ulcers
What is the effectiveness of Endovascular Laser Therapy (EVLT) on healing venous leg ulcers, compared to other treatments (such as other surgical procedures) or conservative management (such as bandaging)?

Ventilation - Non-Invasive
Evidence on clinical and cost-effectiveness of non-invasive ventilation in patients with neuromuscular and chest wall diseases.

Vertebral Balloon Kyphoplasty
What is the effectiveness and cost-effectiveness of balloon kyphoplasty for patients with vertebral compression fractures (as a result of osteoporosis, chronic steroid use or malignancy) who are

refractory to standard medical treatment?

Vertebral Compression Fracture

What is the effectiveness and cost-effectiveness of balloon kyphoplasty for patients with vertebral compression fractures (as a result of osteoporosis, chronic steroid use or malignancy) who are refractory to standard medical treatment?

Very Low Birthweight

What are the outcomes of VLBW infants?

Vitamin C

What treatments have been shown to be effective in the treatment of the common cold?

Vitamin K

What is the evidence for the effectiveness and safety of giving vitamin K to newborns to prevent Haemorrhagic Disease of the Newborn (HDNB), and what is the best means of administration?

Vulnerable Teenagers

What is the effectiveness of mentoring programmes in reducing teenage pregnancy amongst vulnerable groups?

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Requests for Information Completed - W

Waiting Lists

What is the availability of comparative research on the effects/effectiveness of alternative methods of dealing with patients waiting for operations and other procedures ("waiting lists")?

"Watch and Wait" Strategy

Evidence on the effectiveness of brachytherapy uses comparisons with existing standard treatments like EBRT and radical prostatectomy. Following on from this, what is the evidence for the effectiveness of these standard treatments themselves?

Warfarin

ARIF were asked to look at the evidence base to assess the effectiveness and safety for the combination of antiplatelet therapy (aspirin and clopidogrel) plus warfarin (an anticoagulant) in patients receiving a stent for coronary disease, particularly in relation to how patients are monitored.

Weight Loss

What is the effectiveness and cost-effectiveness of providing financial incentive schemes to motivate increasing levels of physical activity?

Weight Management - Children

What is the effectiveness of the MEND programme in treating overweight children?

Wounds

What is the clinical and cost-effectiveness of vacuum assisted wound closure (VAC) therapy for wound management?

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Young People

What is the evidence on the effectiveness of marketing/publicity/media campaigns aimed at reducing alcohol use amongst young people (aged 16-25 years)?

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Zinc

What treatments have been shown to be effective in the treatment of the common cold?

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ARIF Request

PCTA (Angioplasty)
Abciximab
Ischaemic Heart Disease

Table of Contents

The Problem Submitted For ARIF To Advise Upon

Advice on research on the effects/effectiveness of abciximab (intravenous glycoprotein IIb/IIIa receptor (GPIIb/IIIa) inhibitor). ARIF was asked to appraise available research on the above new drug.

Comments

This request was carried out more than four years ago and has not been updated since. The articles identified may no longer be the best available and therefore the commentary may be out of date. As a precaution the information has been removed from this page.

ARIF does not routinely update requests unless specifically asked. If you wish to have the request updated, please contact ARIF.

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ARIF Request

Endovascular Stents (EVAR)
Abdominal Aortic Aneurysm (infrarenal)

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness and cost-effectiveness of EVARs for infrarenal abdominal aortic aneurysms?

Specifically could ARIF appraise the evidence base of NICE Interventional Procedures Guidance (IPG) 163?

Comments

This request was carried out more than four years ago and has not been updated since. The articles identified may no longer be the best available and therefore the commentary may be out of date. As a precaution the information has been removed from this page.

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ARIF Request

Fenestrated Endovascular Repair Abdominal Aortic Aneurysm

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in July 2010.

The Problem Submitted for ARIF to Advise Upon:

What is the evidence of the effectiveness and cost-effectiveness of fenestrated endovascular aortic repair (f-EVAR) for the treatment of abdominal aortic aneurysm (AAA)?

See related request - Fenestrated Endovascular Stents (EVAR)

Reviews Identified

- Nordon IM, Hinchliffe RJ, Holt PJ, Loftus IM, Thompson MM. Modern treatment of juxtarenal abdominal aortic aneurysms with fenestrated endografting and open repair: a systematic review. European Journal of Vascular and Endovascular Surgery 2009;38(1):35-41
- Medical Advisory Secretariat. Fenestrated endovascular grafts for the repair of juxtarenal aortic aneurysms: an evidence-based analysis. Ontario Health Technology Assessment Series 2009;9(4)

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Comments

Two relevant systematic reviews were identified. Both assessed effectiveness of f-EVAR compared with open surgery repair (OSR) for patients with juxtarenal abdominal aortic aneurysms (JRA). Both were published in 2009.

One review (Nordon 2009) included eight studies on f-EVAR and 12 on OSR; both f-EVAR and OSR studies were mixed with prospective and retrospective case series studies. The other (MAS 2009) included one small non-randomised comparative study comparing f-EVAR with OSR, five case series on f-EVAR and seven case series on OSR, with all the f-EVAR studies being prospective and most of those on OSR being retrospective.

The reviews shared three f-EVAR studies and five OSR studies. In both the patients also included those who had JRAs, aortic ulcers, thoracoabdominal aortic aneurysms, suprarenal aortic aneurysms or thoracic aortic aneurysms.

In both reviews data for the f-EVAR studies and OSR studies were pooled and compared. Results from

the reviews suggested that for JRA patients f-EVAR was favourable compared with open surgery in terms of short-term mortality and duration of operation and hospital stay, but involved a higher rate of early secondary re-intervention. However, due to the lack of reliability of the primary studies and the methods employed in the reviews to analyse the findings of these studies, the results should be interpreted with caution.

There appear to be no reviews assessing the effectiveness of f-EVAR compared with standard EVAR or no treatment, and no evidence on the cost-effectiveness of f-EVAR for AAA.

Request Carried Out: July 2010

To see full report - click here

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ARIF Request

Fenestrated Endovascular Stents (EVAR) Abdominal Aortic Aneurysm

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of fenestrated endovascular stents in patients who have abdominal aneurysms. Has the evidence base changed since ARIF last undertook a search for this question?

This page replaces the previous page for the request on this subject in 2005.

See related requests - Endovascular Stents (EVAR)/Aneurysm/Abdominal Aortic Aneurysm, Endovascular Stents (EVAR)/Abdominal Aortic Aneurysm (infrarenal)

Reviews Identified

- Sun Z, Mwipatayi BP, Semmens JB, Lawrence-Brown MM. Short to midterm outcomes of fenestrated endovascular grafts in the treatment of abdominal aortic aneurysms: a systematic review. Journal of Endovascular Therapy 2006;13(6):747-53

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Comments

This was a reasonably well-conducted review which assessed short to midterm outcomes of patients with complicated abdominal aortic aneurysms that had been repaired using a fenestrated endovascular graft. Searches went from 1999 to 2006 and sought only English language studies, which may have introduced some publication bias. In total six studies were included. The primary studies identified by ARIF in 2005 had been incorporated into this review

All of the studies were case series, involving in total 317 who were mainly men with a mean age of 75 years. The most common fenestrated vessels were the renal artery (575 fenestrated), the superior mesenteric arteries (134 fenestrated) and celiac arteries (just 6 fenestrated). Follow-up ranged 0 to 48 months, with a greater than 12 month mean follow-up reported in four studies.

Overall, the review authors concluded that “fenestrated endovascular grafting provides an alternative technique to treat patients with complex aneurysm necks, achieving lower mortality than open repair under comparable conditions” however, “the techniques for fenestrated stent grafts are still in their infancy and the stability and patency of fenestrated vessels remains to be proven in long-term follow up”.

In conclusion short-term outcomes appear to be good, however, it is difficult to compare this technique with open repair or other options of care due to the non-comparative nature of the research evidence and also the inadequate description of the study populations particularly regarding co-morbidities and fitness for open repair.

Request Carried Out: March 2009

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ARIF Request

Endovascular Stents (EVAR)
Aneurysm
Abdominal Aortic Aneurysm

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the clinical and cost-effectiveness of endovascular aneurysm repair (EVAR) in the management of abdominal aortic aneurysms, with particular reference to higher risk patients deemed unfit for surgery?

Abdominal aortic aneurysms (AAA) are swellings of the main blood vessel in the abdomen. They cause problems because they are prone to leakage and even catastrophic rupture. The normal method of treatment is by a major operation ("open repair"), in which the aneurysm is opened and an artificial graft sewn in place to replace the weakened section of blood vessel. This is a serious procedure and surgery has a risk particularly in older, frail patients.

In endovascular stent-grafting (EVAR) the equivalent of the graft in the open repair is put in place by threading it through the main blood vessel in the leg, with the aim of obviating the need for major surgery.

See also related requests - Fenestrated Endovascular Stents (EVAR)/Abdominal Aortic Aneurysm, Endovascular Stents (EVAR)/Abdominal Aortic Aneurysm (infrarenal)

Reviews Identified

- Drury D, Michaels JA, Jones L, Ayiku L. Systematic review of recent evidence for the safety and efficacy of elective endovascular repair in the management of infrarenal abdominal aortic aneurysm. British Journal of Surgery 2005;92(8):937-46
- Wilt TJ, Lederle FA, MacDonald R, Jonk YC, Rector TS, Kane RL. Comparison of endovascular and open surgical repairs for abdominal aortic aneurysm. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ); 2006 http://www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-20060885/frame.html
- Lederle FA, Kane RL, MacDonald R, Wilt TJ. Systematic review: repair of unruptured abdominal aortic aneurysm. Annals of Internal Medicine 2007;146(10):735-41
- Lovegrove RE, Javid M, Magee TR, Galland RB. A meta-analysis of 21,178 patients undergoing open or endovascular repair of abdominal aortic aneurysm. British Journal of Surgery 2008;95:677-

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Randomised Controlled Trials

- Schermerhorn ML, O��Malley AJ, Jhaveri A, Cotterill P, Pomposelli F, Landon B. Endovascular vs. open repair of abdominal aortic aneurysms in the medicare population. New England Journal of Medicine 2008;358:464-74
- EVAR trial participants. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. Lancet 2005;365:2179-86
- EVAR Trial Participants: Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): Randomised controlled trial, Lancet 2005;365:2187�C2192.

Other Evidence

- National Institute for Health and Clinical Excellence Stent-graft placement in abdominal aortic aneurysm Interventional Procedure Guidance 163 (replaces IPG10) London : NICE ; March 2006 http://www.nice.org.uk/nicemedia/pdf/ip/IPG163guidance.pdf
- TA167 Endovascular stent - grafts for the treatment of abdominal aortic aneurysms National Institute for Health and Clinical Excellence (NICE) ; February 2009 http://www.nice.org.uk/guidance/index.jsp?action=byID&o=12129
- Endovascular stents for abdominal aortic aneurysms: a systematic review and economic model CRD/CHE Assessment Group York; April 2008 http://www.nice.org.uk/guidance/index.jsp?action=folder&o=41834
- Epstein DM, Sculpher MJ, Manca A, Michaels J, Thompson SG, Brown LC et al. Modelling the long-term cost-effectiveness of endovascular or open repair for abdominal aortic aneurysm. British Journal of Surgery 2008;95(2):183-90
- Jonk YC, Kane RL, Lederle FA, MacDonald R, Cutting AH,Wilt TJ. Cost-effectiveness of abdominal aortic aneurysm repair: a systematic review International Journal of Technology Assessment in Health Care 2007;23(2):205-15

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Clinical Effectiveness

Three well-conducted SRs of clinical effectiveness were located. The earliest review by Drury et al, provided the evidence base for NICE guidance on stent-graft placement in abdominal aortic aneurysm issued in 2006 and compared EVAR with open repair and no intervention. The later reviews by Wilt et al and Lederle et al updated the evidence base, with searches up to December 2006, and compared the effectiveness of treatment options including active surveillance, open repair and endovascular repair for un-ruptured AAAs.

A large meta-analysis by LOvegrove et al (n=21,178) of randomised and observational trials comparing EVAR with open repair was generally well-conducted, although further clarity on the numbers assessed at 30 days and mean long-term follow-up periods would be helpful. Additionally a large non-randomised trial (n=45,660) assessing matched cohorts of Medicare beneficiaries undergoing EVAR or open repair, with follow-up to 2005 (schermerhorn et al) was identified as of interest.

The evidence from the above suggests that EVAR confers a significant perioperative survival benefit with fewer complications and a shorter recovery in comparison with open repair. Trends in reduced 30-day post-operative mortality and postoperative stay amongst the EVAR group were also observed.

In the longer term there is also evidence to suggest aneurysm related mortality is significantly lower amongst patients undergoing endovascular repair. For all-cause mortality however, levels appear similar following both types of procedure in the longer term.

Amongst high risk patients unfit for open repair evidence from the only RCT conducted to-date (EVAR-2) indicates EVAR does not improve survival. The validity of the EVAR-2 trial results have been

questioned given the negative impact of high crossover and procedural mortality rates. Ideally a further RCT comparing EVAR with observation for high risk patients is required however we are not aware that any additional trials are being planned.

In summary the durability of the survival benefit associated with EVAR appears to be age-dependent and primarily due to differences in perioperative mortality. In the longer term (up to six years) EVAR appears to be associated with lower aneurysm-related mortality than open repair. Repairing AAAs <5.5cm in diameter does not appear to improve survival. Within one to four years differences in all-cause mortality amongst the two procedural groups dissipate however the survival benefit appears more durable amongst older patients (aged ��85 years).

Cost Effectiveness

Two recently published reviews assessed the cost-effectiveness of EVAR or open repair for AAAs. Jonk et al concluded that for patients medically fit for open surgery, mid-term costs were greater for EVAR with no difference in overall survival or quality of life. Epstein et al, modelled the long-term cost-effectiveness of EVAR vs. open repair using a decision model and data largely taken from the EVAR-1 trial. They concluded that in comparison with open repair EVAR is unlikely to be cost-effective on the basis of existing devices, costs and evidence, but there remains considerable uncertainty.

Note: Since ARIF responded to these requests a NICE Technology Appraisal assessing the clinical and cost-effectiveness of endovascular stent-grafts for the repair of AAAs has been published. http://www.nice.org.uk/guidance/index.jsp?action=byID&o=12129

Request Carried Out: September 2008

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ARIF Request

Accident and Emergency
Triage
General Practitioners

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The Problem Submitted For ARIF To Advise Upon

Is there any evidence on the effectiveness of general practitioners (GPs) in accident and emergency (A & E) units and are there any additional benefits compared to if he or she was not present on outcomes such as admission rates?

Comments

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ARIF Request

Laser Therapy
Acne

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of laser therapy for acne?

Comments

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ARIF Request

Laser Therapy
Acne Scarring

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of laser therapy for acne scarring?

Comments

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ARIF Request

Acoustic Neuroma

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The Problem Submitted For ARIF To Advise Upon

What is the 'gold standard' investigation of someone presenting with symptoms suggestive of acoustic neuroma?

Comments

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ARIF Request

Pegvisomant Acromegaly Growth Hormone

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

In 2007, the West Midlands Health Technology Assessment Collaboration (WMHTAC) completed a systematic review that assessed the clinical and cost effectiveness of Pegvisomant (PEG) for use in patients with acromegaly. The conclusion was:

"PEG is highly effective for improving patients IGF-I level. Signs and symptoms of disease improve but evidence is lacking about the long term effects on improved signs and symptoms of disease, quality of life, patient compliance and safety".

ARIF were asked to determine if any new research had been published since the completion of the WMHTAC review and whether this alters the above conclusions.

Reviews Identified

No reviews supersede the WMHTAC review.

Randomised Controlled Trials

- Trainer PJ, Ezzat S, D'Souza GA, Layton G, Strasburger CJ. A randomized, controlled, multicentre trial comparing pegvisomant alone with combination therapy of pegvisomant and long-acting octreotide in patients with acromegaly. Clinical Endocrinology 2009;71(4):549-557

Other Evidence

- Neggers SJ, van Aken MO, de Herder WW, Feelders RA, Janssen JA, Badia X, et al. Quality of life in acromegalic patients during long-term somatostatin analog treatment with and without pegvisomant. Journal of Endocrinology and Metabolism 2008;93(10):3853-3859
- Zgliczynski W, Zdunowski P. [Pegvisomant--growth hormone receptor antagonist in the treatment of acromegaly]. lEndokrynologia Polska 2007;58(5):408-416
- Buhk JH, Jung S, Psychogios MN, Goricke S, Hartz S, Schulz-Heise S, et al. Tumor volume of growth hormone-secreting pituitary adenomas during treatment with pegvisomant: a prospective multicenter study. Journal of Clinical Endocrinology and Metabolism 2010;95(2):552-558
- Jimenez C, Burman P, Abs R, Clemmons DR, Drake WM, Hutson KR, et al. Follow-up of pituitary tumor volume in patients with acromegaly treated with pegvisomant in clinical trials. European

Journal of Endocrinology 2008;159(5):517-523

- Trainer PJ. ACROSTUDY: the first 5 years. European Journal of Endocrinology 2009;161(Suppl 1):S19-S24

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Comments

The ARIF search identified one new randomised controlled trial (Trainer et al 2009), two controlled clinical trials (Neggers et al 2008, Zgliczynski & Zdunowski 2007), two uncontrolled trials (Buhk et al 2010, Jimenez et al 2008) and identified a publication describing the ACROSTUDY which is an international registry of patients being treated with PEG (Trainer 2009). No cost studies were found.

The two new CCTs have very small sample sizes (n=10) therefore do not add substantially to the evidence base. The RCT suggests that PEG and PEG + long acting octreotide (LAR) are equally effective in improving clinical and biological parameters in patients with acromegaly that has not been adequately controlled by first line treatments such as surgery and/or radiotherapy or second line treatments such as LARs as monotherapy. Just one study in the WMHTAC review had tested this modality (Jorgensen 2005). Using PEG as a monotherapy compared to PEG + LAR may have implications regarding cost.

The trial again demonstrates that it is feasible to conduct an RCT in this patient population and that it is possible to measure clinical and patient specific outcomes. This includes the EQ-5D quality of life tool.

Both the registry data and two uncontrolled trials suggest that over the medium term tumour growth only occurs in a relatively small proportion of patients.

These findings do not substantially alter the conclusions of the WMHTAC review.

Further good quality research is required, so that the uncertainty about the effectiveness of PEG versus other treatments can be diminished.

Request Carried Out: April 2010

To see full report - click here

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ARIF Request

Lanreotide
Octreotide
Acromegaly

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of lanreotide and octreotide in the treatment of acromegaly?

Comments

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ARIF Request

Pegvisomant
Acromegaly

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of pegvisomant (Somavert) in the treatment of patients with acromegaly whose disease is not controlled by surgery and subsequent medical therapy?

Comments

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ARIF Request

Acupuncture

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The Problem Submitted For ARIF To Advise Upon

Requestor had been approached with proposals for use of acupuncture in primary care for relief of and wide range of conditions e.g. pain, allergic conditions, nausea in pregnancy, stress, menstrual disorders and polysymptomatic relief for terminal illness. For which of these indications is there evidence of effectiveness?

Comments

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ARIF Request

Laser Acupuncture
Acupuncture - Laser
Chronic Pain
Pain (Chronic)

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of laser acupuncture in patients with chronic pain, relative to other forms of pain relief.

Laser acupuncture is defined as the stimulation of traditional acupuncture points with low-intensity, non-thermal laser irradiation. Low-intensity, non-thermal laser irradiation (also known as low level laser therapy LLLT) can also be used at the site of pain or at trigger points. Acupuncture is described as a “therapy that involves the stimulation of defined points on the skin typically by inserting needles; however, related techniques such as manual (acupressure) electrical or laser stimulation of acupuncture points are also often summarized under this term”. The underlying belief of acupuncture is that it restores and balances an energy (called Qi) which flows through the body along defined paths. Any disturbance in the flow can result in ill health, but by stimulating certain defined points (acupuncture points) along these Qi pathways health is restored.

Reviews Identified

- Bjordal JM, Lopes-Martins RA, Joensen J, Couppe C, Ljunggren AE, Stergioulas A, et al. A systematic review with procedural assessments and meta-analysis of low level laser therapy in lateral elbow tendinopathy (tennis elbow). BMC Musculoskeletal Disorders 2008;9:75
- Green S, Buchbinder R, Barnsley L, Hall S, White M, Smidt N, Assendelft W. Acupuncture for lateral elbow pain. Cochrane Database of Systematic Reviews 2002, Issue 1. Art. No.: CD003527. DOI: 10.1002/14651858.CD003527.
- Piazzini DB, Aprile I, Ferrara PE, Bertolini C, Tonali P, Maggi L, et al. A systematic review of conservative treatment of carpal tunnel syndrome. Clinical Rehabilitation 2007;21(4):299-314.
- White AR, Ernst E. A systematic review of randomized controlled trials of acupuncture for neck pain. Rheumatology (Oxford) 1999;38(2):143-147

Randomised Controlled Trials

- Ebneshahidi NS, Heshmatipour M, Moghaddami A, Eghtesadi-Araghi P. The effects of laser acupuncture on chronic tension headache--a randomised controlled trial. Acupuncture in Medicine 2005;23(1):13-18

- Aigner N, Fialka C, Radda C, Vecsei V. Adjuvant laser acupuncture in the treatment of whiplash injuries: a prospective, randomized placebo-controlled trial. Wiener Klinische Wochenschrift 2006; 118(3-4):95-99
- Yurtkuran M, Alp A, Konur S, Ozcakir S, Bingol U. Laser acupuncture in knee osteoarthritis: a double-blind, randomized controlled study. Photomedicine and Laser Surgery 2007;25(1):14-20

Other Evidence

- Whittaker P. Laser acupuncture: past, present, and future. Lasers Medical Science 2004; 19(2):69-80
- Linde K, Vickers A, Hondras M, ter Riet G, Thormahlen J, Berman B, et al. Systematic reviews of complementary therapies - an annotated bibliography. Part 1: acupuncture. BMC Complementary and Alternative Medicine 2001;1:3

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Comments

The only review that concentrated on laser acupuncture was the narrative review by Whittaker. We identified four systematic reviews that incorporated trials using laser acupuncture for specific painful conditions (6 relevant trials in total), two for 'tennis elbow' , one for carpal tunnel syndrome, and one for neck pain. Of these, one focused on low level light therapy per se and one focused on acupuncture per se. All of the systematic reviews were reasonably well conducted. We also identified three RCTs that investigated laser acupuncture.

None of the RCTs compared laser acupuncture with other pain relieving treatments. Against placebo treatment, four trials reported that laser acupuncture had a positive effect on pain relief, four reported no difference between laser acupuncture and placebo, and one reported a negative effect. This is an oversimplification and doesn't reflect the heterogeneity of the trials. Factors such as cause of pain and duration as well as type of laser acupuncture used (e.g. wavelength, power and length of treatments as well as acupuncture sites) could also affect the results.

In conclusion, the evidence base for laser acupuncture is sparse and its effectiveness is open to debate and judgement.

Request Carried Out: July 2008

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ARIF Request

Statins (High Dose)
Intensive Lipid Lowering Therapy
Acute Coronary Syndrome (ACS)
Unstable Angina

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The Problem Submitted For ARIF To Advise Upon

What is the clinical and cost-effectiveness of early aggressive lipid lowering therapy using very high dose statins (80mg/day) for patients with acute coronary syndrome, patients with crescendo angina, and patients undergoing revascularisation?

Comments

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ARIF Request

Recombinant Tissue Plasminogen Activator (rt-PA) Acute Ischaemic Stroke

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The Problem Submitted For ARIF To Advise Upon

What is known about the effects and effectiveness of tissue plasminogen activator (rt-PA) for acute ischaemic stroke?

Comments

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ARIF Request

Media Campaigns
Health Behaviour/Acute Myocardial Infarction

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The Problem Submitted For ARIF To Advise Upon

What evidence is there on the effectiveness of media campaigns and other interventions which aim to reduce patient delay factors in pain to needle time in acute myocardial infarction?

Comments

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ARIF Request

Acyclovir
Chicken Pox

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The Problem Submitted For ARIF To Advise Upon

What is the evidence that treatment of adult chicken pox with acyclovir helps prevent complications and is cost effective?

Comments

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ARIF Request

Adalimumab
Crohn's Disease

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The Problem Submitted for ARIF to Advise Upon:

To advise on the relative effectiveness of Adalimumab compared to escalating the dose of infliximab in patients with severe Crohn's disease.

Adalimumab and infliximab are tumour necrosis factor inhibitors (anti TNF-α agents), licensed for use in patients with severe Crohn's disease. Licenses cover patients with severe active Crohn's who have not responded to conventional treatment or who have experienced toxicity from these treatments (adalimumab and infliximab) or in fistulising active Crohn's disease (only infliximab).

Reviews Identified

- Dretzke J, Round J, Edlin R et al. Use of tumour necrosis factor alpha (TNFa) inhibitors adalimumab and infliximab for Crohns disease. London: NICE; 2008. http://www.nice.org.uk/nicemedia/pdf/Crohn'sARStrippedToPMForConsultationACS0908.pdf

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Comments

The review by Dretzke 2008 was the most up-to-date and comprehensive of those identified. It aimed to systematically review the evidence for the effectiveness of adalimumab and infliximab in patients with Crohn's disease based on randomised controlled trials (RCTs). Appropriate literature searches were undertaken from 1950 to May 2007 and recognised systematic review methodology was employed.

The review comprised studies of adalimumab and infliximab, both for induction of remission and maintenance of remission after induction, in patients with moderate or severe Crohn's disease. Both types of trials showed adalimumab/infliximab to be effective for the treatment of severe Crohn's compared to placebo.

Because no comparative studies have been undertaken to assess the relative effectiveness of adalimumab and infliximab, a direct comparison cannot be made. Indirect comparison (using a common placebo arm) is likely to be inappropriate due to differences in the trial populations.

One trial did show adalimumab to be effective in patients who were intolerant or un-responsive to

infliximab. Adalimumab may be a successful alternative in these patients.

No trials investigated the effectiveness of dose escalation in non-responding patients (infliximab or adalimumab). There is therefore no conclusive evidence about whether, in non-responders to infliximab, dose escalation of infliximab or switching to adalimumab is more effective.

Request Carried Out: May 2009

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ARIF Request

Adefovir Dipivoxil
Lamivudine-resistant Hepatitis B
Hepatitis B

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of adefovir dipivoxil for the treatment of patients with lamivudine-resistant chronic HBV?

Comments

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ARIF Request

Nicotine Replacement Therapy
Adolescents
Pregnancy
Breastfeeding
Cardiovascular Disease
Combination of NRTs
NRT with Bupropion

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The Problem Submitted for ARIF to Advise Upon:

In 2005 the Healthcare Regulatory (MHRA) undertook a review of the indications for nicotine replacement therapy (NRT). The MHRA reviewed licensing arrangements for NRT with regard to the wider access to NRT products across the following groups:

- Adolescents
- Pregnant women
- Breastfeeding women
- Cardiovascular disease
- Combination NRT

The National Institute for Health and Clinical Effectiveness (NICE) as part of the wider programme of work on smoking and the NHS in England and Wales, commissioned a report from ARIF and the West Midlands Health Technology Assessment Collaboration (follow link below), to identify the best evidence on the clinical and cost-effectiveness of NRT for each of the licences.

Clinical and cost-effectiveness of nicotine replacement therapy for new licensed indications and combination therapy: A summary of best evidence

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ARIF Request

Aetiology
Mental Health
Physical Health

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Does mental health well-being (as opposed to mental illness) affect physical health?

Mental well-being can be defined as "encompassing: emotional well-being (including happiness and confidence and the opposite of depression and anxiety), psychological well-being (including resilience, mastery, confidence, autonomy, attentiveness/involvement and the capacity to manage conflict and problem solve), social well-being (good relationships with others and the opposite of conduct disorder, delinquency, interpersonal violence and bullying)" [Adi Y et al 2007].

Reviews Identified

- Zautra A. Subjective well-being and physical health: a narrative literature review with suggestions for future research. International Journal of Ageing and Human Development 1984;19(2):91-110

Other Evidence

- Koivumaa-Honkanen H, Onkanen R, Viinamaki H. Life dissatisfaction was associated with an increased risk of suicide but adjustment for confounding factors attenuated the association. Evidence-Based Mental Health 4, 122.2001
- Windle G, Hughes D, Linck P, et al. Public health interventions to promote mental well-being in people aged 65 and over: systematic review of effectiveness and cost-effectiveness. NICE Public Health Intervention Guidance 2007 http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11671 [accessed 6 June 2008]
- NICE Public Health Interventions. Promoting mental well-being at work. NICE Public Health Intervention Guidance 2008 http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11669 [accessed 6 June 2008]
- Adi Y, Kiloran A, Janmohamed K, Stewart-Brown S. Systematic review of the effectiveness of interventions to promote mental well-being in primary schools. Report 1: Universal approaches which do not focus on violence or bullying. 2007. Report No.1 http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11948 [accessed 6 June 2008]
- Huppert FA, Whittington JE. Symptoms of psychological distress predict 7-year mortality.

Psychological Medicine 1995;25:1073-1086

- The National Programme for Improving Mental Health and Wellbeing Scotland http://www.wellscotland.info/mentalhealth/national-programme.html [accessed 9 June 2008]

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Comments

We were unable to identify any studies that looked at the aetiological link between mental well-being and physical health, although two cohort studies have been undertaken looking at mental well-being and mortality. Both found that people who had low levels of mental well-being at baseline tended to have higher rates of mortality at follow-up (through both natural disease process or suicide). However, difficulties in defining and measuring well-being make the design of aetiological studies difficult and confounding factors make results difficult to interpret. There are two national initiatives promoting well-being. For England and Wales NICE Public Health Guidance has been issued, promoting well-being in older people, school children and people at work. In Scotland there is the National Programme for Improving Mental Health and Wellbeing in Scotland although the aims of the programme seem to be trying to reduce mental illness rather than physical illness through the promotion of mental well-being.

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ARIF Request

Implantable Intraocular Lens Systems Age-Related Macular Degeneration

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Rapid assessment of implantable intraocular lens systems for age-related macular degeneration (AMD).

AMD is one of the most common causes of visual loss among the elderly. Its target area is the macular, a small region of the retina located at the posterior of the eye, responsible for clear straight ahead vision necessary for everyday functioning.

There are two types of AMD: wet or neovascular and dry or atrophic. There are currently no treatment options available that restore lost vision.

Implantable intraocular lenses are intended for patients suffering from advanced AMD that are not amenable to treatments. The three technologies currently available work on the principle of deflecting a magnified image away from the damaged retina onto healthier macular tissue, such that central vision is rendered on central and peripheral retina.

The assessment is to include information on the technology, the current state of the evidence and an overview of on-going trials.

Reviews Identified

- National Institute for Health and Clinical Excellence. Interventional procedure overview of implantation of lens systems for advanced age-related macular degeneration. London: NICE; 2008 http://www.nice.org.uk/nicemedia/pdf/375_overview_for_web_230408.pdf
- National Institute for Health and Clinical Excellence. implantation of miniature lens systems for advanced age-related macular degeneration. London: NICE; 2008. Interventional procedure guidance 272. http://www.nice.org.uk/Guidance/IPG272/Guidance/pdf/English

Trials Identified

- A study of an implantable miniature telescope in patients with end stage AMD. http://www.clinicaltrials.gov.ct2/show/record/NCT00555165?=macular+degeneration+intr=imt&rank=1

Other Evidence

- Tang Z. Implantable miniature telescope for treating age-related macular degeneration. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2004. http://www.cadth.ca/media/pdf/152_No20_miniaturetelescope_etech_e.pdf
- National Horizon Scanning Centre. Implantable miniature telescopes for advanced, untreatable age-related macular degeneration: horizon scanning review. Birmingham: National Horizon Scanning Centre (NHSC); 2006. http://www.pcpoh.bham.ac.uk/publichealth/horizon/outputs/documents/2006/ImplantableTelescopes.pdf

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Comments

We identified one relevant systematic review, two Horizon Scanning publications and one ongoing clinical trial. The systematic review was part of the evidence considered by the Interventional Procedures Advisory Committee of NICE for their Interventional Procedure Guidance on implantable lens systems for advanced age-related macular degeneration (IPG 272).

The review was described as a "rapid" review and is reasonably up-to-date with the searches going up to January 2008. The searches had a couple of short comings, such as excluding conference abstracts and non-English language articles, which given that this is a new technology may have missed some relevant studies. The review was supplemented by expert opinion of four consultants from the Royal College of Ophthalmologists.

The systematic review included one non-randomised comparative study, detailing the results of a large multicenter Phase II/III clinical trial of the Implantable MiniatureTelescope (IMT); and four case series studies that investigated implantation of all the three different lens systems in patients with AMD. Two of these case series were based on the IMT and one each on the Intra-ocular Lens for Visually Impaired People (IOL-Vip) and the Lipshitz Macular Implant (LMI). All five studies measured visual acuity although they were measured using different scales.

The review also included comments on the validity and generalisability of the studies, citing different visual acuity outcomes making comparisons between studies difficult and failure to specify age limits in two of the studies. Small study size with limited follow-up in some of the studies also made it difficult to exclude the play of chance. An open label study (not blinded) and use of fellow eyes as the control group increase the possibility of bias in the study.

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ARIF Request

Photodynamic Therapy
Age-Related Macular Degeneration (AMD/ARMD)
Sub-foveal Predominantly Classic Choroidal Neovascularisation (CNV)

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The Problem Submitted For ARIF To Advise Upon

Is photodynamic therapy an effective treatment for wet age-related macular degeneration with predominantly classic CNV?

Photodynamic therapy (PDT) is a newly developed type of treatment combining:
- injection of a light-sensitive dye which concentrates in areas of “abnormality”
- low power laser

The rationale is that abnormal cells can be destroyed without damage to nearby normal cells.

Comments

This request was carried out more than four years ago and has not been updated since. The articles identified may no longer be the best available and therefore the commentary may be out of date. As a precaution the information has been removed from this page.

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ARIF Request

Photodynamic Therapy
Age-Related Macular Degeneration (AMD/ARMD)
Sub-foveal Occult Choroidal Neovascularisation

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The Problem Submitted For ARIF To Advise Upon

Is photodynamic therapy an effective treatment for wet age-related macular degeneration with occult CNV?

Photodynamic therapy (PDT) is a newly developed type of treatment combining:

- injection of a light-sensitive dye which concentrates in areas of “abnormality”
- low power laser

The rationale is that abnormal cells can be destroyed without damage to nearby normal cells.

Comments

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ARIF Request

Antiretroviral Agents (Combination Therapy) AIDS/HMV

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The Problem Submitted For ARIF To Advise Upon

What is the evidence base of clinical guidelines on the use of antiretroviral agents e.g. zidovudine and protease inhibitors, particularly their use in combination?

ARIF was asked to contribute to a West Midlands working group on HIV/AIDS care whose aim in December 1996, was to decide the priorities for expenditure in the forthcoming financial year.

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ARIF Request

Alcohol - Promoting Abstinence
Alcohol - Reducing Consumption
Alcohol - Non-Dependent Drinkers
Alcohol - Dependent Drinkers
Alcoholism

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in March 2008.

The Problem Submitted for ARIF to Advise Upon:

What is the long-term effectiveness of interventions aimed at reducing alcohol consumption/promoting abstinence amongst heavy/alcohol dependent drinkers, with specific reference to reducing mortality?

The physical, psychological, social and legal harms of excessive alcohol use represent a major public health problem. For both dependent and non-dependent heavy drinkers sustained excessive alcohol use has a detrimental impact on mortality and morbidity.

See related ARIF request:

What is the clinical and cost-effectiveness of community-based versus inpatient alcohol detoxification regimens for alcohol dependent patients?

Reviews Identified

- Kaner EFS, Dickinson HO, Beyer F, Pienaar E, Campbell F, Schlesinger C, Heather N, Saunders J, Burnand B. Effectiveness of brief alcohol interventions in primary care populations. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD004148. DOI: 10.1002/14651858.CD004148.pub3
- Ferri M, Amato L, Davoli M. Alcoholics Anonymous and other 12-step programmes for alcohol dependence. Cochrane Database of Systematic Reviews 2006, Issue 3.Art. No.: CD005032. DOI: 10.1002/14651858.CD005032.pub2
- Garbutt JC, West SL, Carey TS, Lohr KN, Crews FT. Pharmacological treatment of alcohol dependence: a review of the evidence. JAMA 1999;281(14):1318-1325
- Mann K, Lehert P, Morgan MY The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis. Alcoholism: Clinical and Experimental Research 2004;28(1):51-63
- Streeton C, Whelan G. Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials. Alcohol and Alcoholism 2001;36(6):544-552

Randomised Controlled Trials

- Wutzke SE, Conigrave KM, Saunders JB, Hall WD. The long-term effectiveness of brief interventions for unsafe alcohol consumption: a 10-year follow-up. Addiction 2002;97(6):665-75
- Kristenson H, Osterling A, Nilsson JA, Lindgärde F. Prevention of alcohol-related deaths in middle-aged heavy drinkers. Alcoholism, Clinical and Experimental Research;2002;26(4):478-84

Other Evidence

- Bunn JY, Booth BM, Cook CA, Blow FC, Fortney JC. The relationship between mortality and intensity of inpatient alcoholism treatment. American Journal of Public Health 1994;84(2):211-4

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Comments

Three studies, two RCTs (Wutzke et al, 2002; Kristenson et al, 2002) and one retrospective cohort study (Bunn et al, 1994) examined the longer-term effectiveness of treatment for heavy and alcohol dependent drinkers and provided data on mortality.

In summary the results reported were equivocal. The two RCTs that assessed the impact of brief interventions for non-dependent, heavy drinkers on mortality ten yearsor longer aftert intervention provided seemingly disparate results. Kristenson et al (2002) reported significantly higher survival rates amongst the treatment group whereas Wutzke et al (2002) did not. However the benefits observed by Kristenson et al (2002) may have been influenced by the extended provision of advice for patients in the brief intervention arm of the trial. The cohort study (Bunn et al, 1994) compared the effectiveness of different intensities of inpatient treatment for alcohol dependent drinkers on mortality three years after discharge and reported extended formal inpatient treatment was associated with significantly lower mortality compared with less intensive treatment. However, these findings should be interpreted with a degree of caution as the possibility of bias (selection) in this type of study design cannot be ruled out.

Five systematic reviews (SRs) evaluated the impact of treatment on alcohol consumption patterns (Kaner et al, 2007; Ferri et al, 2006; Garbutt et al, 1999; Mann et al, 2004; Streeton et al, 2001). One SR (Mann et al, 2004) focused predominantly on non-dependent heavy drinkers, assessing the value of brief interventions, delivered in primary care settings, aimed at reducing alcohol consumption. Four SRs (Ferri et al, 2006; Garbutt et al, 1999; Mann et al, 2004; Streeton et al, 2001) focused on alcohol dependent drinkers addressing a variety of outcomes that included reductions in alcohol consumption and abstinence. Of these, one SR (Ferri et al, 2006) compared the effectiveness of Alcoholics Anonymous (AA) programmes with other psychosocial interventions and three SRs (Garbutt et al, 1999; Mann et al, 2004; Streeton et al, 2001) assessed the efficacy of pharmacological treatment (one SR (Garbutt et al,1999) provided a general overview of five categories of drugs used to treat alcohol dependence; one SR (Mann et al, 2004) focused on acamprosate; and one SR (Streeton et al, 2001) focused on naltrexone).

In summary, for heavy non-dependent drinkers brief interventions appear to be effective in reducing alcohol consumption at one-year follow-up. For alcohol dependent drinkers evidence to-date neither supports nor refutes the effectiveness of AA programmes in reducing alcohol use or achieving abstinence over and above that demonstrated by other psychosocial interventions. The SRs assessing the effectiveness of pharmacological treatments for alcohol dependent patients indicate acamprosate (at one-year follow-up) and naltrexone (at 12-weeks follow-up) are effective in reducing relapses to heavy drinking and improving abstinence. However the effectiveness of disulfiram is less clear and serotonergic agents and lithium do not appear to be effective.

In conclusion the evidence identified appears to lend support to a number of interventions aimed at reducing alcohol consumption and promoting abstinence amongst heavy (non-dependent) and alcohol dependent drinkers. To date however research has predominantly assessed the short to medium term impact of treatment. The effectiveness of treatments in the longer term in changing alcohol related behaviour and reducing the negative impact of heavy drinking on health have not been adequately explored.

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ARIF Request

Theatre/Drama Techniques
Alcohol Awareness
School-Aged Children

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of theatre/drama aimed at young people (12-18 year olds) as an intervention to improve alcohol awareness/ability to make safe, sensible choices?

Theatre in Education has been identified as an innovative approach to drug education but although the use of applied drama and theatre in health promotion is increasing, knowledge about its effectiveness for health and well-being is still limited (Joronen 2008).

Reviews Identified

- Joronen K, Rankin SH, and Astedt-Kurki P. School-based drama interventions in health promotion for children and adolescents: systematic review. Journal of Advanced Nursing 2008;63(2):116-131
- Daykin N, Orme J, Evans D. With Salmon, M. McEachran SM and Brain S. The impact of participation in performing arts on adolescent health and behaviour: A systematic review of the literature. Journal of Health Psychology 2008;13(2):251-26

Other Evidence

- Starkey F, Orme J. Evaluation of a primary school drug drama project: Methodological issues and key findings. Health Education Research 2001;16(5):609-622
- Nelson A, Arthur B. Storytelling for empowerment: Decreasing at-risk youth's alcohol and marijuana use. Journal of Primary Prevention 2003;24(2):169-18

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Comments

We were able to identify two systematic reviews that assessed the effectiveness of drama/theatre in health education among school children and adolescents. There were no reviews that solely assessed the effectiveness of drama to convey messages on alcohol use/awareness.

Both of the reviews were quite recent and reasonably well conducted. Joronen (2008) did not include

any studies on the effects of drama on alcohol use; studies assessing this issue were however part of the systematic review by Daykin et al. (2008). It aimed to establish the effect of performing arts (drama, dance and music) for health education in young people aged 11-18 years in non-clinical settings. Two of the 14 papers included in this systematic review examined the effects of drama intervention on alcohol and drug use. Improvements in knowledge and an increased resistance to drug/alcohol use were documented but the review authors did not include any statistical information. However, a detailed assessment of these primary studies revealed methodological weaknesses. The study by Nelson & Arthur (2003) involved a multifaceted intervention, making it difficult to attribute results to the theatre/drama components. Issues of validity arise in the study by Starkey & Orme (2001) mainly due to a non-comparative study design and follow-up bias as only 6 of the 41 schools contributed to the final results.

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ARIF Request

Health Promotion
Brief Interventions
Primary Care
Alcohol Consumption

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to reducing alcohol consumption?

Comments

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ARIF Request

Alcohol Counselling Domestic Violence

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of brief interventions including alcohol counselling services in reducing the frequency and severity of domestic violence?

In particular this request was on the effectiveness of such services on male perpetrators of domestic violence who seek help.

Comments

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ARIF Request

Naltrexone
Opioid Antagonists
Alcohol Dependence

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of naltrexone in alcohol dependent patients?

Following initial detoxification, people with alcohol dependence often require longer-term interventions to maintain abstinence or prevent relapse into heavy drinking and re-establishing dependence.

Naltrexone is an opioid antagonist. Its mode of action is thought to reduce sensations of pleasure from drinking, therefore breaking the positive reinforcement potential of alcohol and reducing the risk of relapse to heavy drinking. [Slattery]

Reviews Identified

- Srisurapanont M, Jarusuraisin N. Opioid antagonists for alcohol dependence. Cochrane Database of Systematic Reviews 2005, Issue 1. Art. No.: CD001867. DOI:10.1002/14651858.CD001867.pub2. http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001867/frame.html [accessed 2nd April 2009]
- Slattery J, Chick J, Cochrane M. et al. Prevention of relapse in alcohol dependence. Health Technology Assessment Report 3. Health Technology Board for Scotland Glasgow: Health Technology Board for Scotland (HTBS), 2003 http://www.nhshealthquality.org/nhsqis/files/Health%20Technology%20Assessment%20Report%20Full%20version.pdf

  [accessed 2nd April 2009]

Other Evidence

- Scottish Intercollegiate Guidelines Network. 74. The management of harmful drinking and alcohol dependence in primary care. A national clinical guideline. September 2003. http://www.sign.ac.uk/pdf/sign74.pdf [accessed 6th April 2009]

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Comments

We identified one systematic review in the Cochrane library, one Health Technology Assessment (HTA) undertaken by the Health Technology Board for Scotland and guidelines on the use of naltrexone in primary care produced by Scottish Intercollegiate Guidelines Network (SIGN). All the reviews were well conducted.

The main restriction on use of naltrexone in the UK appears to be its license status. UK specific guidelines advise that naltrexone is not licensed for use here and therefore has no role to play in the management of patients with alcohol dependence.

Overall, data from the effectiveness reviews suggest that naltrexone has a useful role to play as an adjunct to psychological treatments in helping alcohol dependent patients sustain either abstinence or enable them to control their drinking at a level that is less harmful to their health.

In the short-term naltrexone is more effective than placebo in:

Reducing the number of patients who relapse Relative Risk (RR) 0.64 (95% Confidence Interval (CI) 0.51, 0.82)

- Reducing the number of patients who discontinue treatment RR 0.82 (95% CI 0.70, 0.97)
- Reducing the amount of alcohol consumed Weighted Mean Difference (WMD) –3.40(95% CI -6.46, -0.34)

Naltrexone is also more effective than placebo in reducing the number of patients who return to drinking, although there is a possibility that in some patients there is no advantageous effect as the CI incorporates 1.00, the point of no effect.

For medium-term effects between 12 and 52 weeks:

- Naltrexone is more effective than placebo in reducing the number of patients with relapses RR 0.75 (95% CI 0.59, 0.95)

However, patients taking naltrexone were more likely to suffer from side effects i.e. nausea RR 2.14 (95% CI 1.61, 2.83), dizziness RR 2.09 (95% CI 1.28, 3.39) and fatigue RR 1.35 (95% CI 1.04, 1.75).

Caveats around these findings are that most of the trial data is of short duration (less than 12 weeks) and that most trials used placebo as comparators, which can often amplify a positive effect. Trials were also conducted in mainly tertiary settings therefore caution should be taken if applying the results to the primary care setting, as resources may differ in their availability and patients may have more severe disease.

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ARIF Request

Incentives
Heavy Drinkers
Alcohol Dependent Drinkers

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The Problem Submitted for ARIF to Advise Upon:

What is the clinical and cost-effectiveness of providing incentives to motivate reduced alcohol consumption?

Financial and material incentives are used in many programmes to motivate patients and general populations to change their behaviour. They are used to encourage programme recruitment or reward reduced alcohol consumption/cessation achieved at predefined stages. Rewards may be provided for attendance, irrespective of subsequent performance (i.e. guaranteed), or paid relative to the participant's success within a programme (i.e. contingent).

See related requests: - Provision of incentives to motivate smokers to quit and Provision of financial incentive schemes to motivate increasing levels of physical activity

Reviews Identified

No systematic reviews were identified.

Randomised Controlled Trials

- Glindemann K, Ehrhart IJ, Drake EA, Geller ES. Reducing excessive alcohol consumption at university fraternity parties: a cost-effective incentive/reward intervention. Addictive Behaviors. 2007;32(1):39-48
- Petry NM, Peirce JM, Stitzer ML, Blaine J, Roll JM, Cohen A et al. Effect of prize-based incentives on outcomes in stimulant abusers in outpatient psychosocial treatment programs: a national drug abuse treatment clinical trials network study. Archives of General Psychiatry 2005;62(10):1148-56

Other Evidence

- Leontieva L, Dimmock JA, Gately PW, Gallinger L, Ploutz-Snyder R, Batki SL.Voucher-based incentives for naltrexone treatment attendance in schizophrenia and alcohol use disorders. Psychiatric Services 2008 ;59(3):310-4
- Olmstead TA, Sindelar J L, Petry N M. Cost-effectiveness of prize-based incentives for stimulant abusers in outpatient psychosocial treatment programs. Drug and Alcohol Dependence 2007;

87(2):175-182

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Comments

Glindermann et al's RCT explored the impact of incentives on USA college students' (n=702) intoxication from alcohol consumption at fraternity parties. Results indicated alcohol consumption at parties attended by groups entered in a $100 lottery was significantly lower than that measured for controls. However the longer-term impact was not assessed.

Leontieva et al's uncontrolled study explored the feasibility of voucher based incentives for attendance for naltrexone treatment for alcohol use disorders amongst USA patients with schizophrenia (n=61). Trial results indicated attendance over the 12-week period was high and most patients found the incentive system helpful. However without a control group, causality is uncertain. Longer term impact was not assessed.

Petry et al's RCT explored the efficacy of incentives (chance to win prizes if substance-free urine samples submitted) as an addition to usual care in promoting abstinence amongst cocaine or methamphetamine users (n=415) in USA community treatment sessions over a 12-week period. Results indicated the incentives group remained in treatment for significantly longer than the control group, attended a significantly greater number of counselling sessions, and submitted significantly more stimulant and alcohol-free samples ($p<0.01$). Using effectiveness data from this study Olmstead et al estimated incremental cost-effectiveness ratios. Compared with standard care, duration of confirmed stimulant abstinence was significantly longer and costs significantly higher, amongst the incentives group.

Evidence assessing the clinical and cost-effectiveness of incentives to motivate reduced alcohol consumption is somewhat sparse. The identified studies focus on small population subsets and may not reflect heavy or alcohol dependent drinkers per se. In the short term incentives may motivate individuals to enter treatment programmes and may further help increase abstinence rates. However the longer term impact on alcohol consumption, once incentives have been withdrawn, has not been established.

Request Carried Out: July 2010

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ARIF Request

Detoxification-Alcohol
Community-based Alcohol Detoxification
Inpatient Alcohol Detoxification
Alcohol Dependency
Alcohol Withdrawal Symptoms

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The Problem Submitted for ARIF to Advise Upon:

What is the clinical and cost-effectiveness of community-based versus inpatient alcohol detoxification regimens for alcohol dependent patients?

Alcohol withdrawal is a clinical syndrome that effects people accustomed to sustained, heavy alcohol use who abruptly decrease their alcohol intake or stop drinking completely. Its most common symptoms include tremor, craving for alcohol, insomnia, anxiety, irritability, loss of appetite, nausea, vomiting, headache and sweating. More serious complications are hallucinations, delirium tremens (DTs) and seizures. Detoxification treatment is designed to control these medical and psychological symptoms.

See related ARIF Request:

What is the long-term effectiveness of interventions aimed at reducing alcohol consumption/promoting abstinence amongst heavy/alcohol dependent drinkers - with specific reference to reducing mortality?

Reviews Identified

- Mattick R P, Jarvis T. In-patient setting and long duration for the treatment of alcohol dependence: out-patient care is as good. Drug and Alcohol Review 1994;13(2):127-135
- Fleeman ND . Alcohol home detoxification: a literature review. Alcohol and Alcoholism 1997;32(6):649-56

Randomised Controlled Trials

- Hayashida M, Alterman AJ, McLellan AT, et al. Comparative effectiveness and costs of in-patient and out-patient detoxification of patients with mild-to-moderate alcohol withdrawal syndrome. New England Journal of Medicine 1989;320:358-365
- Alwyn T, John B, Hodgson R J, Phillips C J. The addition of a psychological intervention to a

home detoxification programme. Alcohol and Alcoholism 2004;39(6):536-541

Other Evidence

- Parrot S, Godfrey C, Heather N et al. Cost and outcome analysis of two detoxification services. Alcohol and Alcoholism 2006;41(1):84-91
- Scottish Intercollegiate Guidelines Network. The management of harmful drinking and alcohol dependence in primary care Section 4 Detoxification Guideline No 74;2003

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Comments

For patients likely to experience only mild to moderate withdrawal symptoms, outpatient detoxification seems as safe and effective as inpatient detoxification and significantly cheaper (Mattick, 1994; Hayashida, 1989). Similarly although home detoxification in comparison with inpatient detoxification affords little by way of clinical advantage (Fleeman, 1997) cost savings appear significant (Fleeman, 1997, Alwyn, 2004). Patients with mild to moderate withdrawal symptoms and no serious psychiatric or medical comorbidities can be safely and effectively treated in an outpatient setting or at home (SIGN, 2003). For patients with severe alcohol withdrawal symptoms, previous delirium tremens or seizures, or those with serious psychiatric or medical co-morbidities hospital detoxification is advised (SIGN, 2003).

Request Carried Out: January 2008

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ARIF Request

Alemtuzumab
Chlorambucil
Chronic Lymphocytic Leukaemia
Leukaemia, Chronic Lymphocytic
B-Cell Lymphocytic Leukaemia

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of alemtuzumab in the treatment of chronic lymphocytic leukaemia?

Reviews Identified

- Hadj Tahar A. Alemtuzumab for B-cell chronic lymphocytic leukemia [Issues in emerging health technologies issue 66]. Ottawa: Canadian Coordinating Office for Health Technology Assessment (COOHTA);2005
- Fajemisin B. Alemtuzumab for chronic lymphocytic leukaemias. Bazian Ltd (Editors), Wessex Institute for Health Research and Development, University of Southampton;2003

Randomised Controlled Trials

- Skotnicki AB, Robak T, Mayer J et al. Phase III Study To evaluate the Efficacy and Safety of Front-Line Therapy with Alemtuzumab (CAMPATH,® MABCAMPATH®) vs. Chlorambucil in Patients with Progressive B-Cell Chronic Lymphocytic Leukemia (CAM307). Blood 2003:102(11):439a
- Robak T, Skotnicki AB, Mayer J et al. Interim safety summary of alemtuzumab vs. chlorambucil as front-line therapy for patients with progressive B-cell chronic lymphocytic leukaemia (BCLL). Journal of Clinical Oncology. ASCO Annual Meeting Proceedings 2004;22(14S):Abstract No 6563
- Hillman P, Skotnicki AB, Robak et al. Preliminary Safety and Efficacy Report of a Randomised Trial of Alemtuzumab vs Chlorambucil as Front-Line Therapy in 297 Patients with Progressive B-Cell Chronic Lymphocytic Leukemia. Blood 2004;104(11):687a
- Genzyme. Data from Phase III Comparative Study Show Campath® Superior to Chlorambucil as a First-line Therapy in B-CLL. Genzyme [online], Available from: http://www.genzymeclinicalresearch.com/home/search_clinical_trial_results/gztr_CAM307.asp
- Wendtner CM, Ritgen M, Schweighofer CD et al, German CLL Study Group (GCLLSG). Consolidation with alemtuzumab in patients with chronic lymphocytic leukaemia (CLL) in first remission – experience on safety and efficacy within a randomised multicenter phase III trial of the German CLL Study Group (GCLLSG). Leukemia 2004;18:1093-101

Other Evidence

-

Lundin J et al, Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukaemia (B-CLL). Blood 2002;100:768-73

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Comments

The CCHOTA review (2005) assessed evidence of alemtuzumab's effectiveness in treating chemotherapy-refractory or relapsed patients (salvage therapy), patients with minimal residual disease (consolidation therapy), and previously untreated patients (first-line therapy). As salvage therapy alemtuzumab was associated with an overall response rate (ORR) of 31% to 42% and a complete response (CR) rate of 0% to 6%. As consolidation therapy (following initial chemotherapy), one small RCT (n=21) indicated more patients treated with alemtuzumab achieved remission compared with the control group at a median of seven months follow-up (p=0.048). Also progression-free survival (PFS) showed a significant difference (p=0.036) in favour of the alemtuzumab arm (Wendtner, 2004). As first-line therapy, a case series study (n=41) showed an ORR of 87% and CR of 19% (Lundin, 2002). Adverse treatment effects associated with alemtuzumab included 'first dose' flu-like symptoms and prolonged lymphopenia with a subsequent increased risk of infection.

Results from the CAM307 trial (n=297), a randomised, comparative study of alemtuzumab versus chlorambucil for previously untreated patients, showed a significant difference in favour of alemtuzumab in terms of progression-free survival, with reductions in the risk of disease progression or death of 42% (p=0.0001). Also a significantly increased ORR was seen in the alemtuzumab arm (alemtuzumab 83% vs. chlorambucil 55%, p<0.0001) along with a significantly higher CR (alemtuzumab 24% vs. chlorambucil 2%).

In conclusion results reported from the CAM307 trial appear promising. However much of the evidence of alemtuzumab's effectiveness in salvage and consolidation therapy takes the form of uncontrolled case series and should be interpreted with some caution as the possibility of bias (selection) cannot be ruled out.

Request Carried Out: June 2007

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ARIF Request

Allergies

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The Problem Submitted For ARIF To Advise Upon

What is the strength of the research evidence for the diagnosis and treatment of multiple allergies by provocation-neutralisation techniques (The Miller technique) and controlled environments?

Comments

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ARIF Request

Allogeneic Stem Cell Transplantation (reduced intensity) Nonmyeloblative Stem Cell Transplantation Metastatic Renal Cell Carcinoma

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the evidence of effectiveness of reduced intensity allogeneic stem cell transplantation in patients with metastatic renal cell carcinoma. Does it extend survival, improve quality of life, and what are the side effects?

Allogeneic stem cell transplantation was originally used as a rescue treatment for patients undergoing chemotherapy and radiotherapy for haematological malignancies such as leukaemia. It was observed that patients who developed the adverse event – Graft versus Host Disease (GVHD) had a lower relapse incidence, leading to the concept that the transplant had an antitumour effect - termed Graft versus Tumour effect (GVT) or Graft versus Leukaemia effect (GVL) involving donor T cells as an active component. Modification of the technique has led to a reduced intensity conditioning regimen before transplantation, known as nonmyeloablative stem cell transplantation, which has the aim to reduce transplant related toxicity whilst preserving the GVT effect. The main danger to the patient is severe GVHD, which can be fatal. There are high risks for patients undergoing this treatment because without GVHD there would be no GVT effect. The post transplant phase of treatment involves use of pharmacological immunosuppression to avoid graft rejection and the delayed administration of donor lymphocyte infusions to get the patients into a state of complete donor cell chimerism and thus optimal GVT (Childs).

Reviews Identified

- Blue Cross Blue Shield Association. Nonmyeloablative allogeneic stem-cell transplantation for malignancy.
- Artz AS, Kocherginsky M, Van Besien K. Order of patient entry influences outcomes for metastatic renal cell cancer after non-myeloablative allogeneic stem cell transplantation. British Journal of Haematology 2005;132:747-754
- Childs RW. Nonmyeloablative blood stem cell transplantation as adoptive allogeneic immunotherapy for metastatic renal cell carcinoma. Critical Reviews in Immunology 2001;21:191-203
- Roigas J, Johannsen M, Ringsdorf M, Massenkeil G. Allogeneic stem cell transplantation for patients with metastatic renal cell carcinoma. Expert Review of Anticancer Therapy 2006;6(10):1449-1458
- Gommersall L, Hayne D, Lynch C, Joseph J V, Arya M, Patel RHH. Allogeneic stem-cell transplantation for renal-cell cancer. Lancet Oncology 2004;5:561-567

- Barkholt L, Bregni M, Remberger M, Blaise D, Peccatori J. Allogeneic haematopoietic stem cell transplantation for metastic renal cell carcinoma in Europe. Annals of Oncology 2006;17:1134-1140

Other Evidence

Eleven case series studies and one retrospective case series from 21 centres in Europe.

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Comments

Of the 11 studies in the Roigas review, nine are also included in the review by Artz who used a systematic search to locate studies, therefore it is probably a reasonably comprehensive data set. Roigas reports tumour response whilst Artz reports survival. Neither review reports QoL. Overall, objective remissions occurred in 22% of patients (range 0-57%). Out of these patients 6 achieved a complete response (5%), with 50% of these coming from one study. Twenty-one patients (17%) had a partial remission. Overall, transplant-related mortality occurred in 21 (17%) patients. These rates are similar to those observed in the retrospective analysis reported by Barkholt, where objective responses were observed in 23% of patients (28/124) with 4 patients achieving a complete response and 24 a partial response. Median time to response was 150 days. Transplant-related mortality occurred in 20/124 patients (16%).

Artz reported an overall survival of 100 days achieved by 80% of patients (80/100) and a median survival of 12.3 months (range 1.1 to 27.3).

All of the data from the reviews comes from small case series and is therefore potentially subject to selection bias.

The general consensus of the reviews is that it is a very experimental high-risk procedure that should only be carried out in specialist centres or within the context of clinical studies. We were unable to locate any on-going trials.

Request Carried Out: May 2008

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ARIF Request

Alpha Agonists
Common Cold

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The Problem Submitted For ARIF To Advise Upon

What treatments have been shown to be effective in the treatment of the common cold?

Comments

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ARIF Request

Donepezil (Aricept)
Dementia - Alzheimer's Disease

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The Problem Submitted For ARIF To Advise Upon

What is the evidence on the effects/effectiveness of donepezil (Aricept)?

Comments

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ARIF Request

Donepezil
Alzheimer's Disease

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The Problem Submitted For ARIF To Advise Upon

Is there any new evidence of benefits for people with Alzheimer's Disease, from treatment with Donepezil, since the West Midlands Regional Anti-Dementia Drugs Working Party Recommendations and the establishment of the AD2000 trial? What are the current indications for treatment with Donepezil?

Comments

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ARIF request

Galantamine
Alzheimer's Disease

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of galantamine in the treatment of Alzheimer's disease (AD)?

Comments

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ARIF Request

Screening
Triple Test
Amniocentesis
Down's Syndrome

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the most effective and cost-effective way of screening for Down's syndrome in older women (>35 years).

More specifically:

- Does the triple test [human chorionic gonadotrophin (hCG) + alphafetoprotien (AFP) +unconjugated oestriol (uE3) tested between 14 to 20 weeks] and maternal age have lower detection rates and higher false positive rates in advanced maternal age (>35 years)?
- Is routine amniocentesis (without prior screening tests) still justified in advanced maternal age?

Down's syndrome is a congenital condition that arises when the affected baby has an extra copy of chromosome 21. The alternative name for the syndrome is trisomy 21. The main clinical features are intellectual impairment which can be severe in up to 80%. However, congenital malformations (particularly cardiac abnormalities), leukaemia, thyroid disorders, epilepsy and Alzheimer's disease are also associated with the condition. Birth incidence in England and Wales was 6.2/10,000 live and still births in 1998 (UK National Screening Committee 2003). The odds of having a baby with Down's syndrome increase with age. At 20 years the risk is approximately 1:1,440, at 35 years it is 1:338 and at 45 years it is 1:32.

Antenatal screening tests and diagnostic tests are available in the UK. This request investigated the triple test (a screening test) and amniocentesis (a diagnostic test).

The triple test is a blood test, which measures the levels of human chorionic gonadotrophin (hCG), alphafetoprotien (AFP) and unconjugated oestriol (uE3) between 14 to 20 weeks. The risk of the baby having Down syndrome is then calculated.

Amniocentesis is an invasive test, which involves inserting a needle into the uterus and removing a small amount of amniotic fluid from the sac surrounding the fetus (O'Connell R 2006). This is tested for chromosomal abnormalities by karyotyping (O'Connell 2006). Amniocentesis carries a 1% risk of miscarriage.

Reviews Identified

- O'Connell R., Stephenson M. Weir R. Screening strategies for antenatal Down syndrome screening. 253. 2006. New Zealand Health Technology Assessment (NZHTA).

Other Evidence

- UK National Screening Committee. Screening for Down Syndrome. In: Royal College of Obstetricians and Gynaecologists, editor. Antenatal care: routine care for the healthy pregnant woman. London: National Collaborating Centre for Women's and Children's Health & NICE; 2003. p.74-78.
- Cochrane Collaboration [accessed 19th December 2007] http://www3.interscience.wiley.com/homepages/106568753/DTAP1.pdf

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Comments

Our searches identified guidelines relating to the UK and several international systematic reviews looking at various aspects of Down's syndrome screening.

The most recent systematic review was undertaken by O'Connell and colleagues in 2006 and appears to be the most relevant to this request, although there is no data presented regarding the accuracy of the triple test in relation to maternal age. However, the Cochrane collaboration are currently undertaking a review on Down's Syndrome Screening, which may help with this question.

Overall the review by O'Connell and colleagues was well conducted, with searches undertaken between January 2000 and June 2006. Eleven studies were identified that investigated the detection rate and false positive rate of the accuracy of using maternal age alone with other screening strategies.

Study	DR (%) (95% CI)	FPR (%) (95% CI)
1st Trimester - using age alone		
Gasiorek-Wiens 2001	66.7 (60-73)	35.7 (35.0 - 36.3)
Schuchter 2002	64.3 (39.1 - 89.4)	12.8
von Kaisenberg 2002	52.6 (30.2 - 75.1)	35.7 (34.1 - 37.2)
Scott 2004	80	29
with an FPR at 5%		
Wapner 2003	32.8	5
Avgidou 2005	31.5 (24.6 - 37.6)	5
Montalvo 2005	21.1 (6.1 - 45.6)	5
2nd Trimester - using age alone		
Wald 2003a	≥ 35 years 51% (41-62) For a fixed 5% FPR 26% (17-35%) For a fixed 5% FPR + fetal loss adjustment 24% (17-35%)	14.3% (14.0 - 14.7) 5% 5%
Benn 2003	≥ 35 years 53.3%	17.1%
*Muller 2002a	≥ 38 years 9.5% (8-11)	1.6% (1.59 - 1.65)
|Muller 2003b (Twins)	≥ 37 years 27.3% (6-61)	6.5% (5.6 - 7.4)

DR (detection rate); FPR (false positive rate).
* Only 1.7% of the population were over 38 years as the national screening policy was to offer amniocentesis to these women, which may account for the very low DR and FPR.

The results from the review above show that using maternal age alone does not meet the standards set out by the national UK Screening Committee Guidelines 2003 (i.e. a detection rate of at least 60% with a false positive rate of 5% or less (benchmark 2004/5) and then a detection rate of greater than 75% with a false positive rate of less than 3% (benchmark April 2007).

Request Carried Out: December 2006

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ARIF Request

Exercise ECG
Angina

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The Problem Submitted For ARIF To Advise Upon

What are the implications of implementing the recommendation from the North of England Guideline Development Group (BMJ 1996; 312: 827-832) that all patients with angina should have an exercise ECG test?

Comments

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ARIF Request

Coronary Artery Bypass Grafting (CABG) and other Interventional Cardiological Procedures (PTCA)
Angina/Myocardial Infarction (MI) - Ischaemic Heart Disease (IHD)

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The Problem Submitted For ARIF To Advise Upon

What are the effects/effectiveness of CABG and other interventional cardiological procedures i.e. PTCA, specifically in relationship to prioritisation of those procedures?

Comments

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ARIF Request

Cardiac Rehabilitation
Coronary Heart Disease
Myocardial Infarction
Angina

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of cardiac rehabilitation particularly in respect to: mortality, tackling depression, return to work and ensuring continued access to GP for medication?

Cardiac rehabilitation is a multidisciplinary activity that aims to facilitate physical, psychological and emotional recovery and to enable patients to achieve and maintain better health. This is generally achieved through exercise, relaxation and health education, usually provided to groups of patients within a hospital or community setting. (As stated in reference below - Jolly K et al. Home-based cardiac rehabilitation compared with centre-based...).

See related web page which deals with uptake, adherence and access issues.

Reviews Identified

- NICE. Prophylaxis for patients who have experienced a myocardial infarction: drug treatment, cardiac rehabilitation and dietary manipulation - inherited guideline 2001. http://guidance.nice.org.uk/CGA/niceguidance/pdf/English
- North of England Evidence-based Guidelines Development Project, NICE. Prophylaxis for patients who have experienced a myocardial infarction: drug treatment, cardiac rehabilitation and dietary manipulation. 2001 http://guidance.nice.org.uk/CGA/guidance/pdf/English
- Clark AM, Hartling L, Vandermeer B, McAlister FA. Meta-analysis: secondary prevention programs for patients with coronary artery disease. Annals of Internal Medicine 2005;143(9):659-672
- Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. American Journal of Medicine 2004;116(10):682-692
- Jolliffe JA, Rees K, Taylor RS, Thompson D, Oldridge N, Ebrahim S. Exercise-based rehabilitation for coronary heart disease. Cochrane Database Systematic Reviews 2001;(1):CD001800
- Jolly K, Taylor RS, Lip GY, Stevens A. Home-based cardiac rehabilitation compared with centre-based rehabilitation and usual care: a systematic review and meta-analysis. International Journal of

Cardiology 2006; 111(3):343-351

Randomised Controlled Trials

- Jolly K, Lip GY, Taylor RS, Mant JW, Lane DA, Lee KW, et al. Recruitment of ethnic minority patients to a cardiac rehabilitation trial: the Birmingham Rehabilitation Uptake Maximisation (BRUM) study [ISRCTN72884263]. BMC Medical Research Methodology 2005;5(1):1

Other Evidence

- Taylor RS, Unal B, Critchley JA, Capewell S. Mortality reductions in patients receiving exercise-based cardiac rehabilitation: how much can be attributed to cardiovascular risk factor improvements? European Journal of Cardiovascular Prevention and Rehabilitation 2006;13(3):369-374

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Comments

The NICE Guidelines recommend that patients should be offered enrolment in a rehabilitation programme that has a prominent exercise component in it – evidence strength A. This recommendation was based on systematic review data which showed that mortality was reduced OR 0.74 (95% CI: 0.62, 0.88) for patients receiving cardiac rehabilitation with an exercise component. However, the trials are old, most dating to the 1980's when secondary preventative medicines were not in regular use. Also the review only included trials with an exercise component. It cannot be assumed that cardiac rehabilitation without an exercise component is not beneficial.

The most up-to-date systematic review was by Clark, with searches up to 2004. It included 63 trials: 17 were exercise programmes only, 19 were exercise plus other cardiac interventions such as education about risk factors and lifestyle counselling, and 23 were cardiac rehabilitation without exercise. Forty trials measured all cause mortality. For all trials there was a survival benefit in favour of the intervention (RR 0.85 (95% CI: 0.77, 0.94). The treatment effects did not differ substantially depending on the type of rehabilitation. Few studies have measured outcomes of depression, or return to work, however, 50% of all trials that investigated it found that patients receive better prescribing of efficacious medicines. The other two reviews by Taylor and Jolliffe just looked at cardiac rehabilitation with an exercise component. Both showed that cardiac rehabilitation reduced mortality and also reduced the number of MI reoccurences at 1 year. The review by Jolly 2006 found that home-based cardiac rehabilitation was not inferior to centre based cardiac rehabilitation.

In summary, all of the cardiac rehabilitation programmes seemed to be of some benefit, particularly in relation to mortality, despite a variation in the type of activities they included and the places where they were given. This indicates there is scope to offer tailored cardiac rehabilitation, which may help uptake and adherence. The effects of cardiac rehabilitation on other outcomes like depression need more research.

Request Carried Out: April 2007

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ARIF Request

Cardiac Rehabilitation, Access, Uptake
Coronary Heart Disease
Myocardial Infarction
Angina

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The Problem Submitted for ARIF to Advise Upon:

Has anyone designed and evaluated alternative approaches to cardiac rehabilitation which overcome access issues by ethnic minority groups or low income groups?

There is very low attendance at cardiac rehabilitation. In England in 2000 45-67% of eligible patients were referred for cardiac rehabilitation, with 27-41% attending outpatient cardiac rehabilitation. If all eligible patients are considered, this amounts to just 22-33% of the total eligible patients referred and 13-20% of the total eligible patients attending cardiac rehabilitation. (Beswick AD et al 2004) Referral and attendance were particularly low in women and older people, with the suggestion that patients from ethnic minorities and those with angina or heart failure were also less likely to attend.

See related web page - Effectiveness of Cardiac Rehabilitation

Reviews Identified

- Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR, et al. Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups. Health Technology Assessment 2004; 8(41)
- Rees K, Victory J, Beswick AD, Turner SC, Griebsch I, Taylor FC, et al. Cardiac rehabilitation in the UK: uptake among under-represented groups. Heart 2005;91(3):375-376
- Cooper AF, Jackson G, Weinman J, Horne R. Factors associated with cardiac rehabilitation attendance: a systematic review of the literature. Clinical Rehabilitation 2002;16(5):541-552

OtherEvidence

- Cooper AF, Jackson G, Weinman J, Horne R. Factors associated with cardiac rehabilitation attendance: a systematic review of the literature. Clinical Rehabilitation 2002;16(5):541-552
- Jolly K, Greenfield SM, Hare R. Attendance of ethnic minority patients in cardiac rehabilitation. Journal of Cardiopulmonary Rehabilitation 2004;24(5):308-312

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Comments

There is little data collected about the characteristics of people attending and those who do not attend or complete cardiac rehabilitation schemes. Survey data has found that providers in the UK do actively promote their schemes with 34% actively promoting their services specifically to ethnic minority groups (Rees et al 2005). General initiatives to promote uptake and adherence include follow-up telephone calls, free transport, home visits, and personalised invitations. Specific initiatives for under represented groups included individualised classes, buddy systems and allowing the attendance of a relative or spouse. However, most of these initiatives are unevaluated.

Request Carried Out: April 2007

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ARIF Request

Enhanced External Counterpulsation
Angina Chronic Refractory

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

To find information regarding the clinical effectiveness of treatment of enhanced external counterpulsation (EECP) in patients with angina which cannot be relieved by conventional treatment.

The primary indication for EECP treatment is chronic stable angina. EECP may be used as a potential treatment modality for angina patients, in whom invasive revascularization procedures do not offer a survival benefit, or as an alternative to PTCA or CABG. EECP may be particularly useful in patients considered high risk for revascularization procedures or in whom revascularization is not technically possible.

Reviews Identified

- McKenna C, McDaid C, Suekarran S, Hawkins N, Claxton K, Light K et al. Enhanced external counterpulsation for the treatment of stable angina and heart failure: a systematic review and economic analysis. Health Technology Assessment 2009;13:(24):13
- Amin F, Al HA, Civelek B, Fedorowicz Z, Manzer BM. Enhanced external counterpulsation for chronic angina pectoris. Cochrane Database of Systematic Reviews: Protocols. Cochrane Database of Systematic Reviews 2008 Issue 3. Chichester (UK): John Wiley & Sons, Ltd; 2008

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Comments

Standard ARIF searches identified one HTA report (McKenna 2009), and one Cochrane review protocol (Amin 2008).

The HTA aimed to determine the clinical and cost-effectiveness of EECP compared with usual care and placebo for refractory stable angina and heart failure, and to undertake analyses of the expected value of information to assess the potential value of future research on EECP.

The HTA was very well conducted. Searches were up to March 2008 and five trials met its inclusion criteria, four of which were relevant to this request: one RCT, two CCTs and one observational study, all published between 1999 and 2008.

The RCT assessed the safety and efficacy of EECP in patients with chronic stable angina. The trial was powered (80%) to detect a 45-second difference in exercise duration resulting in 72 patients assigned to EECP treatment and 67 to sham-EECP. However, the clinical relevance of the power calculation base is questionable; it would require a larger sample size to detect between group differences in the other more clinically relevant outcome measures rather than surrogate outcome measures, such as angina episodes and nitroglycerin (NTG) use. All of the patients were classified as I (26%), II (50%) or III (24%) chronic stable angina according to the Canadian Cardiovascular Society (CCS) Classification, with I being the least severe. The review authors pointed out that the results of this trial were unlikely to be generalised to patients with truly severe refractory angina.

Outcomes were assessed at the end of the treatment. Of the effectiveness outcomes measured, only time to ≥ 1-mm ST segment depression reached statistical significance which favoured EECP. However this was not an Intention to Treat (ITT) calculation being based on only around 80% of the original patients thus likely to be subject to attrition bias and potentially an overestimation of the treatment effect. Exercise duration, angina episodes, and NTG use did not show significant changes from baseline. Health related quality of life (HRQoL) assessed at 12 month follow-up showed limited benefit with EECP; this was however based on only about half of the original patients that were evaluable. Assessment of adverse events, based on ITT calculation, showed significantly more patients had adverse events in the EECP group than in the control.

Sample size in the two CCTs was only 25 and 40 respectively, giving a combined total of 35 patients treated with EECP and 30 treated with usual care. The observational study was a comparison of two registries, one for EECP with 323 patients and the other for percutaneous coronary intervention (PCI) with 428 patients. The three studies were all judged to have high risk of selection bias and measurement bias. In the CCTs, CCS classification and NTG use from baseline to the end of the treatment showed some significant improvement with EECP compared to no significant changes with the usual care. However, in the observational study at 12 month follow-up EECP was significantly outweighed by PCI in improving angina symptoms and CCS classification.

Overall, data from the review suggest that evidence on the effectiveness of EECP for chronic stable angina is sparse and weak. It should be noted that there are potentially adverse events associated with EECP. Decisions on the use of EECP would rely on firm evidence from further better quality RCTs regarding the effectiveness and adverse effects with EECP in this population. NICE have published a draft scope for a clinical practice guideline on the management of stable angina; the anticipated publication date is July 2011.

Request Carried Out: September 2009

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ARIF Request

Angiotensin II Receptor Antagonists Blood Pressure Lowering

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The Problem Submitted For ARIF To Advise Upon

What is the relative effectiveness of the different angiotensin II receptor antagonists (AIIRAs) in lowering blood pressure?

Comments

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ARIF Request

In-patient Treatment
Out-patient Treatment
Anorexia Nervosa
Eating Disorders

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

- How does the effectiveness of in-patient treatment compare to (intensive) out-patient treatment for patients with severe or moderate anorexia nervosa?
- What type of out-patient treatment is most effective?

Anorexia nervosa is associated with significant morbidity and mortality. Treatment generally includes a variety of interventions of varying intensity (pharmacological, dietary advice and individual, group and family psychotherapies). These may be offered in an in-patient or out-patient setting. Patients may also move from one setting to another during the course of their treatment. There appears to be a shift towards offering more out-patient based treatments, but the evidence base for this is uncertain.

Reviews Identified

- Meads C, Gold L, Burls A, Jobanputra P. In-patient versus out-patient care for eating disorders. University of Birmingham, Department of Public Health and Epidemiology 1999;58.
- Fisher CA, Hetrick SE, Rushford N. Family therapy for anorexia nervosa. Family therapy for anorexia nervosa. Cochrane Database of Systematic Reviews 2010 (4): CD004780 http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004780/frame.html
- Hay P, Bacaltchuk J, Claudino A, Ben-Tovim D, Yong PY, Hay P, et al. Individual psychotherapy in the outpatient treatment of adults with anorexia nervosa. Cochrane Database of Systematic Reviews 2003;(4):CD003909 http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003909/frame.html

Randomised Controlled Trials

- Gowers S, Clark A, Roberts C, Griffiths A, Edwards V, Bryan C, et al. Clinical effectiveness of treatments for anorexia nervosa in adolescents. British Journal of Psychiatry 2007;191:427-435 http://bjp.rcpsych.org/cgi/reprint/191/5/427
- Byford S, Barrett B, Roberts C, Clark A, Edwards V, Smethurst N, et al. Economic evaluation of a randomised controlled trial for anorexia nervosa in adolescents. British Journal of Psychiatry 2007; 191:436-440 http://bjp.rcpsych.org/cgi/reprint/191/5/436
- Crisp AH, Norton K, Gowers S, Halek C, Bowyer C, Yeldham D, et al. A controlled study of the

effect of therapies aimed at adolescent and family psychopathology in anorexia nervosa. British Journal of Psychiatry 1991;159:325-333 http://bjp.rcpsych.org/cgi/reprint/159/3/325

- Gowers S, Norton K, Halek C, Crisp AH. Outcome of out-patient psychotherapy in a random allocation treatment study of anorexia nervosa. International Journal of Eating Disorders 1994; 15(2):165-177

Other Evidence

- Current Controlled Trials. A multiCentre randomised trial of the outcome, acceptability and cost-effectiveness of family therapy and multi-family day treatment compared with inpatient care and outpatient family therapy for adolescent anorexia nervosa. http://www.controlled-trials.com/ISRCTN11275465

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Comments

In-versus out-patient treatment:

Searches identified only one systematic review from 1999, which directly addressed the question of interest. A further five reviews and two guidelines were found, which partially addressed the question. Upon closer scrutiny of all reviews, it was found that there was limited evidence only in the form of two randomised controlled trials (RCTs, n=90 and n=170). These were appraised in detail.

Results suggested that out-patient treatment is similarly effective to in-patient treatment in young (mainly female) patients with a BMI of around 15. Both trials are fairly small, and both suffer from lack of patient compliance and/or drop-outs, therefore results must be treated with some caution. The larger of the trials had a follow-up of two years only, so it is not known what the long-term outcomes are. The specific nature of the treatments offered in the trials should be taken into account when interpreting the results. It is not known whether the risk of death differs according to treatment.

One ongoing trial comparing in- and out-patient therapy in adolescents was indentified, no published results were identified and no further information could be obtained.

Different types of out-patient treatment:

Two well conducted, recent systematic reviews were identified (searches completed or updated in 2008), which are likely to have identified the majority of relevant studies. One included 13 RCTs and reviewed the effectiveness of family therapies compared to ‘usual’ treatment, psychological treatment or different types of family therapy; the other included 9 RCTs and looked at psychological treatments compared to ‘usual’ treatment, dietary advice or other psychological interventions.

All included RCTs were small (between 13 and 90 participants) and at risk of bias. Reporting of results was frequently inconsistent or incomplete. A variety of treatments were compared across trials and many different outcome measures were used, so only few (or one) trials contributed to a particular result. Results suggest that family therapy may be more effective compared to standard out-patient treatment in the short term, but there appears to be little advantage of family therapy over other forms of psychological interventions. Different types of family therapy appear to be of similar efficacy. There is limited evidence to suggest that a specific psychotherapy may be more effective than no treatment or treatment as usual. There is insufficient evidence to determine the relative effectiveness of different psychological therapies. No conclusions regarding the likelihood of deaths with different treatments could be drawn from these reviews. Given that the trials were most likely underpowered, there is a need for a large, well-conducted RCT in this area in order to show any potential differences in treatment effects.

Request Carried Out: June 2010

To see full report - click here

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ARIF Request

Anterior Cruciate Ligament (ACL) Tears of Knee Surgery - Repair and Augmented Repair

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The Problem Submitted For ARIF To Advise Upon

What are the effects and effectiveness of surgical repair of acute tears of the anterior cruciate ligament (particular emphasis on incomplete tears where there is little instability of the knee)?

Comments

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ARIF Request

Anthrosophical Medicine
Chronic Fatigue Syndrome

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The Problem Submitted For ARIF To Advise Upon

What is the evidence on effectiveness of anthroposophical medicine in the treatment of chronic fatigue syndrome (CFS)?

Comments

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ARIF Request

Antibiotics
Bronchiolitis

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The Problem Submitted For ARIF To Advise Upon

What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Comments

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ARIF Request

Antibiotics
Pelvic Inflammatory Disease

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The Problem Submitted For ARIF To Advise Upon

What is the evidence on effectiveness of antibiotic regimes in the treatment of pelvic inflammatory disease (PID)?

Comments

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ARIF Request

Prescribing Antibiotics Antimicrobials

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The Problem Submitted for ARIF to Advise Upon:

Interventions to improve prescribing practice of antibiotics in primary care and ambulatory/community settings with the aim of reducing inappropriate prescribing.

Growing antibiotic resistance is a major concern. By understanding the effectiveness of different approaches to reducing inappropriate antibiotic prescribing, particularly in primary care and ambulatory/community settings, is an important contributor to any strategy to reduce the emergence of antibiotic resistant strains of bacteria.

Reviews Identified

- Spurling GKP, Del Mar CB, Dooley L, Foxlee R. Delayed antibiotics for respiratory infections. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD004417
- Arroll B, Kenealy T, Kerse Ngaire. Do delayed prescriptions reduce antibiotic use in respiratory tract infections – a systematic review. British Journal of General Practice 2003 53, 871-877
- Steinman MA, Ranji SR, Shojania KG, Gonzales R. Improving antibiotic selection: a systematic review and quantitative analysis of quality improvement strategies. Medical Care 2006;44(7):617-628
- von Gunten V, Reymond J, Beney J. Clinical and economic outcomes of pharmaceutical services related to antibiotic use: a literature survey. Pharmacy World and Science 2007;29:146-163
- Patel SJ, Larson EL, Kubin CJ, Saiman L. A review of antimicrobial control strategies in hospitalized and ambulatory pediatric populations. Pediatric Infectious Disease Journal 2007;26(6):531-537
- Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD003539

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Comments

Six recent reviews have attempted to answer the question - which interventions improve antibiotic prescribing practice in primary care and ambulatory/community settings?

All have focused on different aspects of interventions, populations, comparators and outcomes. This makes it difficult to contrast and compare the reviews. It also highlights the difficulties of undertaking systematic reviews on complex and varied interventions that are open to interpretation and which produce data that cannot reasonably be meta-analysed due to clinical and methodological heterogeneity.

From previous reviews, successful interventions seem to be those that are for specific diseases, specific antibiotics and aimed at specific prescribers. Active educational sessions also seem to have been successful, although audit and feedback appears to have had a detrimental affect. However, progress in audit and feedback techniques may have improved the situation in more up-to-date studies. Accounting for cultural differences also seems to play a role as to the success of interventions particularly in educational interventions. Very few of the included studies have investigated the wider question of the effects of the interventions on microbial resistance and even fewer studies have investigated any adverse events on patients who receive inappropriate antibiotics.

Request Carried Out: April 2008

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ARIF Request

Probiotics
Antibiotic Associated Diarrhoea
Diarrhoea (Antibiotic Associated)

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The Problem Submitted for ARIF to Advise Upon:

Are probiotics, particularly Saccharomyces boulardii, effective in reducing antibiotic associated diarrhoea?

Prevention of antibiotic associated diarrhoea needs to be distinguished from treatment of established antibiotic diarrhoea, such as that associated with Clostridium difficile.

Reviews Identified

- Cremonini F, Di Caro, Nista EC et al. Meta-analysis: the effect of probiotic administration on antibiotic associated diarrhoea. Alimentary Pharmacology & Therapeutics 2002;16(8):1461-1467
- D'Souza AL, Rajkumar C, Cooke J et al. Probiotics in the prevention of antiobiotic associated diarrhoea. BMJ 2002;324:1361-1364

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Comments

Both systematic reviews of RCTs are well conducted with meta-analyses indicating that probiotics are effective in preventing antibiotic associated diarrhoea. Evidence concerning treatment of C difficile associated diarrhoea is not addressed, but the review by D'Souza indicates that there is at least one RCT addressing this problem.

The possibility that probiotics represent a highly cost-effective intervention is raised by the effectiveness evidence, given that the cost of the intervention is low and complication prevented being potential seriousness in critically ill patients. This however requires formal assessment of health economic impact, which does not appear to have been done.

Request Carried Out: October 2004

Update: July 2006

A Regional Evaluation Panel (REP) Report was completed in November 2005. This updates

and extends the systematic reviews identified and makes an assessment of the cost literature. The West Midlands Regional Evaluation Panel "recommended" use of probiotics for prevention of antibiotic associated diarrhoea on the basis of the report

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ARIF Request

Anticholinergics
Common Cold

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The Problem Submitted For ARIF To Advise Upon

What treatments have been shown to be effective in the treatment of the common cold?

Comments

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ARIF Request

Anti-Coagulation Clinics

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The Problem Submitted For ARIF To Advise Upon

Siting and staffing of anti-coagulation clinics; what is the variation in effectiveness and cost-effectiveness?

Comments

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ARIF Request

Antihistamines
Common Cold

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The Problem Submitted For ARIF To Advise Upon

What treatments have been shown to be effective in the treatment of the common cold?

Comments

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ARIF Request

Antihistamines and Decongestants
Glue Ear

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The Problem Submitted For ARIF To Advise Upon

What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Comments

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ARIF Request

Antimicrobial Drugs
Glue Ear

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The Problem Submitted For ARIF To Advise Upon

What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Comments

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ARIF Request

Anti-vascular Endothelial Growth Factor Agents
Anti VEGF
Avastin
Lucentis
Ranibizumab
Bevacizumab
Vascular Endothelial Growth Factor
Eye Conditions
VEGF

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The Problem Submitted for ARIF to Advise Upon:

What is the quantity and quality of the evidence regarding ranibizumab (Lucentis) and bevacizumab (Avastin) in the treatment of eye conditions (excluding age-related macular degeneration), thought to be related to vascular endothelial growth factor?

Reviews Identified

- Andriolo RB, Puga ME, Belfort JR, Atallah AN. Bevacizumab for ocular neovascular diseases: a systematic review. Sao Paulo Medical Journal 2009;127(2):84-91
- Parravano M, Menchini F, Virgili G. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for diabetic macular oedema. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD007419. DOI: 10.1002/14651858.CD007419.pub2.
- Martinez-Carpio PA, Bonafonte-Marquez E, Heredia-Garcia CD, Bonafonte-Royo S. Efficacy and safety of intravitreal injection of bevacizumab in the treatment of neovascular glaucoma: systematic review. Archivos de la Sociedad Española de Oftalmología2008; 83(10):579-588
- Micieli JA, Surkont M, Smith AF. A systematic analysis of the off-label use of bevacizumab for severe retinopathy of prematurity. American Journal of Ophthalmology 2009;148(4):536-543

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Comments

Four up-to-date and well conducted reviews were identified, which altogether included five RCTs, and 32 case reports/series. Most of the studies were small, with heterogeneous populations, intervention and outcomes. None of the published literature had investigated ranibizumab (Lucentis). Four of the

RCTs were undertaken in patients with diabetic retinopathy, the fifth in patients with diabetic macular oedema. Of the case reports/series, 26 were in patients with neovascular glaucoma and nine in babies with retinopathy of prematurity.

All of the review authors conclude that because of the paucity of trial data, the role of anti-VEGF agents in the eye conditions so far studied is very uncertain. There is a need for larger more robust studies to be conducted to address this uncertainty.

NIne ongoing trials were also identified. One (NCT00545870) is a head-to-head trial of bevacizumab versus ranibizumab, which is currently recruiting patients with diabetic retinopathy. Of the remaining trials five are investigating ranibizumab, two bevacizumab and one has not specified the anti-VEGF agent.

In conclusion, there is a paucity of evidence regarding the use of bevacizumab and ranibizumab in eye conditions that are caused by increased levels of VEGF. A number of ongoing trials in progress are due to report, therefore we would suggest that this topic is revisited towards the end of 2010.

Request Carried Out: January 2010

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ARIF Request

Arthroscopic Surgery
Hip Impingement
Femoro-acetabular Impingement
Pain

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The Problem Submitted for ARIF to Advise Upon:

What is the clinical effectiveness and cost-effectiveness of arthroscopic treatment for young people (of working age) with hip impingement (femoro-acetabular impingement) and/or hip pain and what group(s) of patients may be expected to be benefit from it?

Arthroscopic femoro-acetabular surgery, which is less invasive compared with traditional open surgery, has been used for hip impingement and hip pain, to improve pain, range of movement, resumption of activities, etc for patients.

Reviews Identified

- Bedi A, Chen N, Robertson W, Kelly BT. Systematic review: the management of labral tears and femoroacetabular impingement of the hip in the young, active patient. Arthroscopy 2008;24(10):1135-1145
- National Institute for Health and Clinical Excellence. Interventional procedures overview of arthroscopic femoro-acetabular surgery for hip impingement syndrome. London: NICE; 2006. Interventional Procedures Programme, IP365. Available from http://www.nice.org.uk/IPG213
- National Institute for Health and Clinical Excellence. Arthroscopic femoro-acetabular surgery for hip impingement syndrome. London: National Institute for Health and Clinical Excellence (NICE); 2007. Available from http://www.nice.org.uk/IPG213

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Comments

One systematic review and one NICE guidance with its associated documents were identified.

The systematic review (Bedi 2008) aimed to assess studies on surgical treatment of labral tears and femoroacetabular impingement (FAI). Searches were up to May 2008. The analysis was descriptive.

However, the results were presented in a format that makes the results difficult to interpret.

The NICE document contained a rapid systematic review. It aimed to assess the safety and efficacy of arthroscopic femoro-acetabular surgery for hip impingement syndrome. The review is of reasonable methodological quality. Searches were up to September 2006.

The main limitation with the data identified in both reviews was that it had been derived from retrospective case series. Therefore, the effectiveness of arthroscopic surgery for hip impingement and/or hip pain compared with any conventional approach cannot be determined overall and within any particular subgroups. Neither review evaluated cost-effectiveness of this procedure.

Request Carried Out: February 2010

To see full report - click here

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ARIF Request

Combined use of Aspirin, Clopidogrel and Warfarin
Stents
Percutaneous Coronary Intervention (PCI)
Cardiovascular Disease

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in March 2009.

The Problem Submitted for ARIF to Advise Upon:

ARIF were asked to look at the evidence base to assess the effectiveness and safety for the combination of antiplatelet therapy (aspirin and clopidogrel) plus warfarin (an anticoagulant) in patients receiving a stent for coronary disease, particularly in relation to how patients are monitored.

Reviews Identified

- Hermosillo AJ, Spinler SA. Aspirin, clopidogrel, and warfarin: is the combination appropriate and effective or inappropriate and too dangerous? Annals of Pharmacotherapy 2008;42:790-805
- Arab D, Lewis B, Cho L, Steen L, Joyal D, Leya F. Antiplatelet therapy in anticoagulated patients requiring coronary intervention. Journal of Invasive Cardiology 2005;17:549-54

Primary Studies

- Anand S, Yusuf S, Xie C, Pogue J, Eikelboom J, Budaj A et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. New England Journal ofMedicine 2007;357:217-27

Other Evidence

- Vik-Mo H, Slette M, Hegbom K. Antithrombotic therapy after percutanous coronary intervention with stenting. Tidsskrift for den Norske lægeforening 2008;128:436-9
- Lip GY,.Karpha M. Anticoagulant and antiplatelet therapy use in patients with atrial fibrillation undergoing percutaneous coronary intervention: the need for consensus and a management guideline. Chest 2006;130:1823-7

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Comments

We focused on the most recent review by Hermosillo AJ et al 2008. It contained some elements of a systematic review methodology but read like an narrative review. Searches (Medline only) were up to 2007.

The review identified nine primary studies: two case series, six retrospective cohort studies, and one large RCT. All of the studies, except the RCT, involved patients who had co-morbidities that required warfarin treatment and all of the studies reported bleeding events.

Obviously caution is required in interpreting the results from case series and cohorts given their inherent potential for bias and confounding factors. Despite this there does seem to be a trend towards increased bleeding episodes in patients on combined therapy of aspirin, clopidogrel and warfarin, which may have implications regarding how patients are monitored when taking this combination.

We critically appraised the RCT Anand et al 2007, which included 2161 patients in 80 centres worldwide, although none were in the UK. The intervention consisted of just one antiplatelet (mainly aspirin) combined with warfarin, the control just took an antiplatelet. All the patients had peripheral artery disease and none had comorbidities that required the use of warfarin. There were no differences in cardiovascular outcomes but there was a statistically significant increase in bleeding outcomes in the intervention group, however, the number of bleeding events was quite small, for example for fatal bleeding the RR was 3.34 (95% CI 0.92, 12.1) with the number of events at 10 (0.9%) for the intervention group and 3 (0.3%) for the control group.

No information was given in the review nor in the published reports of the RCT regarding monitoring, which is a potential confounder within these studies, particularly given that in many of the studies the dose may have varied, as it was left to the prescribing physician to set the therapeutic dose.

In conclusion, the data from both the review and RCT suggest a trend toward increased bleeding in patients who take an antiplatelet combined with an anticoagulant. Therapeutic effects, regarding thrombus formation and cardiovascular events appears to be less studied, with mixed benefits reported. Expert opinion suggests that decisions to use aspirin, clopidogrel and warfarin, should take into account the risks and benefits for each patient.

Request Carried Out: March 2009

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ARIF Request

Assisted Ventilation
Bronchiolitis

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The Problem Submitted For ARIF To Advise Upon

What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Comments

This request was carried out more than four years ago and has not been updated since. The articles identified may no longer be the best available and therefore the commentary may be out of date. As a precaution the information has been removed from this page.

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ARIF Request

Atenolol
Betablocker
Hypertension

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The Problem Submitted For ARIF To Advise Upon

What is the quality of a recent systematic review (Carlberg et al, 2004) assessing the effect of atenolol on cardiovascular morbidity and mortality in hypertensive patients?

Comments

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ARIF Request

Dyadic Developmental Psychotherapy Attachment Disorder 'Looked After' Children

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The Problem Submitted For ARIF To Advise Upon

What is the evidence on the effectiveness/cost-effectiveness of dyadic developmental psychotherapy in the treatment of children with attachment disorders and particularly the effect on adoption rates amongst 'looked after' children?

Comments

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ARIF Request

Ritalin
Attention Deficit Hyperactivity Disorder

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The Problem Submitted For ARIF To Advise Upon

What is the benefit of continuing treatment with Ritalin in adulthood for patients who have been treated with Ritalin (as children) for ADHD?

Comments

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ARIF Request

Audiological Screening
Down's Syndrome

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The Problem Submitted For ARIF To Advise Upon

What is the strength of the evidence that screening adults with Downs Syndrome for hearing impairment is of benefit and is cost-effective?

Comments

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ARIF Request

Autoinflation
Glue Ear

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The Problem Submitted For ARIF To Advise Upon

What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Comments

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ARIF Request

Automated Peritoneal Dialysis
Renal Failure

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The Problem Submitted For ARIF To Advise Upon

Are there any recognised criteria for the use of automated peritoneal dialysis and is it a cost-effective form of treatment for end stage renal failure?

Comments

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ARIF Request

Gastrointestinal Disease
Autism

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The Problem Submitted For ARIF To Advise Upon

What is the extent of the association between autism and chronic gastrointestinal disease?

Comments

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ARIF Request

Gluten-Free Diets
Autism

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of gluten-free diets for autistic children?

Comments

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ARIF Request

Sensory Integration Therapy Autism

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The Problem Submitted For ARIF To Advise Upon

What is the evidence on the effectiveness of sensory integrated therapy provided by occupational therapists to children with autism? In particular, is there any evidence for the most effective number of sessions or length of treatment?

Sensory integrated therapy involves using pieces of equipment to provide sensory awareness of one's own body and position. The aim is to encourage children to make adaptive responses to the stimuli in order to improve how the brain processes and organises sensory input.

Comments

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ARIF Request

Autologous Stem Cell Transplant
Stem Cell Transplant
Systemic Sclerosis

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of autologous stem cell transplantation for systemic sclerosis?

Comments

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ARIF Request

Automated Implantable Cardioverter Defibrillators Cardiac Arrhythmias

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The Problem Submitted For ARIF To Advise Upon

What is known about the effectiveness and cost-effectiveness of automatic implantable cardioverter defibrillators (ICD) in the management of ventricular arrhythmias?

Comments

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ARIF Request

Awareness Campaigns
Health Promotion
Cancer

Table of Contents

WARNING
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The Problem Submitted for ARIF to Advise Upon:

Do awareness campaigns targeted at the public or GPs which are aimed at reducing delays to diagnostic and specialised health care services, improve survival for cancer?

Patient delay (either presentation to primary care or referral for diagnostic tests) has been seen as a factor for poor survival in some cancers. However, cancer is an uncommon event in the life of a patient and in the work of a GP. A GP may only see about 7.5 new cancer cases per year, making diagnosis difficult. This is further compounded by the non specific symptoms such as headache, low back pain and fatigue which occurs in many patients consulting primary care.

Reviews Identified

Three relevant publications were identified:

- Referral guidelines for suspected cancer in adults and children. Clinical guideline no. 27. Developed by the National Collaborating Centre for Primary Care June 2005. Available from: http://www.nice.org.uk/Guidance/CG27/Guidance/pdf/English
- Naldi L, Buzzetti R, Cecchi C, Baldwin L, Battistutta D, Benvenuto C, et al. Educational programmes for skin cancer prevention. Cochrane Reviews: Protocol. Cochrane Database of Systematic Reviews 2004 Issue 1. Chichester (UK): John Wiley & Sons, Ltd; 2004. http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004686/frame.html

Other Evidence

- Newsletter. National Awareness and Early Diagnosis Initiative (NAEDI) Newsletter July 2008 Available from: www.ncri.org.uk [accessed 9-9-08] or naedi@cancer.org.uk

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Comments

The review by the National Collaborating Centre for Primary Care fed into NICE guidelines about

referral of patients with first episode of suspected cancer presenting in primary care (see CG27 Referral for suspected cancer: NICE guideline). 9 primary studies and 5 systematic reviews examined interventions for prevention of delay.

Referral guidelines, educational outreach visits, reminders, and multifaceted interventions (e.g. audit, reminders, local consensus, marketing) have some positive effect on referral practices for patients with cancer. However, overall, the quality and quantity of evidence is not sufficient to inform practice. It is recommended that an RCT should be undertaken.

The Newsletter followed the first Steering Group meeting of NAEDI that took place on 20th June 2008. Seven workstreams are described, three of which are relevant:

1. A review of the evidence base on links between early diagnosis and survival.
2. Interventions to promote early presentation, focusing on evaluation and dissemination.
3. Interventions in primary care and understanding the nature of primary care delay.

NAEDI hope to set up a national database of local interventions designed to improve cancer awareness and early detection. A conference is planned in London for the 21st November 2008.

Request Carried Out: October 2008

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ARIF Request

Baclofen (Continuous Intrathecal) Spasticity

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in July 2002 and Updates in 2003 and 2006.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of intrathecal baclofen for treating patients with severe spasticity/mobility problems?

Spasticity is abnormally increased tone in muscles causing pain or difficulty moving. Where the person with spasticity is dependent on others to help with care, the increased tone makes the carer's task more difficult. Spasticity can result from a number of different medical conditions, but two types are commonly recognised:

- Spasticity of spinal origin e.g. resulting from spinal cord injury or multiple sclerosis
- Spasticity of cerebral origin e.g. resulting from cerebral palsy

Baclofen is a drug which reduces tone. However, although effective when taken by mouth its effects are difficult to control. Injecting small amounts of baclofen directly into the space around of the spinal cord (continuous intrathecal baclofen) has been explored as a way of overcoming the limitations of oral baclofen.

This request deals with evidence on effectiveness of continuous intrathecal baclofen generally, irrespective of the cause of spasticity. A related request looks specifically at evidence on its use in children with spasticity resulting from cerebral palsy. There is a separate web page updating this advice on general effectiveness of intrathecal baclofen (see below).

Reviews Identified

- Sampson FC, Hayward A, Evans G, Touch S, Morton R, Vloeburghs M, Playford D, Collett B J, Critchley P. The effectiveness of intrathecal baclofen in the management of patients with severe spasticity. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield; 2000. Guidance Note for Purchasers:00/01.
- Shakespeare DT, Boggild M, Young C. Anti-spasticity agents for multiple sclerosis (Cochrane Review). In: The Cochrane Library, Issue 2, 2002. Oxford: Update Software. .
- Taricco M, Adone R, Pagliacci C, Telaro E. Pharmacological interventions for spasticity following spinal cord injury. In: The Cochrane Library, Issue 2, 2002. Oxford: Update Software.

There are protocols for further directly and indirectly relevant Cochrane reviews.

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Comments

We identified a number of systematic reviews on the treatment of patients with spasticity that wholly or in part assess the evidence base underlying the use of intrathecal baclofen to treat spasticity associated with a variety of conditions. The most broadly relevant of these is the review by Sampson et al. All the reviews were generally well conducted. The conclusions drawn are that although intrathecal baclofen appears to be a promising technique the volume of evidence is limited. The small number of trials enroll small numbers of patients and do not aim to assess the comparative efficacy/effectiveness of intrathecal baclofen against alternative interventions. They have short duration of follow up and rarely measure patient-centered or quality of life related outcomes. Further robust research is required to address these limitations.

Request Carried Out: July 2002

Updated: April 2003

Updated: May 2006 New web page with further update see Bacolofen (Continuous Intrathecal)/Spasticity - Any Cause

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ARIF Request

Baclofen (Continuous Intrathecal)
Spasticity of Cerebral Origin
Cerebral Palsy

Table of Contents

WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of continuous intrathecal baclofen for treating children with severe spasticity/mobility problems caused by cerebral palsy?

Spasticity is abnormally increased tone in muscles causing pain or difficulty moving. Where the person with spasticity is dependent on others to help with care, the increased tone makes the carer's task more difficult. Spasticity can result from a number of different medical conditions, but two types are commonly recognised:

- Spasticity of spinal origin e.g. resulting from spinal cord injury or multiple sclerosis
- Spasticity of cerebral origin e.g. resulting from cerebral palsy

Baclofen is a drug which reduces tone. However, although effective when taken by mouth its effects are difficult to control. Injecting small amounts of baclofen directly into the space around of the spinal cord (continuous intrathecal baclofen) has been explored as a way of overcoming the limitations of oral baclofen.

This request deals with evidence on effectiveness of continuous intrathecal baclofen in children with spasticity resulting from cerebral palsy. A related request looks at evidence on its effectiveness generally, irrespective of the cause of spasticity. This request on general effectiveness has been further updated (see below).

Reviews Identified

- Sampson FC, Hayward A, Evans G, Touch S, Morton R, Vloeburghs M, Playford D, Collett B J, Critchley P. The effectiveness of intrathecal baclofen in the management of patients with severe spasticity. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield; 2000. Guidance Note for Purchasers:00/01.

In-progress Review

- Howard, DC. Anti-spastic medication for spasticity in cerebral palsy (Protocol for a Cochrane Review). In: The Cochrane Library, Issue 2, 2002. Oxford: Update Software

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Comments

The review by Sampson et al is generally systematic in approach. However, whilst cautiously optimistic about the use of continuous intrathecal baclofen in general, it is more guarded about the effectiveness in children with spasticity resulting from cerebral palsy, because the evidence on effectiveness is very limited indeed. The committee assessing the report by Sampson et al in 2000 recommended that, “Children receiving continuous intrathecal baclofen should be offered treatment within the context of a national study.”

Ultimately it is hoped that the Cochrane Review in progress will provide a further update on the effectiveness of continuous intrathecal baclofen, particularly in relation to other treatments. In lieu of this, ARIF identified whether any further trials appeared to have been conducted since the Sampson et al review was completed. We identified and appraised a number of possible new trials (further details available on request). On close examination these were not true randomised controlled trials and add little to the quantity and quality of the research evidence available in the review by Sampson et al particularly with respect to impact on function in the children affected. Our view is thus that the advice appended to the Sampson et al review in 2000 should stand.

Request Carried Out: January 2003

This web-page replaces a previous page, detailing a request carried out on the same subject in January 1999/ updated July 2000. Although the details and text have changed, the conclusions remain similar.

Updated: May 2006 New web page with further update see Bacolofen (Continuous Intrathecal)/Spasticity - Any Cause

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ARIF Request

Baclofen (Continuous Intrathecal) Spasticity - Any Cause

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The Problem Submitted for ARIF to Advise Upon:

In 2003 ARIF investigated the role of intrathecal baclofen in the treatment of spasticity for any cause and spasticity due to cerebral palsy in children (see previous request). We were asked to update this request in 2006.

Population = patients with spasticity – any cause
Intervention = intrathecal baclofen
Control = other interventions, treatments in use
Outcomes = effectiveness of intrathecal baclofen, improved health outcomes, particularly long term

Reviews Identified

- Taricco M, Adone R, Pagliacci C, Telaro E. Pharmacological interventions for spasticity following spinal cord injury. The Cochrane Database of Systematic Reviews 2006; Issue 2
- Beard S, Hunn A, Wight J. Treatments for spasticity and pain in multiple sclerosis: a systematic review. Health Technology Assessessment 2003;7(40).
- Simpson BJ, Middleton P, Madddern G. Implantable Spinal Infusion devices for Chronic Pain and Spasticity: An accelerated systematic review. ASERNIP-S Report No 42 2003.
- Rice JE, O'Donnell ME. Intrathecal Baclofen for treating spasticity in children with cerebral palsy. (Protocol). The Cochrane Database of Systematic Reviews 2004; Issue 1.
- Howard DC. Anti spastic medication for spasticity in cerebral palsy. (Protocol). The Cochrane Database of Systematic Reviews 2000; Issue 2.
- Medical Advisory Secretariat, Ontario. Intrathecal Baclofen Pump for Spasticity. 2005

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Comments

Rice 2004 – Cochrane protocol. Aim to assess intrathecal baclofen in treating spasticity in children with cerebral palsy. Due for publication in the Autumn 2006.

Howard 2004 – Cochrane protocol. Identified in 2003, no information regarding publication.

Tarrico 2006 – most recent review. Aim to assess the effectiveness and safety of different treatments

for people (any age) with long term spasticity due to spinal cord injury (SCI). Standard searches up to 2004. Included 3 trials Penn 1989, Kravitiz 1992 (which was a subgroup analysis of Penn – 6 patients, evaluating intrathecal baclofen on sleep quality) and Hugeenoltz 1992. Both Penn 1989 and Hugeenoltz 1992 were RCTs which then went onto open label long-term evaluation. The RCT phase of the studies was 6 days duration for Penn and 11 days for Hugeenoltz. Open label phases averaged 19 months in Penn and 30 days for Hugeenoltz. In total only 26 patients were included in these trials, and most of the time of the trial was in open label, with the potential for bias particularly in subjective outcome measures. Very little numerical data was given in the trial reports, with improvements being described rather than quantified. Overall the results favoured the intervention. There were adverse events reported in 6 patients. The review authors are cautious in their conclusions, and state that intrathecal baclofen should be restricted only to true non-responders. They also call for further better quality research, given that the trials included date from 1989 and 1992.

Beard 2003 – NICE HTA. Aim to investigate treatments for spasticity and pain in multiple sclerosis (MS). Standard searches to March 2002. Fifteen studies included. One was a double blind RCT of 13 weeks duration (n = 22 patients) by Middel 1997. One was the cross over study by Penn 1989 (included in Taricco above). One was an open label study with initial assessment randomised by Coffey 1993 (75 patients). The remaining 12 trials were longitudinal open labelled, uncontrolled designs or case series. Treatment durations ranged from 4 months to 6 years, with sample sizes from 6 to 93. All 15 trials reported positive findings. Complications were mainly problems regarding the pump and catheter, such as kinking and dislodging. Pump failure particularly in the older models was also a problem. The review authors conclude that in spite of the study design weaknesses there are striking benefits seen in these studies and that intrathecal baclofen has a positive outcome for MS patients with severe spasticity. Again the studies included in this review are quite old, ranging from 1985 to 1998.

Simpson 2003 – ARSERNIP-S, Australia. Aim to look at the safety and efficacy of implantable spinal infusion devices for treating chronic pain and spasticity. Excluded studies which used intrathecal baclofen vs placebo such as saline solution. Standard searches up to April 2003. Two studies looking at intrathecal baclofen were included. Both were case series. The first by Ordia 2002 involved 131 patients with SCI and a follow up of 73 months. Eight patients had their pumps removed during that time. The study found statistical decreases in the Ashworth score and spasm frequency score, with some non ambulatory patients able to walk and some able to drive. Complications were reported infrequently. The second study by Stempien 2000 was a clinical survey involving a mixed population. The survey was given to 115 centres using intrathecal baclofen but only 40 replied, however 936 pumps were evaluated. Improvements were reported in areas of daily care, such as improved transfers, improved sitting tolerance, easier dressing and hygiene activities. Mixed results were found for motor functions such as swallowing, head, bladder and bowel control. Complications were reported with a 7% pump replacement rate and a 7% catheter replacement rate. The review authors conclude that overall implantable infusion devices appear safe and effective but that this conclusion is based on limited evidence.

Overview – Medical Advisory Secrtariat, Ontario Ministry of Health and Long-Term Care. Aim to assess intrathecal baclofen in the treatment of spasticity from any cause. Searches up to April 2004. It identified 6 health technology assessments, three guideline documents (one a NICE guideline on use in MS), four cost analyses and seven primary studies. The authors conclusions are generally in favour of the treatment, but the level of evidence on which these conclusions are based is from non randomised trials or observational studies or expert opinion. The main value of this overview document is that it does bring together the systematic reviews that have been undertaken to date for this technology. This overview also conducted searches for more recent primary studies. They found 7 studies that were published in 2004 and 2003. Again they are fairly small studies with observational study designs, but they do offer more up-to-date evidence than the studies included in the reviews, which are pre-2000. With a complex technology such as intrathecal baclofen one would prefer to look at data that is more up-to-date as development in pump technology, surgical insertion techniques and drug monitoring would hopefully have developed for the better.

To summarize, there have been 3 recent systematic reviews since ARIF last looked at this question. Two of these reviews are favourable to the intervention, the third is cautious in its recommendation. All three reviews have included studies that are pre 2000, with some studies dating back to the 1980's. All the reviews underline their conclusions with the caveat that the evidence base is weak because of study design (mostly observational), study conduct (outcome measures difficult to quantify) and in the most case small sample sizes. The overview undertaken in Ontario also had similar conclusions, but did include more up-to-date material. They identified one ongoing trial with an RCT design being

undertaken at the Queens Medical Centre in Nottingham . None of the new completed reviews update information regarding using intrathecal baclofen in children with cerebral palsy, which was the subject of our request in 2003.

Request Carried Out: May 2006

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ARIF Request

Mycophenolate Mofetil
Behcet's Disease/Syndrome

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the clinical effectiveness of mycophenolate mofetil for patients with Behcet's disease who are intolerant of immunosuppressive treatment with methotrexate, cyclosporine and azathioprine?

Reviews Identified

No systematic reviews, health technology assessments or randomised controlled trials were identified.

Other Evidence

- Adler YD, Mansmann U, Zouboulis CC. Mycophenolate mofetil is ineffective in the treatment of mucocutaneous Adamantiades-Behcet's disease. Dermatology 2001;203(4):322-4
- Neri P, Mariotti C, Cimino L, Mercanti L, Giovannini A. Long-term control of cystoid macular oedema in noninfectious uveitis with Mycophenolate Mofetil. International Ophthalmology 2009;29(3):127-33
- Llinares-Tello F, Hernandez-Prats C, Munoz-Ruiz C, Selva-Otaolaurruchi J, Ordovas-Baines JP. Monitoring trough plasma concentrations of mycophenolate mofetil in patients with uveitis. Journal of Clinical Pharmacy & Therapeutics 2004;29(1):53-8

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Comments

Systematic reviews, health technology assessments and primary studies of any type were searched. However, only three primary studies were identified which were of some relevance.

All three were case series. One intended to investigate the effectiveness and toxicity of mycophenolate mofetil (MMF) in 30 patients with Behcet's disease. However the study was interrupted for ethical reasons due to inefficacy of MMF after the intermediate evaluation of the first six patients. The other two included only one and three patients with Behcet's disease respectively. The three studies, with a total of only ten relevant patients, add little value to the question posed.

In conclusion the current evidence base for the treatment of these patients with MMF is very limited.

Request Carried Out: June 2010

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ARIF Request

Photokinetic Vaporisation of the Prostate (PKVP)
Bipolar Electrosurgical Transurethral Resection of the Prostate (TURP)
Benign Prostatic Hypertrophy or Hyperplasia
Benign Prostatic Obstruction or Enlargement
Prostatism

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness and cost-effectiveness of Gyrus PKVP versus standard therapy, unipolar TURP, for benign prostatic hypertrophy?

Benign prostatic obstruction is a common problem in older men leading to problems passing urine. The most common of these, often referred to together as “prostatism” are:

- Having to pass urine frequently, often having to get up at night to do so (nocturia)
- A weak and intermittent urine stream
- Difficulty starting to pass urine and difficulty stopping

The most common method of surgical treatment is transurethral resection of the prostate (TURP), but this is recognised to have some limitations. In consequence many new techniques have been developed. PKVP is one of these techniques. Both TURP and PKVP involve cutting away the portion of the prostate gland obstructing the passage of urine. The theoretical advantage of PKVP is that it does this causing less damage and bleeding.

See also photoselective vaporisation of the prostate (PVP) using green-light laser/potassium-titanyl-phosphate(KTP) laser.

Reviews Identified

No sufficiently up-to-date systematic reviews incorporating all recent RCTs were identified .

Randomised Controlled Trials

- de Sio M, Autorino R, Quarto G, Damiano R, Perdona S, di Lorenzo G et al Gyrus bipolar versus standard monopolar transurethral resection of the prostate: a randomized prospective trial. Urology 2006;67(1):69-72.
- Fung BT, Li SK, Yu CF, Lau BE, Hou SS. Prospective randomized controlled trial comparing

plasmakinetic vaporesection and conventional transurethral resection of the prostate. Asian Journal of Surgery. 2005;28(1):24-8

- Seckiner I, Yesilli C, Akduman B, Altan K, Mungan NA A prospective randomized study for comparing bipolar plasmakinetic resection of the prostate with standard TURP. Urologia Internationalis 2006;76(2): 139-43
- Yang S, Lin WC, Chang HK, Hsu JM, Lin WR, Chow YC et al Gyrus plasmasect: is it better than monopolar transurethral resection of prostate? Urologia Internationalis. 2004;73(3): 258-61
- Coppinger SW, Hon NHY, Brathwaite D, Hussain Z, Ghiblawi S, Brace H et al (Shrewsbury UK) Physiological changes, early complications and long-term outcome of bipolar plasmakinetic vaporisation of the prostate (PKV): comparison with standard TURP American Urological Association Annual Meeting 2006 - ABST [1434] May 23, 2006
- Lloyd SN (Leeds, United Kingdom) A multicentre comparative study of the Gyrus plasmakinetic bipolar electrosurgical system and conventional monopolar loop TURP in BHP American Urological Association Annual Meeting 2004 - ABST [1531] 11 May 2004

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Comments

Scrutiny of the above RCTs suggests that there is not unanimity about the size of clinical benefit associated with use of PKVP. Clarity about the size of benefit is an essential pre-requisite for decisions on cost-effectiveness.

This request has identified an urgent need for a systematic review of RCTs assessing the effectiveness of PKVP relative standard TURP.

Questions about the relative effectiveness and cost-effectiveness of new techniques for the resection of prostate relative to each other are also raised.

Request Carried Out: February 2007

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ARIF Request

Photoselective Vaporisation of the Prostate (PVP)
Green-Light Laser
Potassium-titanyl-phosphate (KTP) Laser
Benign Prostatic Hypertrophy or Hyperplasia
Benign Prostatic Obstruction or Enlargement
Prostatism

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of PVP using the green-light (KTP) laser?

Benign prostatic obstruction is a common problem in older men leading to problems passing urine. The most common of these, often referred to together as “prostatism” are:

- Having to pass urine frequently, often having to get up at night to do so (nocturia)
- A weak and intermittent urine stream
- Difficulty starting to pass urine and difficulty stopping

The most common method of surgical treatment is transurethral resection of the prostate (TURP), but this is recognised to have some limitations. In consequence many new techniques have been developed. PVP is one of these techniques. Both TURP and PVP involve cutting away the portion of the prostate gland obstructing the passage of urine. The theoretical advantage of PVP is that it does this causing less damage and bleeding.

Reviews Identified

- Potassium-titanyl-phosphate (KTP) laser vaporisation of the prostate for benign prostatic obstruction – guidance IPG 120 NICE; May 2005 http://www.nice.org.uk/page.aspx?o=IPG120guidance
- Interventional procedures overview of KTP laser vaporisation for benign prostatic obstruction http://www.nice.org.uk/page.aspx?o=IPG189overview

Randomised Controlled Trials

- Bouchier-Hayes DM, Anderson P, Van Appledorn S, Bugeja P, Costello AJ. KTP laser versus transurethral resection: early results of a randomized trial. Journal of Endourology 2006;20(8):580-5.

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Comments

The literature review underpinning the NICE guidance is generally systematic, although the methods are brief. However, the main limitation is that the evidence identified are case-series which are highly susceptible to selection and information bias. In addition the case-series do not directly answer the key question of whether PVP offers advantages over existing treatments.

We identified one RCT comparing PVP with TURP published since NICE guidance was published. There may be others because we have not searched all possible sources of RCTs. There are important provisos concerning its interpretation particularly that the method of randomisation is unclear and that the report is an interim analysis half-way through the trial. Despite this it does provide early evidence that PVP may be a useful alternative to TURP. However, in our view widespread implementation should await:

- Full publication of the trial by Bouchier-Hayes et al, including full details about method
- A systematic review confirming that there are no other RCTs addressing similar issues recently published, completed but not yet published or in progress
- Economic modelling exploring the cost-effectiveness

Request Carried Out: October 2006

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ARIF Request

Bosentan
Sildenafil
Berapost
Iloprost
Pulmonary Arterial Hypertension

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The Problem Submitted For ARIF To Advise Upon

Critical appraisal of “Goal-orientated treatment and combination therapy for pulmonary arterial hypertension” Hoeper MM, Markevych I, Spiekerkoetter E. et al. European Respiratory Journal 2005;26(5) 858-863 in relation to assessment of study design and interpretation of the results particularly regarding the effectiveness of dual therapy relative to monotherapy.

Comments

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ARIF Request

Bilateral Subthalamic Stimulation
Deep Brain Stimulation
Surgery
Parkinson's Disease

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness and cost-effectiveness of bilateral subthalamic stimulation in patients with Parkinson's disease, compared to standard medical treatment or no treatment in patients who have failed medical management.

From NICE IPG background:

Parkinson's disease is caused by the diminished function of the substantia nigra in the brain. It is a chronic disease with symptoms such as gradually worsening tremor, muscle rigidity and difficulties with starting and stopping movements. The standard treatment is with drugs. Surgery may be considered in people who have responded poorly to drugs, who have severe side effects from medication or who have severe fluctuations in response to drugs (on-off syndrome). The most common surgery to be considered is bilateral subthalamic simulation a type of deep brain stimulation.

See ARIF related requests - Deep Brain Stimulation/Dystonia

Reviews Identified

- Royal College of Physicians L. The National Collaborating Centre for Chronic Conditions. Parkinson's Disease: National clinical guideline for diagnosis and managment in primary and secondary care. 2006. Available at http://www.nice.org.uk/CG035
- Developed by the National Collaborating Centre for Chronic Conditions. NICE clinical guideline 35. Parkinson's disease. Diagnosis and managment in primary and secondary care. 2006. Available at:http://www.nice.org.uk/CG035
- NICE clinical guideline 35. Developed by the National Collaborating Centre for Chronic Conditions. Quick reference guide: Parkinson's disease - diagnosis and management in primary and secondary care.2006. Available at:http://www.nice.org.uk/CG035
- NICE. Understanding NICE guidance. Information for people who use NHS services - Parkinson's disease. 2006. Available at:http://www.nice.org.uk/CG035
- NICE. Interventional Procedure Guidance 19. Deep brain stimulation for Parkinson's disease. 2003. Available at http://www.nice.org.uk/nicemedia/pdf/ip/IPG019guidance.pdf

Blue Cross Shield Association. Bilateral DBS of the subthalamic nucleus or the globus pallidus interna for treatment of advanced Parkinson's disease. 2002

- L'Agence Nationale d'Accreditation d'Evaluation en Sante (ANAES). Evaluation of deep brain stimulation in idiopathic Parkinson's disease: progress report. 2003
- Ontario Ministry of Health and Long-Term Care. Deep brain stimulation for Parkinson's disease and other movement disorders. 2005
- Hamani C, Richter E, Schwalb JM, Lozano AM. Bilateral subthalamic nucleus stimulation for Parkinson's disease: a systematic review of the clinical literature. Neurosurgery 2005;56(6):1313-1321
- Kleiner-Fisman G, Herzog J, Fisman DN, Tamma F, Lyons KE, Pahwa R, et al. Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. Movement Disorders 2006;21(Suppl 14):S290-S304
- Motto C, Tamma F, Candelise L. Deep brain stimulation of subthalamic nucleus for Parkinson's disease. Cochrane Database of Systematic Reviews Protocols Issue 2 John Wiley & Sons, Ltd Chichester , UK . 2003
- Temel Y, Kessels A, Tan S, Topdag A, Boon P, Visser-Vandewalle V. Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: a systematic review. Parkinsonism Related Disorders 2006;12(5):265-272
- Piasecki SD , Jefferson JW. Psychiatric complications of deep brain stimulation for Parkinson's disease. Journal of Clinical Psychiatry 2004;65(6):845-849 , Jefferson JW. Psychiatric complications of deep brain stimulation for Parkinson's disease. Journal of Clinical Psychiatry 2004;65(6):845-849
- Parsons TD, Rogers SA, Braaten AJ, Woods SP, Troster AI. Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. Lancet Neurology 2006;5(7):578-588

Randomised Controlled Trials

- Caroline Rick TC. PD SURG Trial, Protocol Summary. 2007. Available at: http://www.pdsurg.bham.ac.uk

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Comments

There are NICE guidelines and guidance relating to this procedure. The evidence supporting these reports however, stems from case series studies, with many inherent problems. Many of these studies were undertaken in the late 1990's and technology may have changed in that time. Another concern is the length of follow up, both for efficacy and adverse events. Additionally, case series cannot answer whether STN-DBS is more effective than standard medical management. There is an RCT currently ongoing, which may answer some of these questions with the first results expected in the autumn of 2008 (see http://www.pdsurg.bham.ac.uk for further details). In the meantime, patients undergoing the treatment should be aware that there are uncertainties regarding the treatment and that they should consult the NICE guidance for more information.

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ARIF Request

Bisphosphonates
Cancer, Bone Metastases

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of bisphosphonates for cancer patients (particularly those with breast cancer, prostate cancer and myeloma) with, or at risk of developing, bone metastases?

Reviews Identified

- Ross JR, Saunders Y, Edmonds P M, Patel S, Wonderling D, Normand C, Broadley K. A systematic review of the role of bisphosphonates in metastatic disease. Health Technology Assessment 2004; 8 (4)
- Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. Cochrane Database of Systematic Reviews: Reviews 2002 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD002068
- Pavlakis N, Schmidt RL, Stockler M. Bisphosphonates for breast cancer. Cochrane Database of Systematic Reviews: Reviews 2005 Issue 3 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD003474.pub2
- Yuen KK, Shelley M, Sze WM, Wilt T, Mason MD. Bisphosphonates for advanced prostate cancer. Cochrane Database of Systematic Reviews: Reviews 2006 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD006250
- Djulbegovic B, Wheatley K, Ross J, Clark O, Bos G, Goldschmidt H, Cremer F, Alsina M, Glasmacher A. Bisphosphonates in multiple myeloma. Cochrane Database of Systematic Reviews: Reviews 2002 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD003188

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Comments

All systematic reviews were well conducted. Those by Ross and Wong assessed the role of bisphosphonates for bone metastases resulting from any type of primary cancer.

Ross modelled the cost-effectiveness of bisphosphonates in the treatment of hypercalcaemia and prevention of skeletal morbidity. The results indicate high dose aminobisphosphonates are most effective for the treatment of hypercalcaemia and delay time to relapse. Bisphosphonates also significantly reduce skeletal related events (SREs) and delay the time to developing SREs in patients

with bony metastatic disease but do not affect survival. The greatest body of evidence supports the use of intravenous bisphosphonates. More evidence is required to support the use of bisphosphonates in an adjuvant setting.

The review by Wong focused on the role of bisphosphonates for the relief of pain from bone metastases. The results indicate there is evidence to support the effectiveness of bisphosphonates in providing some relief from pain. However there is insufficient evidence to recommend them as first line therapy.

These trends are generally mirrored in the remaining systematic reviews. However Djulbegovic reports a lack of effect in the reduction of hypercalcaemia, a trend also documented in Ross after sub analysis of the disease groups.

Finally there appears to be a requirement for further research on the relative effectiveness of the different drugs within the class, the optimal timing for the initiation of treatment and the optimal duration of therapy

Request Carried Out: July 2007

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ARIF Request

Biventricular Pacing
Severe Heart Failure

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of biventricular pacing in patients with severe heart failure who have not responded to other treatment?

Comments

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ARIF Request

The Bobath Method Cerebral Palsy

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The Problem Submitted For ARIF To Advise Upon

How effective is the Bobath method as a therapy for children with cerebral palsy?

Comments

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ARIF Request

Bone Anchored Hearing Aids (Bilateral)
Conductive Hearing Loss
Deafness

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The Problem Submitted For ARIF To Advise Upon

What is the clinical and cost-effectiveness of bilateral bone anchored hearing aids (BAHAs) in comparison with unilateral bone anchored hearing aids?

Comments

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ARIF Request

Bone Densitometry
Osteoporosis

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The Problem Submitted For ARIF To Advise Upon

What is the contribution of bone densitometry in the prediction of osteoporosis fracture and diagnosing osteoporosis. In particular, how does it help identify populations at risk of osteoporosis?

Comments

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ARIF Request

Bosentan
Pulmonary Hypertension

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of bosentan for the treatment of pulmonary hypertension?

See ARIF related request - Bosentan/Sildenafil/Beraprost/Pulmonary Arterial Hypertension

Comments

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ARIF Request

Botulinum Toxic Type A (BTX-A)
Limb Spasticity, Cerebral Palsy

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The Problem Submitted For ARIF To Advise Upon

Is BTX-A a safe and effective treatment for the relief of limb spasticity in cerebral palsy?

Comments

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ARIF Request

Brachytherapy (High Dose Rate)
Iridium
External Beam Radiotherapy
Localised Prostate Cancer
Early Prostate Cancer

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of high dose rate brachytherapy using temporarily inserted iridium isotopes in combination with external beam radiotherapy (EBRT) versus EBRT alone in localised prostate cancer ?

Prostate cancer is the second most common cancer in men. However in many men it progresses slowly and may not be the ultimate cause of death. As most cancer treatments have side-effects, it is thus essential that the benefits associated with treatment of early prostate cancer outweigh any side-effects.

This request up-dates and supersedes a previous request completed over 4 years ago.

Reviews Identified

- National Institute for Clinical Excellence Interventional Procedures Guidance no 174. High dose rate brachytherapy in combination with external-beam radiotherapy for localised prostate cancer. National Institute for Clinical Excellence (NICE); 2005.

Randomised Controlled Trials

- Sathya JR, Davis IR, Julian JA, Guo Q, Daya D, Dayes IS et al. Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. Journal of Clinical Oncology 2005;23(6):1192-9 .

A further on-going trial which has completed recruitment was identified from the NHS National Research Register .

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Comments

We confirmed that the supporting document for the NICE IPG represented the most systematic up-to-date review of the research evidence available at the time of the request. The guidance indicates, “Current evidence on the safety and efficacy of high dose rate (HDR) brachytherapy in combination with external-beam radiotherapy for localised prostate cancer appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance.”

This guidance was based on evidence that was highly susceptible to selection and information bias. It is thus fortunate that a recently conducted RCT has confirmed early research findings suggesting clinical effectiveness of high dose rate brachytherapy combined with external-beam radiotherapy with respect to control of prostate cancer. This did not appear to be offset by a marked excess of side-effects.

Further evidence from at least one further RCT should become available soon.

We identified no information on cost-effectiveness of HDR brachytherapy.

Request Carried Out: September-October 2006

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ARIF Request

Brachytherapy (Low Dose Rate)
Iodine - 125
Palladium - 103
Localised Prostate Cancer
Early Prostate Cancer

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of low dose rate brachytherapy using inserted iodine or palladium radioactive isotopes compared to other common methods of treatment such as radical prostatectomy or external beam radiotherapy (EBRT) ?

Prostate cancer is the second most common cancer in men. However in many men it progresses slowly and may not be the ultimate cause of death. As most cancer treatments have side-effects, it is thus essential that the benefits associated with treatment of early prostate cancer outweigh any side-effects.

See also requests "high dose rate brachytherapy in localised prostate cancer" and "external beam radiation, radical prostatectomy and watch & wait for localised prostate cancer"

Reviews Identified

- Alibhai SMH, Klotz LH. A systematic review of randomized controlled trials in localized prostate cancer. The Canadian Journal of Urology 2004;11(1):2110-2117

Randomised Controlled Trials

None identified other than those included in the review above.

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Comments

Although not completely systematic, the review suggested provides a simple summary of the existing RCT evidence, and also highlights additional important RCTs in progress.

The RCT evidence base for the effectiveness of EBRT for localised prostate cancer is limited,

restricted to comparisons of EBRT with surgery and needs to be interpreted cautiously. There are no RCTs comparing EBRT with “watch and wait” strategies.

The RCT evidence base for the effectiveness of radical prostatectomy is more convincing, and in favour of surgery relative to “watch and wait” strategies. There are important trade-offs between benefits and side-effects for patients however.

Request Carried Out: December 2006

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ARIF Request

pro-Brain Natriuetic Peptide Heart Failure

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The Problem Submitted For ARIF To Advise Upon

What is the accuracy of pro-Brain Natriuretic Peptide (proBNP) in the diagnosis of heart failure?

Comments

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ARIF Request

Temozolomide
Brain Tumours (Glioblastoma)

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of temozolomide in addition to surgery and radiotherapy for newly diagnosed glioblastoma multiforme?

Comments

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ARIF Request

Gliadel Wafer
Carmustine Implants
Glioblastoma Multiforme (GBM)
Brain Tumour

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of Gliadel wafer implants in the treatment of recurrent glioblastoma multiforme (GBM)?

Comments

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ARIF Request

Breakspear Hospital
Multiple Allergy Syndrome
Multiple Chemical Sensitivity
Chronic Fatigue Syndrome

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

ARIF has received many requests concerning the evidence on effectiveness of the services by the Breakspear Hospital.

The Breakspear Hospital is a facility in Hertfordshire which offers care for a wide range of disorders.

There are related web pages on Provocation-neutralisation Therapy and Enzyme Potentiated Desensitisation.

Reviews Identified

ARIF briefing to the Regional Evaluation Panel (REP) 2003.

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Comments

The briefing paper summarises requests received up to 2003. A problem addressing requests for information concerning the effectiveness of the services of the Breakspear, is that they offer a wide range of treatments for a wide range of conditions. Many requests would be required to investigate the availability of evidence for all treatments offered in all conditions.

However, most requests to us have concerned the effectiveness of provocation-neutralisation in conditions like multiple allergy syndrome, multiple chemical sensitivity, candidal hypersensitivity and chronic fatigue syndrome.

Repeated searches have confirmed an absence of RCT evidence on the use of this therapy for the complex conditions in question. There are RCTs on simpler conditions like asthma, eczema and hay-fever. However, it is highly debatable whether findings from these studies can be reasonably used to underpin treatment in more complex and ill-defined disorders.

There is an urgent need for rigorous research on many of the services offered by the Breakspear

Hospital.

Request Carried Out: October 2003

Update: July 2006 - ARIF were asked to review the evidence provided by the Breakspear Hospital to support their use of provocation-neutralisation therapy. No new evidence prior to and after the conclusions above were identified.

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ARIF Request

Trastuzumab Herceptin Breast Cancer

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The Problem Submitted for ARIF to Advise Upon:

Evidence on effectiveness of herceptin in small size tumours (equal to or less than 0.5cm) and lymphovascular invasion HER-2 positive early-stage breast cancer.

Standard treatments for early stage breast cancer are surgery, radiotherapy and standard chemotherapy. Trastuzumab (herceptin) is licensed for the treatment of early-stage HER2-positive breast cancer, following surgery, chemotherapy (adjuvant or neoadjuvant) and radiotherapy (if applicable).

See related ARIF request: Breast Cancer (early stage; HER2-positive)

Reviews Identified

- NICE. Trastuzumab as adjuvant therapy for early stage breast cancer. 2006. Available from: http://www.nice.org.uk/guidance/index.jsp?action=byId&o=11585&history=t [accessed 14-08-09]
- Viani GA, Afonso SL, Stefano EJ, De Fendi LI, Soares FV. Adjuvant trastuzumab in the treatment of HER-2-positive early breast cancer: a meta-analysis of published randomized trials. BMC Cancer 2007;7:153
- Madarnas Y, Trudeau M, Franek JA, McCready D, Pritchard KI, Messersmith H. Adjuvant/neoadjuvant trastuzumab therapy in women with HER-2/neu-overexpressing breast cancer: a systematic review. Cancer Treat Rev 2008;34(6):539-557
- Dahabreh IJ, Linardou H, Siannis F, Fountzilas G, Murray S. Trastuzumab in the adjuvant treatment of early-stage breast cancer: a systematic review and meta-analysis of randomized controlled trials. Oncologist 2008;13(6):620-630

Randomised Controlled Trials

- Dowsett M, Procter M, Caskill-Stevens W, de AE, Dafni U, Rueschoff J et al. Disease-free survival according to degree of HER2 amplification for patients treated with adjuvant chemotherapy with or without 1 year of trastuzumab: the HERA Trial. Journal of Clinical Oncology 2009; 27(18):2962-2969
- Untch M, Gelber RD, Jackisch C, Procter M, Baselga J, Bell R et al. Estimating the magnitude of

trastuzumab effects within patient subgroups in the HERA trial. Ann Oncol 2008;19(6):1090-1096

- Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet 2007;369(9555):29-36
- Halyard MY, Pisansky TM, Dueck AC, Suman V, Pierce L, Solin L et al. Radiotherapy and adjuvant trastuzumab in operable breast cancer: tolerability and adverse event data from the NCCTG Phase III Trial N9831. J Clin Oncol 2009;27(16):2638-2644
- Guarneri V, Frassoldati A, Bruzzi P, D'Amico R, Belfiglio M, Molino A et al. Multicentric, randomized phase III trial of two different adjuvant chemotherapy regimens plus three versus twelve months of trastuzumab in patients with HER2- positive breast cancer (Short-HER Trial; NCT00629278). Clin Breast Cancer 2008;8(5):453-456

Other Evidence

- Hoda SA, Hoda RS, Merlin S, Shamonki J, Rivera M. Issues relating to lymphovascular invasion in breast carcinoma. Adv Anat Pathol 2006;13:308-315
- Soerjomataram I, Louwman MWJ, Ribot JG., Roukema JA., Coebergh JWW. An overview of prognostic factors for long-term survivors of breast cancer. Breast Cancer Res Treat 2008; 107:309-330
- Chivukula M, Brufsky A, Davidson NE. Small Beginnings: Do They Matter? The Importance of Lymphovascular Invasion in Early Breast Cancer. J Natl Cancer Inst 2009;101(10):698-699

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Comments

Our search identified three systematic reviews and one piece of NICE guidance with its associated documents.

All of the reviews are of reasonable quality, with good search strategies, the latest being up to May 2007. The evidence base up to May 2007 was limited to six randomized controlled trials: BCIRG 006, HERA, NCCTG N9831, NSABP -B31, FinHer trial, ECOG E2198 (abstract publication). The NICE guidance took into account four of these trials (BCIRG 006, HERA, NCCTG N9831, and NSABP -B31), all of which administered trastuzumab over 12 months.

In this ARIF request we have focused on the patient population, particularly regarding tumour size and the presence of lymphovascular invasion.

With regard to the tumour size the NICE guidance stated that for women with HER2-positive, node-negative, and small primary tumours, there was a lower risk of recurrence, therefore absolute benefit these women would gain from trastuzumab treatment would be smaller than for the group as a whole. Expert opinion suggests that in England and Wales only women considered to be at a higher risk of recurrence would be offered adjuvant chemotherapy. Thus the patients normally considered eligible for adjuvant chemotherapy would be equivalent to those patients shown to achieve benefit from trastuzumab in the main registration study.

In relation to the tumour size, it is unclear in the supporting evidence for the NICE guidance how many patients had tumour size <0.5 cm; the data suggested that 40% of the women had a tumour size <2 cm.

In the three systematic reviews it is also unclear how many patients had tumour size of <0.5cm. This gap in the evidence is discussed in two of the reviews. Madarnas 2008 considered that as the trials did not include women with tumours less than 1cm, the generalizability of trials to that population is limited, with Viani 2007 suggesting that women with smaller tumours should be included in the next generation of trials. Madarnas also stated that the lack of evidence for under-represented population should not preclude these patients from receiving treatment, but that greater individual consideration should be given to these patients when prescribing trastuzumab, particularly with respect to the potential for increased cardiac complication with increasing age although there is no trastuzumab-associated data to suggest this at this time.

With regard to lymphovascular invasion, we did not find any information about the patients'

lymphovascular invasion in the NICE guidance nor within the three systematic reviews. We identified an ongoing trial that has included patients with lymphovascular invasion. This trial is due to complete in 2010.

There have been publications suggesting that issue relating to lymphovascular invasion is a very under-studied area, with much debate as to whether its presence converts a small low risk tumour to a high risk tumour.

In summary, lack of details regarding the reporting of baseline characteristics make it difficult to ascertain how many women with small tumours <1cm were enrolled in the trials included in the reviews and what effect trastuzumab had on these patients. An individual patient data review (IPD) could possibly be a way forward in answering this question. Very little data was found relating to lymphovascular invasion. Gaps in the evidence, differential definitions of high and low risk tumours, short follow up and the potential risk of serious cardio toxicity, makes for an uncertain risk/benefit profile in women with small tumours and lymphovascular invasion.

Request Carried Out: August 2009

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ARIF Request

Herceptin
Trastuzumab
Breast Cancer (early stage; HER2-positive)

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the quality of two recently published articles reporting the results of three randomised controlled trials assessing the effectiveness of trastuzumab (Herceptin) in the treatment of HER2-positive, early-stage breast cancer?

The HER2 protein controls growth of cells and is present in excess amounts in up to ¼ of women with breast cancer. Trastuzumab is a new drug (a monoclonal antibody) which attaches to the HER2 protein and so interferes with the growth of the breast cancer cells.

Reviews Identified

Not searched for.

Randomised Controlled Trials

- B-31 Trial and N9831 Trial
  Piccart-Gebhart, M.J. et al. Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer. The New England Journal of Medicine 2005; 353: 1659-1672
- HERA Trial
  Romond, E.H, Perez, E.A. et al. Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer. The New England Journal of Medicine 2005; 353: 1673-1684

Other Evidence

Economic evaluations and health technology assessments were sought, but none were identified.

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Comments

The Piccart-Gebhart, M.J. et al article presents the combined, relevant results of two randomised controlled trials (B-31 and N9831 trials), which assessed the effectiveness of trastuzumab initiated concurrently with adjuvant chemotherapy (paclitaxel) after doxorubicin and cyclophosphamide, in the

treatment of surgically removed HER2-positive early breast cancer.

The authors conclude that trastuzumab combined with paclitaxel after doxorubicin and cyclophosphamide improves outcomes among women with surgically removed HER2-positive breast cancer. In particular it reduces disease free survival and time to recurrence by around fifty percent.

The Romond, E.H, Perez, E.A. et al article presents the results of the randomised controlled HERA trial, which assessed the effectiveness and safety of trastuzumab initiated after the completion of chemotherapy, in the treatment of surgically removed HER2-positive early-stage breast cancer.

The authors conclude that one year of treatment with trastuzumab after adjuvant chemotherapy significantly improves disease-free survival and time to distant recurrence by around fifty percent among women with HER2-positive breast cancer.

Critical appraisals of the papers (available from ARIF on request) identified some threats to the validity of the results (limited information on allocation concealment and blinding status) and highlighted increased cardiac adverse events associated with trastuzumab. However, on balance it was felt that these were insufficient to undermine the large beneficial effect observed in the RCTs.

The high cost of trastuzumab (around £21000 per annum) may also need to be considered in commissioning decisions concerning trastuzumab in early-stage breast cancer. However no economic evaluations assessing the cost-effectiveness of trastuzumab in this indication were identified. A clearer picture of the relation between benefits, disbenefits and costs requires such an evaluation.

Request Carried Out: November 2005

Update: December 2005 - Shortly after the request was completed a health economic article was published :

- An economic evaluation of Herceptin ® in adjuvant setting: the Breast Cancer International Research Group 006 trial
  Annals of Oncology Advance Access (30.11.05) Doi:10.1093/annonc/mdj101

This is a well conducted economic model of costs associated with breast cancer treatment. It confirms that trastuzumab greatly increases these costs. It speculates how great the effectiveness would need to be to achieve an acceptable ratio between benefit and cost. It does not, however, provide an estimate of cost-effectiveness as such. On this basis the advice in our original response that a formal assessment of cost-effectiveness is required remains unchanged.

Update: June 2006 - An additional published randomised controlled trial assessing the effectiveness of trastuzumab in the treatment of HER-2 positive, early breast cancer has been identified and an appraisal from ARIF requested:

- FinHer Trial
  Joensuu, H et al. Adjuvant Docetaxel or Vinorelbine with or without Trastuzumab for Breast Cancer. The New England Journal of Medicine 2006;354:809-820

The trial assessed the effects of trastuzumab administered for 9 weeks concomitantly with docetaxel or vinorelbine. The results showed a significant improvement in disease free survival and distant recurrence free survival. However the trial was too small to detect a significant improvement in overall survival.

A critical appraisal of the trial (available from ARIF on request) highlighted that the trial was generally well conducted with the only threats to validity being the blinding status and sample size.

A table summarising the characteristics and results of the FinHer trial, Hera trial, and N9831 & B-31 meta-analysis suggest that the lower dose of trastuzumab used in the FinHer trial does not seem to obviously impair the beneficial effects of herceptin, and indeed cardiac side-effects appear to be reduced.

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ARIF Request

Screening in those with Family History Breast Cancer

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The Problem Submitted For ARIF To Advise Upon

What is the evidence base of the proposals made for the West Midlands Familial Cancer Initiative, particularly those concerning screening of individuals with a positive family history of breast cancer?

Comments

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ARIF Request

Docetaxel (Taxotere)
Breast Cancer (Advanced)

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The Problem Submitted For ARIF To Advise Upon

Is docetaxel effective in the management of patients with advanced breast cancer?

Comments

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ARIF Request

Health Promotion
Brief Interventions
Primary Care
Diet

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to diet?

Comments

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ARIF Request

Health Promotion
Brief Interventions
Primary Care
Exercise
Physical Activity

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to increasing physical activity?

Comments

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ARIF Request

Health Promotion
Brief Interventions
Primary Care
Falls in Older People

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to the prevention of falls amongst older people?

Comments

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ARIF Request

Health Promotion
Brief Interventions
Primary Care
First Intercourse Amongst Adolescents

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to advice on delaying the time of first intercourse?

Comments

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ARIF Request

Health Promotion
Brief Interventions
Primary Care
Illicit Drug Use

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to the prevention/reduction of illicit drug use amongst young people?

Comments

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ARIF Request

Health Promotion
Brief Interventions
Primary Care
Safe Sex

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to safe sex?

Comments

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ARIF Request

Health Promotion
Brief Interventions
Primary Care
Smoking Cessation

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to smoking cessation?

Comments

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ARIF Request

Bronchodilators
Bronchiolitis

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The Problem Submitted For ARIF To Advise Upon

What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Comments

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ARIF Request

Continuous Negative Extrathoracic Pressure Bronchiolitis

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The Problem Submitted For ARIF To Advise Upon

What is the evidence base for the treatments of infants with bronchiolitis with Continuous Negative Extrathoracic Pressure (CNEP) ventilation?

Comments

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ARIF Request

Immunoglobulin Bronchiolitis

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The Problem Submitted For ARIF To Advise Upon

What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Comments

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ARIF Request

Ribavirin
Bronchiolitis

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The Problem Submitted For ARIF To Advise Upon

What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Comments

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ARIF Request

Steroids
Bronchiolitis

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The Problem Submitted For ARIF To Advise Upon

What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Comments

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ARIF Request

Buccal Nitrates
Heart Failure after Myocardial Infarction

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness and cost effectiveness of using buccal nitrates in primary care, in the management of patients with heart failure after a myocardial infarction?

Comments

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ARIF Request

Buprenorphine Detoxification Opiate Addiction

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The Problem Submitted For ARIF To Advise Upon

Is there any evidence on the effectiveness of buprenorphine in the management of detoxification for opiate addiction?

Comments

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ARIF Request

C1 Esterase Inhibitor Concentrate Hereditary Angioedema (HAE)

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The Problem Submitted For ARIF To Advise Upon

What is the evidence for using C1 Esterase Inhibitor Concentrate as a long-term prophylaxis in patients with severe Hereditary Angioedema (HAE)?

Comments

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ARIF Request

Clinical Nurse Specialists
Cancer

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The Problem Submitted For ARIF To Advise Upon

What evidence is there that clinical nurse specialists are effective, particularly in the care of cancer patients?

Comments

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ARIF Request

Influenza Vaccination
Flu Vaccination
Pneumococcal Vaccination
Cancer

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The Problem Submitted for ARIF to Advise Upon:

ARIF were asked if vaccinations for influenza and pnuemococcal disease improve survival for patients with cancer who have had systemic therapy (chemotherapy, hormonal therapy or radiotherapy).

Patients with haematological and solid tumour malignancies often require treatment with cytotoxic chemotherapy. This treatment causes immunosuppression, so that patients have an increased risk of contracting influenza at the time of epidemics. If these patients develop influenza they may experience prolonged morbidity and excess mortality, as they are at increased risk of complications. Infections also delay chemotherapy and may necessitate hospitalisation and antibiotic administration. For this reason, American and British guidelines recommend annual vaccination against influenza for adults and children who are immunosuppressed because of disease or treatment. However, lack of knowledge and misconceptions, among both patients and physicians about the potential benefits of vaccine mean that it is often not administered. This may be particularly true for immunosuppressed patients in whom concerns are also expressed about the safety and side-effects of the vaccine (Ring et al 2002).

Reviews Identified

- Ring A, Marx G, Steer C, Harper P. Influenza vaccination and chemotherapy: a shot in the dark?. Supportive Care in Cancer 2002;10(6):462-5
- Arrowood JR, Hayney MS Immunization recommendations for adults with cancer. Annals of Pharmacotherapy 2002;36(7-8):1219-29

Other Evidence

- Goossen GM, Kremer LCM, van de Wetering MD. Influenza vaccination in children being treated with chemotherapy for cancer. (Protocol) Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD006484. DOI: 10.1002/14651858.CD006484. http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD006484/pdf_fs.html [accessed 14 Oct 2008]
- Cheuk DKL, Chiang AKS, Lee TL, Chan GCF, Ha SY, YL Lau. Vaccines for prophylaxis of viral infections in patients with hematological malignancies. (Protocol) Cochrane Database of Systematic

Reviews 2007, Issue 2. Art. No.: CD006505. DOI: 10.1002/14651858.CD006505.
http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD006505/pdf_fs.html
[accessed 14 Oct 2008]

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Comments

We identified two reviews and two Cochrane review protocols on this topic. Both of the completed reviews overlap to some extent with five shared studies.

Both reviews have several limitations, therefore the information within them should be viewed with some caution. Limitations stem from the age of the research literature, the heterogeneity of the study populations and limited outcomes assessed i.e. most of the studies only investigated seroconversion rates. Both reviews are also semi-systematic i.e. both had systematic review features but the data in both was presented in a narrative format.

Overall, both reviews reported that adverse events were mild and that the main problem for cancer patients with compromised immune systems, is their ability to have an immune response to vaccines, which is strong enough to protect them from influenza. Both reviews conclude that published guidelines that recommend influenza vaccination in immunocompromised cancer patients should be followed but that there was also a need for further evaluation to find out what the optimal schedules are and which patients would derive the most benefit.

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ARIF Request

Strategies to Improve Uptake of Cancer Screening Cancer

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The Problem Submitted for ARIF to Advise Upon:

Is there firm outcome evidence to support strategies and campaigns to improve uptake of the 3 UK cancer screening programmes (breast, cervical, bowel), and if so what is the cost to save an additional life based on this evidence?

In the UK there are three national cancer screening programmes, one for breast cancer which utilizes mammography, one for cervical cancer utilizing Pap smears and a new screening programme for bowel cancer utilizing Faecal Occult Blood Testing. Further information about the individual screening programmes can be found at : http://www.cancerscreening.nhs.uk/index.html

Reviews Identified

- Jepson R, Clegg A, Forbes C, Lewis R, Sowden A, Kleijnen J. The determinants of screening uptake and interventions for increasing uptake: a systematic review (Structured abstract) Health Technology Assessment 2000;4(14) 1-133 http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-20008567/frame.html [accessed 8 December 2008]

Other Evidence

- Andersen MR, Urban N, Ramsey S, Briss PA. Examining the cost-effectiveness of cancer screening promotion (Brief record) Cancer 2004;101(5 Supplement S) :1229-1238 http://www.mrw.interscience.wiley.com/cochrane/cleed/articles/NHSEED-20041192/frame.html [accessed 8 December 2008]

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Comments

Our searches identified several reviews that mainly focused on breast screening (mammography). The most comprehensive and relevant review was by Jepson 2000, which we critically appraised.

Overall, the review was well conducted, but the last searches were undertaken in 1999 so the review is

outdated. The review included 190 primary studies. Of these 104 relate to mammography, 66 to Pap smear and 45 to Faecal Occult Blood testing (FOBT) for bowel cancer. The majority of studies were undertaken in North America, but nine mammography studies, six Pap smear studies and ten FOBT were conducted in the UK. Sample sizes ranged from small studies involving around 200 patients to very large studies involving 4,000 patients. A summary of the review findings were clearly presented and have been reproduced below:

Interventions shown to be effective were: Invitation appointments (fixed better than open); invitation letters (more effective for Pap smears than mammography); invitation telephone calls and telephone counselling; removal of financial barriers; physician reminders.

Interventions that may be effective: Educational home visits; opportunistic screening; multi-component community interventions; simpler procedures; a combination of different components aimed at individuals; reminders for non attendees = effective for mammography; invitation follow-up prompts; physician office systems; physician audit and feedback increase uptake.

Interventions with limited effectiveness: Printed educational materials; audio-visual educational materials; group educational sessions; individual educational sessions; risk factor questionnaires; face-to -face counselling.

Interventions shown to be ineffective: Patient rewards and incentives.

Interventions for which there is no good-quality evidence or not enough evidence: Inconsistent evidence of effectiveness for letters vs. telephone calls; not enough evidence to detect whether GP letters are more effective than those from another source; mass media campaigns & community education as single strategies; loss vs. gain messages; physician reminders combined with invitations to individuals.

Interventions aimed at individuals versus interventions aimed at physicians: Small beneficial effect of interventions aimed at individuals rather than interventions aimed at physicians.

Unfortunately the review does not examine survival and only addresses costs patchily within the narrative of the clinical effectiveness results. We therefore made reference to a discussion document, which explored the issues around estimating the cost-effectiveness of cancer screening promotion.

In summary, we identified one relevant review but survival and costs had not been explicitly examined. Overall the literature base is out-dated with most of the information written circa 2000. This is an area that requires more up-to-date research.

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ARIF Request

Community Chemotherapy Chemotherapy Cancer

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The Problem Submitted for ARIF to Advise Upon:

To assess the feasibility of cancer chemotherapy being delivered to patients in the community.

Population: two types of cancer patient considered, those who are essentially 'well' and receiving chemotherapy as an adjuvant treatment and those patients who have metastatic disease receiving cancer chemotherapy. Any type of chemotherapy given, using any route for example oral, intravenous or intra muscular.

Intervention: standard chemotherapy delivered in the community, any location considered, for example: home, general practice, community hospital, acute hospital trust, and mobile centres.

Comparator: standard chemotherapy delivered in specialist oncology centres.

Outcomes - patient safety e.g. adverse events and hospital inpatient episodes; staff safety relating to preparing, handling and transporting chemotherapy; quality of life; cost-effectiveness: cost per Quality Adjusted Life Year (QALY), societal and NHS perspective. Cost of implementation of service and running costs.

Reviews Identified

- Adams P, Hardwich J, Embree V, Sinclair S, Conn B, Bishop J. Literature review. Models of cancer services for rural and remote communities. Sydney: Cancer Institute New South Wales, March 2009
- Campbell ND, Ritchie LD, Cassidy J, Little J. Systematic review of cancer treatment programmes in remote and rural areas. British Journal of Cancer 1999;80(8):1275-1280
- Boothroyd L, Lehoux P. Home-based chemotherapy for cancer: issues for patients, caregivers and the health care system. Montreal: Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) 2004: 77

Other Evidence

- Chahed S, Marcon E, Sahin E, Feillet D, Dallery Y. Exploring New Operational Research Opportunities within the Home Care Context: The Chemotherapy at Home. Health Care

Management Science 2009;12(2):179-191

- Kelly D et al. Achieving change in the NHS: a study to explore the feasibility of a home-based cancer chemotherapy service. International Journal of Nursing Studies 2004; 41(2):215-224
- Smith SM, Campbell NC, Provision of oncology services in remote and rural areas: a Scottish perspective. European Journal of Cancer Care 2004;13:185-192

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Comments

One overview (Adams 2009) looking at cancer treatment in rural and remote areas, one systematic review that investigated the effectiveness of programmes in remote and rural areas (Campbell 1999) and another on the effectiveness of home based chemotherapy(Boothroyd 2004) were identified. In addition three background papers were identified, but not formally critically appraised. (Chahed 2009, Kelly 2004, Smith 2004).

Much of the research is out of date and of variable quality and focus, therefore it is difficult to draw specific conclusions regarding best practice. Several challenges of research in this area were identified.

It may be that a diversity of approaches are needed to tailor care to local conditions, which in itself creates fundamental problems in evaluating such research.

Request Carried Out: November 2009

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ARIF Request

Chronic Pain
Intractable Pain
Cancer Pain
Neuralgia

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The Problem Submitted For ARIF To Advise Upon

What interventions should a pain clinic be offering?

Comments

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ARIF Request

Provocation-neutralisation Technique
Miller Technique
Multiple Allergy Syndrome
Multiple Chemical Sensitivity
Chronic Fatigue Syndrome
Candidal Hypersensitivity
Post-chemotherapy Therapy

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The Problem Submitted For ARIF To Advise Upon

ARIF has received many requests concerning the effectiveness of provocation-neutralisation therapy.

There are related web pages on Enzyme Potentiated Desensitisation and Breakspear Hospital.

Comments

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ARIF Request

Haemodialysis and CAPD
Chronic Renal Failure

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The Problem Submitted For ARIF To Advise Upon

What is the evidence on the effectiveness of different methods of renal replacement therapy, other than renal transplant?

Comments

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ARIF Request

Hyperbaric Oxygen Therapy
Carbon Monoxide Poisoning

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The Problem Submitted For ARIF To Advise Upon

What is the evidence for hyperbaric oxygen in the management of patients with acute carbon monoxide poisoning?

Comments

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ARIF Request

LUCAS Device Cardiac Arrest

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The Problem Submitted For ARIF To Advise Upon

Is the Lucas device effective/cost effective particularly in the context of an ambulance service?

Comments

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ARIF Request

Cardiac Rehabilitation
Cardiac Disease

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The Problem Submitted For ARIF To Advise Upon

Is cardiac rehabilitation an effective and cost-effective service?

Comments

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ARIF Request

Cardiac Rehabilitation (Risk Stratification, Exercise Testing) Cardiac Disease

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The Problem Submitted For ARIF To Advise Upon

Is there any evidence on the role of risk stratification, and in particular by exercise tests, for cardiac rehabilitation?

Comments

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ARIF Request

Phosphate Binders (Calcium Carbonate, Calcium Acetate, Sevelamer, Lanthanum)
Kidney, Dialysis, Cardiovascular Disease
Haemodialysis

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The Problem Submitted for ARIF to Advise Upon:

Is there a reduction in cardiovascular mortality, morbidity and risk in patients with kidney failure and hyperphosphataemia taking non-metal containing phosphate binders (sevelamer and lanthanum) compared to patients taking calcium-containing phosphate binders (calcium acetate and calcium carbonate)?

See related ARIF Request (Archived) - What is the effectiveness of sevelamer (Renagel®) for the treatment of hyperphosphataemia in patients on haemodialysis?

Reviews Identified

- Sprague SM. A comparative review of the efficacy and safety of established phosphate binders: calcium, sevelamer, and lanthanum carbonate. Current Medical Research and Opinion 2007;23:3167-75
- Tonelli M, Wiebe N, Culleton B, Lee H, Klarenbach S, Shrive F et al. Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients. Nephrology, Dialysis and Transplantation 2007;22:2856-66
- Manns B, Tonelli M, Shrive F., Wiebe, N., Klarenbach, S., Lee, B., and Culleton, B. Sevelamer in patients with end-stage renal disease: a systematic review and economic evaluation. [Technology Report No. 71] Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006
- Manns B, Klarenbach S, Lee H, Culleton B, Shrive F, Tonelli M. Economic evaluation of sevelamer in patients with end-stage renal disease. Nephrology, Dialysis and Transplantation 2007;22:2867-78

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Comments

Two reviews were identified.

The review by Sprague aimed to compare the efficacy and safety of sevelamer, lanthanum and calcium-based phosphate binders. Overall, the review reads as a narrative review so its usefulness in

providing an unbiased systematic assessment of the research literature regarding the effectiveness and safety of sevelamer and lanthanum carbonate is limited.

The second review compared sevelamer with calcium phosphate binders. Two published papers (one an effectiveness review, the other an economic analysis) stemmed from work undertaken under the auspices of the Canadian Agency for Drugs and Technologies in Health (CADTH). Data considered in this ARIF request was taken from these published papers.

Standard methods were used to assess effectiveness and cost-effectiveness. Ten RCTs and 31 non controlled studies were included. Five RCTs contributed data to one of the clinical outcomes of interest, i.e. all cause mortality, with three RCTs contributing to an assessment of cardiovascular mortality. Risk difference was reported, for all cause mortality a risk difference of –2% in favour of sevelamer was estimated but this was not statistically significant (95% CI –6, 2%). For cardiovascular mortality the risk difference was slightly in favour of sevelamer at –1% but this was not statistically significant (95% CI –4, 2%). For the economic analysis, the base case cost per QALY gained in using sevelamer, utilising the above results which offer no survival advantage was estimated at CAN$157.000 (costs from 2004). Sensitivity analysis was undertaken. Assuming that sevelamer offered a survival advantage the cost per QALY was still high with an estimated range of CAN$127.000 to CAN$278.000, the lowest cost per QALY was CAN$77,000 achieved by excluding the cost of dialysis and transplantation.

The major problem regarding the Canadian assessment of sevelamer was that most of the analysis utilized data from a single trial by Suki et al 2005 which lost 48% of its patients in both the sevelamer and calcium phosphate binder arms to follow-up. This makes the results of the trial unreliable; therefore the effective and cost-effective analysis above should be viewed with extreme caution.

To conclude, due to the paucity of data it is still unclear if using calcium or non calcium based phosphate binders in patients with hyperphosphataemia secondary to kidney failure, can reduce cardiovascular mortality, morbidity and risk in patients. This is an area where more research is needed.

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ARIF Request

Electrodiagnostic Techniques
Pre-surgical Assessment
Carpal Tunnel Syndrome

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The Problem Submitted For ARIF To Advise Upon

What is the usefulness of electrodiagnostic techniques as a prognostic tool in pre-surgical assessment of patients with carpal tunnel syndrome?

Comments

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ARIF Request

Ceramic Joint Implants
Metatarsophalangeal Joint Disease
Forefoot Disease

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The Problem Submitted For ARIF To Advise Upon

What is the evidence of effectiveness of ceramic joint implants in the treatment of metatarsophalangeal joint disease?

Comments

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ARIF Request

Conductive Education
Cerebral Palsy

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The Problem Submitted For ARIF To Advise Upon

Does conductive education for the treatment of cerebral palsy achieve better long term results than conventional treatment?

Comments

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ARIF Request

Targeted Training Therapy
Cerebral Palsy

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

ARIF was asked to assess the effectiveness of targeted training therapy in the treatment of patients with Cerebral Palsy.

Targeted training uses specially designed equipment to provide support so that the child can learn to control only one or two joints at a time. After assessment, the highest body segment lacking control is 'targeted' for therapy (often the head in children with cerebral palsy). Once control is achieved, the target of the therapy moves down the body to the next area that lacks control. Daily use of the equipment is necessary but the patient can be supervised by their parent, carer or regular physiotherapist. For a more in depth description see the publication by Major RE, Johnson GR, Butler PB. Learning motor control in the upright position: a mechanical engineering approach. Proc.Inst.Mech.Eng [H.] 2001;215:315-23.

Reviews Identified

No systematic reviews were identified.

Other Evidence

- The Movement Centre. Targeted Training Outcomes after Ten Years Operation. 2006.
- Butler PB. A preliminary report on the effectiveness of trunk targeting in achieving independent sitting balance in children with cerebral palsy. Clinical Rehabilitation 1998;12:281-93.
- Farmer SE, Butler PB, Major RE. Targeted Training for Crouch Posture in Cerebral Palsy. Physiotherapy 85(4), 240-245. 1999.

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Comments

Three case reports were identified and critically appraised.

The first report described the results of ten years of Targeted Training at the Movement Centre. It presented graphically the results of four outcome measures: Gross Motor Function Measure; Chaily

Levels of Ability; Edinburgh Visual Gait Score, and the Pediatric Evaluation of Disability Inventory. Improvements after targeted training were observed in all outcome measures. Unfortunately, the sample size and completeness of the sample was not included in the report. This makes it difficult to evaluate the precision of the results and eliminate the possibility that the results only represent children who successfully completed the therapy.

The second report describes a case series of six children who utilised targeted training to improve their sitting balance. Overall, this case series was well described with all of the children making improvements. The shortcoming was the very small number of children involved.

The final report was of a single case study of a boy of seven with diplegic cerebral palsy who received six months targeted training. Positive improvements were made in standing posture, walking gait and improvement in popliteal angle. This is obviously limited as it represents only a single case study.

Overall, there seems to be a paucity of research evidence to support or refute targeted training. This area needs more research to ensure that patients are getting appropriate treatment.

Request Carried Out: December 2007

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ARIF Request

Ceredase/Cerezyme
Gaucher's Disease

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence of effectiveness and cost effectiveness of Ceredase (Alglucerase) or Cerezyme (Imiglucerase) in the treatment of Gaucher's disease?

Reviews Identified

- Bryant J, Hallam L. Ceredase in the treatment of Type 1 Gaucher's disease. Winchester: Wessex Institute of Public Health Medicine, Development and Evaluation Committee Report No 49, 1996. pp13

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Comments

Response to this request was co-ordinated by the Department of Pharmacy Policy and Practice, University of Keele. The DEC report provides a useful summary of the relevant issues.

In summary the evidence on effectiveness is that provided the patient has severe Type 1 Gaucher's disease then there is evidence to demonstrate some clinical benefit. There is considerable debate regarding the optimal dose, a critical point considering the high cost of treatment.

Request Carried Out: August 1996

Footnote: 10 July 1997
The Gaucher's Association, responding to the information above, which they believe significantly understates the value of ceredase, have asked us to make readers of this page aware of the availability of a "Helpline for Clinicians" based at the Gauchers Disease Clinic at Addenbrooke's Hospital, Cambridge which is supervised by Professor Timothy Cox. The number is: 01223 216295.

Update: May 2003 - At the time of the above request, placental derived glucocerebrosidase (alglucerase, Ceredase®) was the treatment of choice. Since then there has been a shift from the use of placental derived glucocerebrosidase to treatment using recombinant glucocerebrosidase (imiglucerase, Cerezyme®) due to the finite availability of placentae and the remote possibility of transmission of infective agents.

Our searches for this update identified no new systematic reviews on this topic however a small number of newer primary studies have been published.

A randomised controlled trial suggests that the effectiveness of cerezyme may be similar to that of ceredase:

- Grabowski GA, Barton NW, Pastores G, Dambrosia JM, Banerjee TK, McKee MA et al. Enzyme therapy in type 1 Gaucher disease: comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources. Annals of Internal Medicine 1995; 122(1):33-9

Given all the above, our original conclusions still stand that there is evidence to demonstrate some clinical benefit of enzyme replacement therapy in the treatment of type 1 Gaucher's disease.

Update: July 2006 - A recent health technology assessment undertaken by WMHTAC/ARIF for the NHS HTA programme has been published on this topic.

- Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, et al. The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: systematic review. Health Technology Assessment 2006;10(24)

We recommend reading this report as it is the most current and robust review of the clinical and cost-effectiveness of enzyme replacement therapy for patients with Gaucher's disease.

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ARIF Request

Colposcopy
Cervical Screening
Mild Dyskaryosis
Cervical Cancer

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The Problem Submitted for ARIF to Advise Upon:

ARIF were asked to investigate the impact of changing referral practice in cervical screening, both on the individual regarding patient benefit and on the service regarding cost and impact on service provision, for women presenting with mild dyskaryosis.

NHSCSP (NHS Cancer Screening Programmes) Guidelines recommend that women found to have mild dyskaryosis on an initial cytological smear test, ideally should be referred for colposcopy, however, they also say that it remains acceptable to recommend a repeat cytology test.

Reviews Identified

- Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Kehoe S, Flannelly G, Mitrou S, et al. Management of minor cervical cytological abnormalities: a systematic review and a meta-analysis of the literature. Cancer Treatment Reviews 2007; 33(6):514-520

Randomised Controlled Trials

- Cotton SC, Sharp L, Little J, Duncan I, Alexander L, Cruickshank ME et al. Trial of management of borderline and other low-grade abnormal smears (TOMBOLA): Trial design. Contemporary Clinical Trials 2006;27(5):449-471

Other Evidence

- Luesley DM, Leeson S. Colposcopy and programme management. Guidelines for the NHS Cervical Screening Programme. 2004. Report No. NHSCSP Publication No. 20
- Eggington S, Hadwin R, Brennan A, Walker P. Modelling the impact of referral guideline changes for mild dyskaryosis on colposcopy services in England. 2006. Report No. NHSCSP Publication No. 24
- Cervical screening models - Scharr website. http://www.shef.ac.uk/scharr/sections/heds/modelling/cervical-screening [accessed 1st November 2007]

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Comments

The literature assessed in this ARIF request recommends that the ideal patient treatment pathway for women with mild dyskaryosis found on cytological screening is to refer them for colposcopy after one cytology test rather than repeating the cytology test. (Luesley et al 2004, Kyrgiou et al 2007) However, it must be borne in mind that this literature is potentially biased in favour of this intervention and leaves many unanswered questions particularly in relation to the populations and exact nature of the intervention in the review by Kyrgiou. There is currently an ongoing RCT (Cotton et al 2006) examining this question, which may improve our understanding as to which screening strategy is most beneficial.

Using the economic models which are available on the Scharr website we were able to explore service and cost implications for the PCT that made the initial enquiry using local population data.

Request Carried Out: December 2007

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ARIF Request

Cervical Screening

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The Problem Submitted For ARIF To Advise Upon

What evidence is there on the effects/effectiveness of 3 year and 5 year screening intervals for cervical cancer?

Comments

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ARIF Request

Chelation Therapy
Peripheral Vascular Disease

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The Problem Submitted For ARIF To Advise Upon

Is chelation therapy effective for the treatment of peripheral vascular disease?

Comments

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ARIF Request

Chest Pain Services
South Asian Communities
Deprived Communities
Chest Pain Assessment

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

To gain an understanding of the current knowledge base regarding chest pain presentations to both primary and secondary care services:

- Are patients with chest pain who present to primary and secondary healthcare services treated differently depending upon ethnicity (South Asian) and deprivation?
- If there is a difference, why that is:
  Is this difference due to physiological differences (resulting in atypical presentation of signs and symptoms)?
  Or is it due to social/cultural differences?
  Or it is due to access difficulties?
- Does this difference (if it exists) lead to suboptimal care?
- Are there any interventions that improve outcomes in this population?

Reviews Identified

- Cooper A, Calvert N, Skinner J, Sawyer L, Sparrow K, Timmis A et al. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. Full guideline. Final draft - January 2010 London: National Clinical Guideline Centre for Acute and Chronic Conditions; 2010.

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Comments

NICE are due to publish guidelines on the management of patients presenting with chest pain of cardiac origin. The guidelines have taken into account two studies that have examined whether patients from Asian origin have atypical chest pain, and whether this should be considered during patient assessment.

Both studies found that Asian patients were younger and more likely to have diabetes. Weak evidence

suggests that there were more Asian patients with atypical symptoms than Caucasians. This is also an area that needs further research.

Request Carried Out: March 2010

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ARIF Request

Non-Invasive Ventilation
Ventilation - Non-Invasive
Neuromuscular Diseases
Chest Wall Diseases

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Evidence on clinical and cost-effectiveness of non-invasive ventilation in patients with neuromuscular and chest wall diseases.

Reviews Identified

- Annane D, Orlikowski D, Chevret S, Chevrolet JC, Raphaël JC. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD001941. DOI: 10.1002/14651858.CD001941.pub2.
- Piepers S, Berg J-PVD, Kalmijn S, Van Der Pol WL, Wokke JHJ, Lindeman E et al. Effect of non-invasive ventilation on survival, quality of life, respiratory function and cognition: A review of the literature. Amyotrophic Lateral Sclerosis 2006;7(4):195-200

Ongoing Review

- Leigh PN, Annane D, Jewitt K, Mustfa N. Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease (Protocol). Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD004427. DOI: 10.1002/14651858.CD004427

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Comments

Searches identified two relevant systematic reviews and one Cochrane review protocol. No reviews on cost effectiveness were found. The two complete reviews are of reasonable quality.

The review by Annane (2007) aimed to examine the effects of nocturnal mechanical ventilation in people with neuromuscular or chest wall disorders. Searches were up to June 2006 and eight randomised controlled trials (RCTs) met the review's inclusion criteria. Of these, six were relevant to the request. All had very small sample sizes, ranging from 5 to 41 patients. They were published

between 1987 and 2006, with four of them being over one to two decades old. Two of these were crossover trials. However, ventilation was delivered non-invasively.

The review authors concluded that "Current evidence about the therapeutic benefit of mechanical ventilation is weak but consistent, suggesting alleviation of the symptoms of chronic hypoventilation in the short-term. In three small studies survival was prolonged mainly in participants with motor neuron diseases. "

Three of the trials tested the ventilation for only one night and all measured short-term outcomes e.g. blood gas and hypoventilation symptoms. One also measured the long-term (mean 52 months) outcomes, e.g. unplanned admission to hospital, death, etc., and was included in the analyses of long-term effect of the intervention. It is doubtful that any of these long-term outcomes could be attributable to a single night NIPPV treatment.

In all relevant studies, outcomes assessed were summarised using meta-analysis and favoured or tended to favour the intervention. However, they were all based on very small sample sizes, ranging from 10 to 80 patients.

The review by Piepers (2006) aimed to analyse what is known of the effect of non-invasive home mechanical ventilation (NIV) for amyotrophic lateral sclerosis (ALS) patients on survival, quality of life (QoL), respiratory function and symptoms of (nocturnal) hypoventilation.

The searches there were up to May 2005. Twelve studies were included which were published between 1995 and 2003. Of the 12 studies 11 were observational studies, three of which used control groups. One study was a quasi-RCT (with only 20 patients) which was also included in the Annane 2007 review.

Sample size in the studies varied from 10 to 122, giving a number of 411 patients. Median follow-up length varied from 1.5 to 100 months. The review stated that all the studies had methodological flaws, and ‘however they seem to suggest that NIV leads to a longer survival time, better QoL, no decline in respiratory function, fewer respiratory symptoms and improved cognition.’

Comparing the two reviews, though both of them covered literature from similar time periods, Piepers 2006 focused on patients with ALS and non-invasive ventilation for home use only but allowed observational studies, while Annane 2007 was restricted to RCTs but included a wider population and wider settings. However, in both reviews, there were major shortcomings with the studies assessed, including very small sample sizes, low quality level of study design and methodological issues.

Overall, data from the reviews suggest that non-invasive ventilation might have potential positive clinical effects on patients with neuromuscular and chest wall diseases, however, this may be attributable to publication bias and biases due to methodological flaws of the studies reviewed. Well designed large randomised controlled trials and cost-effectiveness studies would fill the gap in evidence informing the use of the device for this patient population. NICE have published a draft scope for a clinical practice guideline on use of non-invasive ventilation for motor neurone disease; the anticipated publication date for the guideline is July 2010.

Request Carried Out: September 2009

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ARIF Request

Nocturnal Mechanical Ventilation
Neuromuscular Disorders
Chest Wall Disorders

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of nocturnal mechanical ventilation in relieving symptoms of hypoventilation in patients with neuromuscular and chest wall disorders?

Comments

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ARIF Request

Fish Oil Supplements
Essential Fatty Acids (*n*-3 series)
Child Behaviour

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The Problem Submitted For ARIF To Advise Upon

What is the evidence on the effectiveness of fish oil supplements on school aged children's behaviour and educational attainment?

Comments

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ARIF Request

UK Health Visitors
Child Health

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The Problem Submitted for ARIF to Advise Upon:

Assessment of the effectiveness of health visitors activities in the NHS.

What is the effectiveness of a universal health visiting service with regard to breast feeding rates, childhood accidents, developmental delay, child abuse, failure to thrive, smoking, hospital admission rates and mental well being.

Reviews Identified

- Elkan R, Kendrick D, Hewitt M, Robinson JJA, Tolley K, Blair M et al The effectiveness of domiciliary health visiting: a systematic review of international studies and a selective review of the British literature Health Technology Assessment 2000;4(13)

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Comments

This was a well-conducted systematic review. One hundred and six primary studies and 6 reviews were included in the systematic part of the review. Despite the authors efforts in retrieving studies equivalent to UK health visiting practice, most of the included studies came from North America and concentrated on high-risk populations in contrast to the UK universal health visiting system. The review authors try to put this research into the context of UK health visiting practice, but without research evidence available regarding universal health visiting, judgements regarding the effectiveness of universal health visiting are difficult to make.

Request Carried Out: June 2006

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ARIF Request

Fertility Preservation
Reproductive Function, Preservation
Childhood Cancer - Treatment Effects on Fertility
Survivors of Childhood Cancer
Infertility after Childhood Cancer Treatment

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The Problem Submitted for ARIF to Advise Upon:

What is the impact of childhood cancer treatment on women of reproductive age and what possible strategies would address their needs (with specific reference to reproductive function)?

Each year approximately 120 per million children in Britain suffer from cancer. Improvements in treatment have increased overall survival, five years after diagnosis, to 75%. However the successful treatment of childhood cancer can be associated with impaired fertility in approximately 15% of survivors.

Reviews Identified

None identified.

OtherEvidence

- A strategy for fertility services for survivors of childhood cancer by a Multidisciplinary Group convened by the British Fertility Society July 2003 http://www.britishfertilitysociety.org.uk/practicepolicy/documents/fccpaper.pdf#search=%22childhood%20cancer%20fertility%22
- Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, Beck LN, Brennan LV, Oktay K. American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients. Journal of Clinical Oncology 2006;24(18):1-15
- Thompson AB, Critchley HOD, Kelnar CJH, Wallace WHB. Late reproductive sequelae following treatment of childhood cancer and options for fertility preservation. Best Practice and Research Clinical Endocrinology and Metabolism 2002;16(2):311-34
- Wallace WHB, Blacklay A, Eiser C, Davies H, Hawkins M, Levitt GA, Jenney MEM. Developing strategies for long term follow up of survivors of childhood cancer. BMJ 2001;323:271-4

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Comments

The impact of childhood cancer treatment on women of reproductive age and the options available for fertility preservation are usefully summarised by Thompson et al (2002) and Lee et al (2006). Cytotoxic chemotherapy and radiotherapy may damage gonadal tissue and result in long-lasting or permanent sterility. Whilst cancer therapy may damage the developing gonad its full impact generally remains latent in childhood and manifests only in adulthood as infertility or a permanent menopause. Rates of permanent and compromised fertility after cancer treatment vary and depend on many factors that include the drug or size/location of the radiation field, dose, dose-intensity, method of administration, disease, age and pre-treatment fertility of the patient. Currently embryo cryopreservation and ovarian transposition are the only viable fertility preservation strategies available. Other potentially available strategies such as oocyte and ovarian cryopreservation are at an experimental stage.

To date a strategy to provide a reproductive health service that addresses the needs of childhood cancer survivors is not in place. However, the British Fertility Society's (2003) report makes a series of recommendations to facilitate the development of a properly funded, ethically sound and scientifically based service for childhood cancer survivors.

Request Carried Out: January 2007

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ARIF Request

Dermasilk
Clothing - Therapeutic
Dermatitis - Severe
Children

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the clinical effectiveness of DermaSilk therapeutic clothing for children with severe dermatitis?

DermaSilk therapeutic clothing is a specially knitted sericin-free silk fabric treated with AEGIS AEM5772/5 which has antibacterial properties. It is made into garments e.g. a T-shirt or an arm tube for dressing, and used in the treatment of various forms of dermatitis, eczema and allergic skin conditions. It is believed to be capable of absorbing moisture without causing irritation to the skin, and allows the free movement of air through the fabric, thus allowing the skin to breathe more easily, reduce itching and promote faster healing.

Reviews Identified

No systematic reviews or health technology assessments were identified.

Randomised Controlled Trials

- Stinco G, Piccirillo F, Valent F. A randomized double-blind study to investigate the clinical efficacy of adding a non-migrating antimicrobial to a special silk fabric in the treatment of atopic dermatitis. Dermatology. 2008;217(3):191-5

Other Evidence

- Koller DY, Halmerbauer G, Böck A, Engstler G. Action of a silk fabric treated with AEGISTM in children with atopic dermatitis: A 3-month trial. Pediatric Allergy and Immunology. 2007;18(4):335-338
- Ricci G, Patrizi A, Bendandi B, Menna G, Varotti E, Masi M. Clinical effectiveness of a silk fabric in the treatment of atopic dermatitis. British Journal of Dermatology. 2004;150(1):127-31
- Senti G, Steinmann L S, Fischer B, Kurmann R, Storni T, Johansen P, Schmid-Grendelmeier P, Wüthrich B, Kündig T M. Antimicrobial silk clothing in the treatment of atopic dermatitis proves comparable to topical corticosteroid treatment. Dermatology 2006;213:228-233
- Ricci G, Patrizi A, Mandrioli P, Specchia F, Medri M, Menna G, Masi M. Evaluation of the antibacterial activity of a special silk textile in the treatment of atopic dermatitis. Dermatology

2006;213:224-227

- National Institute for Health and Clinical Excellence. Atopic eczema in children. Management of atopic eczema in children from birth up to the age of 12 years. NICE clinical guideline 57. London: National Institute for Health and Clinical Excellence (NICE); 2007. Available from http://www.nice.org.uk/nicemedia/pdf/CG057NICEguideline.pdf [Accessed on 10-03-2010]

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Comments

No systematic reviews or health technology assessments were identified. Five trials were identified and appraised.

Of the five trials, one controlled trial compared DermaSilk with a topical corticosteroid in the treatment of atopic dermatitis (AD) (Senti 2006); none of the others compared DermaSilk with a standard therapy that was recommended by NICE (NICE 2007). The RCT (Stinco 2008) and one controlled trial (Ricci 2006) compared DermaSilk with the same fabric without the AEGIS AEM 5772/5 antimicrobial; of the remaining two, one (Ricci 2004) compared DermaSilk with cotton clothes and the other (Koller 2007) with simple silk followed by cotton clothes.

The RCT (Stinco 2008) included both adults and children, however, the results were not reported separately for the children. In three controlled trials the children were either a mixture of mild-to-severe (Ricci 2004), or mild-to-moderate (Koller 2007), or moderate AD only (Senti 2006). In the RCT (Stinco 2008) and the other controlled trial (Ricci 2006) the patients had AD with eczematous lesions, but the severity of the condition was not classified.

Sample sizes were all small, ranging from 12 to 46 patients and giving 125 patients in total. Methodological quality was reasonable in the RCT but was limited in the controlled trials. Study duration in two trials (Ricci 2004, 2006) was only 7 days; in one of these (Ricci 2004) further information on the treatments being received before the study and whether a washout phase was given was not reported, thus it was unclear whether there could be any carry-over effect on the results. Also, in this study eight children were excluded (26%) because they did not follow the instructions correctly, but there was no intention to treat analysis.

Results from the trials all showed that DermaSilk therapeutic clothing can be beneficial. However, small sample size and weak study design limited the reliability and the usefulness of the results.

In conclusion, evidence on the clinical effectiveness of DermaSilk therapeutic clothing for children with dermatitis is currently very limited. It suggests that this therapy can be beneficial for patients with atopic dermatitis, however, the usefulness of the results is greatly limited due to paucity and poor quality of the data. Large studies with improved methodology would fill the gap in evidence informing the use of the therapy for this patient population.

Request Carried Out: March 2010

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ARIF Request

Parent Education Programmes
Children with Conduct Disorders
Conduct Disorders

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The Problem Submitted For ARIF To Advise Upon

The effect of parent education programmes on the behaviour and mental health of children with conduct disorders and their parents.

Comments

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ARIF Request

Photodynamic Therapy
Pathological Myopia
Choroidal Neovascularisation

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The Problem Submitted For ARIF To Advise Upon

Photodynamic therapy (PDT) is a newly developed type of treatment combining

- injection of a light-sensitive dye which concentrates in areas of “abnormality”
- low power laser

The rationale is that abnormal cells can be destroyed without damage to nearby normal cells.

PDT has applications in a number of areas, particularly cancer. However, requests to ARIF have focused on the use of this technology in treatment of eye disease. In this application the only currently commercially available light sensitive dye is verteporfin.

Comments

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Archived ARIF Request

Provocation-neutralisation Technique
Miller technique
Multiple Allergy Syndrome
Multiple Chemical Sensitivity
Chronic Fatigue Syndrome
Candidal Hypersensitivity
Post-chemotherapy Therapy

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

ARIF has received many requests concerning the effectiveness of provocation-neutralisation therapy.

There are related web pages on Enzyme Potentiated Desensitisation and Breakspear Hospital.

Reviews Identified

ARIF briefing to Regional Evaluation Panel (REP) 2003.

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Comments

The briefing paper summarises requests received up to 2003. Repeated searches indicate an absence of RCT evidence on the effectiveness of provocation-neutralisation for complex ill-defined syndromes like multiple allergy syndrome and multiple chemical sensitivity. There are RCTs for simpler allergic conditions with an allergic basis, but many of these RCTs have not been systematically reviewed.

To help address this a REP report on REP report on "Provocation-neutralisation Testing and Therapy for Food Allergy" was completed in 2004. Their recommendation was of insufficient evidence with a need for further research.

The urgent need for new rigorous primary and secondary research could be extended to all aspects of provocation-neutralisation therapy.

Request Carried Out: October 2003

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ARIF Request

Enzyme Potentiated Desensitisation (EPD)
Multiple Chemical Sensitivity
Formaldehyde Poisoning
Chronic Fatigue Syndrome
Gulf War Syndrome

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The Problem Submitted For ARIF To Advise Upon

ARIF has received several requests concerning the effectiveness of EPD.

Comments

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ARIF Request

Cognitive Behavioural Therapy and Other Treatments Chronic Fatigue Syndrome (ME)

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The Problem Submitted For ARIF To Advise Upon

What is the evidence on the effects/effectiveness of treatments for chronic fatigue syndrome?

Comments

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ARIF Request

Enzyme Potentiated Desensitisation Chronic Fatigue Syndrome

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of enzyme potentiated desensitisation (EPD) for chronic fatigue syndrome (CFS)?

Comments

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ARIF Request

Photopheresis
Extracorporeal Photochemotherapy (ECP)
Chronic Graft-Versus-Host Disease (cGVHD)

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The Problem Submitted for ARIF to Advise Upon:

ARIF were asked to evaluate the effectiveness and safety of Extracorporeal Photochemotherapy (ECP) in children who have steroid refractory cutanous chronic graft-versus-host disease (cGVHD).

“ECP is a therapeutic procedure where mononuclear blood cells are exposed ex vivo to a chemical and their subsequent interaction is triggered by light” (Chan 2006). “Chronic graft-versus-host disease remains a significant cause of late morbidity and mortality following allogeneic stem cell transplantation” (Farag 2004). The first line of therapy is treatment with steroids, however, in a proportion of patients this is not successful. ECP is one of a few experimental treatments which have been investigated in the treatment of these patients.

Reviews Identified

- Scarisbrick JJ, Taylor P, Holtick U, Makar Y, Douglas K, Berlin G et al. UK consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. British Journal of Dermatology 2008;158(4):659-678
- OHTAC (Ontario Health Technology Advisory Committee). Extracorporeal Photopheresis. Health Technology Policy Assessment - Pre-Edit Proof, March 2006. http://www.health.gov.on.ca/english/providers/program/ohtac/tech/reviews/sum_ecp_030106.html

Other Evidence

- Farag SS. Mini review. Chronic graft-versus-host disease: where do we go from here? Bone Marrow Transplantation (2004) 33, 569-577
- Chan KW. Extracorporeal photopheresis in children with graft-versus-host disease. Journal of Clinical Apheresis 2006;21(1):60-64

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Comments

Our ARIF searches identified several relevant reviews. We undertook detailed assessment of two which we felt were the most appropriate for the UK setting (Scarisbrick and up-to-date OHTAC).

The review by Scarisbrick gives clear detailed information about ECP’s optimum use. It recommends the following: “The combination of lack of evidence for the effectiveness of ECP as primary treatment

and its high cost made this group recommend ECP only as a second line, third line or subsequent salvage therapy. Best responses to ECP therapy have been observed in cutaneous, mucous membrane and hepatic manifestations of cGVHD. …Therefore the group recommend that patients with disease affecting these organs should be given priority for treatment. However, evidence of consistent responses is insufficient to recommend routine therapy "except under exceptional circumstances" (see page 669-670 Scarisbrick).

The OHTAC review concluded that the evidence suggests that ECP improves patient response rates and survival, but that the evidence is poor quality, therefore uncertainties exist and further research is likely to have an important impact on the confidence of the estimate of effect and this is likely to change.

The literature in this area consists of case series studies, therefore effectiveness against other treatments or no treatment cannot be estimated. Aspects of design of the two reviews evaluated also allow their conclusions to be open to interpretation. The main aim of the publication by Scarisbrick was to formulate a consensus document to provide a standardized eligibility assessment and treatment strategy across the UK, therefore only guidelines not primary studies were sought. The OHTAC report was a review of reviews with gaps filled by primary studies. Both publications are therefore limited by the aim of their searches which could be considered to be suboptimal compared to standard systematic review searching techniques, giving rise to publication bias. Both publications also suffered from vague inclusion criteria and outcome reporting.

Request Carried Out: November 2008

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ARIF Request

Spinal Cord Stimulation
Chronic Neuropathic Pain
"Failed" Back Surgery Syndrome
Complex Regional Pain Syndrome

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of spinal cord stimulation for chronic neuropathic pain, particularly in “failed” back surgery syndrome and complex regional pain syndrome?

Comments

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ARIF Request

Chronic Obstructive Airways Disease (Chronic Obstructive Pulmonary Disease)
Pulmonary Rehabilitation (Respiratory Rehabilitation)

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The Problem Submitted For ARIF To Advise Upon

What is the evidence for respiratory rehabilitation for those with chronic obstructive pulmonary/airways disease?

Comments

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ARIF Request

Spirometry
Oximeters
Chronic Obstructive Pulmonary Disease (COPD)

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence to advocate the use of spirometry and oximeters to improve and manage symptoms of patients with chronic obstructive pulmonary disease (COPD) who are treated in primary care?

COPD is “characterised by airflow obstruction. The airflow obstruction is usually progressive, not fully reversible and does not change markedly over several months. The disease is predominantly caused by smoking.

Spirometry and oximetry are both diagnostic tests. In testing effectiveness users firstly have to understand what exactly it is that the tests are measuring.

Spirometry is a test that measures the amount of air a patient can exhale in one second (FEV1) and the total amount of air a patient can blow out in one breath (FEV). In obstructive airways disease the amount of air a person can blow out quickly is reduced. If the FEV1 is less than 80% of the predictive value (based on age, sex and size) or if the FEV1/FVC ratio is 0.7 or less this is indicative of airway obstruction.

Oximetry is designed to measure the arterial oxygen saturation of haemoglobin. It does not give information regarding the ventilation of the patient (so doesn’t measure CO2 excretion).

Reviews Identified

- Cranston JM. Crockett AJ. Moss JR. Pegram RW. Stocks NP. Models of chronic disease management in primary care for patients with mild-to-moderate asthma or COPD: a narrative review. Medical Journal of Australia. 2008;188(8 Suppl):S50-2
- Cranston JM, Crockett AJ, Moss JR et al Models of chronic disease management in primary care for patients with mild to moderate asthma or COPD. Canberra: Australian Primary Health Care Research Institute, 2006. http://www.anu.edu.au/aphcri/Domain/ChronicDiseaseMgmt/Final_1_Crockett.pdf [accessed 5th December 2008]

Other Evidence

- Chronic obstructive pulmonary disease. Management of COPD in adults in primary and secondary care. NICE Clinical Guideline 12; 2004 http://www.nice.org.uk/nicemedia/pdf/CG012_niceguideline.pdf [accessed 5th December 2008]

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Comments

The NICE guidelines are general guidelines on the management of COPD in adults in primary care and secondary care. They give recommendations on when and how to use spirometry and oximeters in practice in patients with COPD. All of the recommendations have a D rating, which according to the NICE hierarchy of evidence scheme means that the evidence has originated from expert committee reports or opinions and/or clinical experience of respected authorities or has been extrapolated from data obtained from trials.

The methodology of the review was of a reasonable systematic review standard. Searches were up to January 2006. A narrative format was presented. Patients had to have mild to moderate COPD and the setting was primary care. The review was conducted in Australia and thus had that focus.

The authors of the review found that there was no consensus as to the definition of COPD and the scale of airway obstruction as read by spirometry. Lack of consensus can lead to an increase in false positives particularly in a test that is used as a screening tool where prevalence of the disease is low. The review authors also noted that test accuracy could also vary according to how the test was conducted, variation in accuracy could stem from the proficiency of the health professional administering the test and also how easy it was for the patient to undertake the test. Diagnostic tests should also only be used when there are effective treatments available, particularly if it is used as a screening tool. The review authors state that "spirometry appears unlikely to be useful in mild to moderate COPD for monitoring response to therapies or altering treatments in primary care as benefits of these therapies are greatest in patients with the most severe disease". However, they then go on to say that spirometry could be used to identify a threshold level when treatment should be initiated. They also investigated the use of spirometry in encouraging patients to stop smoking, which is the main factor in progression of COPD. A pooled estimate from four studies gave an odds ratio of 1.21 (95% CI 0.60, 2.42) in favour of smoking cessation but this was not statistically significant.

In conclusion, despite the publication of recent systematic reviews, which have investigated the use of spirometry in the management of patients with COPD in primary care, it is difficult to determine its effectiveness due to the paucity of data in the primary research literature. It appears to be an area that needs more primary research, particularly given the prevalence of COPD. Oximetry, was not identified as a test that has been used in patients with mild to moderate COPD, within the NICE guidelines this test is generally recommended for patients suffering from acute exacerbations of COPD.

Request Carried Out: December 2008

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ARIF Request

Domicillary Oxygen
Chronic Obstructive Pulmonary Disease

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The Problem Submitted For ARIF To Advise Upon

When is domiciliary oxygen effective?

Comments

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ARIF Request

Spirometry
Chronic Obstructive Pulmonary Disease (COPD)

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of spirometry and screening for chronic obstructive pulmonary disease (COPD) in primary versus secondary care?

Comments

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ARIF Request

Non-Invasive Positive Pressure Ventilation Chronic Obstructive Pulmonary Disease

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of non-invasive positive pressure ventilation (NPPV) for patients with stable hypercapnic chronic obstructive pulmonary disease (COPD) in a domiciliary environment?

Comments

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ARIF Request

Percutaneous Electrical Stimulation (PENS) Chronic Pain (Breast and Back) Pain

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of PENS in reducing back and breast pain?

PENS is a pain relieving procedure where needles are inserted to a depth of 1 to 4 cm around or adjacent to the nerves serving the area of pain and an electrical current is then put through the needles to stimulate the area. PENS is not a form of acupuncture. Neither should it be confused with transcutanous electrical nerve stimulation (TENS), where the electrical stimulation is delivered through probes placed onto the skin.

ARIF requests have been completed which relate to different types of electrical stimulation for other conditions: Spinal Cord Stimulation/Chronic Neuropathic Pain/"Failed" Back Surgery Syndrome/Complex Regional Pain Syndrome and Occipital Nerve Stimulation/Migraine, Chronic

Reviews Identified

- Blue Cross of Idaho. Percutaneous Electrical Nerve Stimulation (PENS) or Percutaneous Neuromodulation Therapy. http://www.bcidaho.com/providers/medical_policies/sur/mp_70129.asp

Randomised Controlled Trials

- Ghoname EA, White PF Ahmed HE et al. Percutaneous electrical nerve stimulation: an alternative to TENS in the management of sciatica. Pain 1999;83(2):193-9
- Ghoname EA, Craig WF, White PF et al. Percutanous electrical nerve stimulation for low back pain: a randomised crossover study. JAMA 1999;281(9):818-23
- Hamza MA, Ghoname EA, White PF et al. Effect of the duration of electrical stimulation on the analgesic response in patients with low back pain. Anesthesiology 1999;91(6):1622-7
- Ghoname ES, Craig WF, White PF et al. The effect of stimulus frequency on the analgesic response to percutaneous electrical nerve stimulation in patients with chronic low back pain. Anesthesia and Analgesia 1999;88(4):841-6
- White PF, Ghoname EA, Ahmed HE et al. The effect of montage on the analgesic response to percutaneous neuromodulation therapy. Anesthesia and Analgesia 2001;92(2):483-7

- Weiner DK, Rudy TE, Glick RM et al. Efficacy of percutaneous nerve stimulation for the treatment of chronic low back pain in older adults. Journal of the American Geriatrics Society 2003;51(5):599-608
- Yokoyama M, Sun X, Oku S. et al. Comparison of percutaneous electrical nerve stimulation with transcutaneous electrical nerve stimulation for long term pain relief in patients with chronic low back pain. Anesthesia and Analgesia 2004;98(6):1552-6
- White PF, Craig WF, Vakharia AS et al. Percutaneous neruomodulation therapy: does the location of electrical stimulation affect the acute analgesic response? Anesthesia and Analgesia 2000; 91(4):949-54

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Comments

The review had a USA perspective with the aim of investigating the effectiveness of PENS to determine a policy statement regarding its use in USA Medicare and Medicaid Services. It was last updated April 2006 and included 10 RCTs, 7 concerning low back pain, with 1 each for chronic neck pain, chronic diabetic neuropathy and chronic headache. Of these the low back pain were the most relevant to the request. Five of the low back pain RCTs came from the same centre. Their purpose seemed to be preliminary work on PENS attemping to optimise the treatment. They looked at differences in effect of alternative frequencies, duration of treatment, and patterns of needle placement. All five trials found PENS improved pain scores, physical activity and quality of sleep. Additionally patients had a reduction in usage of oral analgesics and preferred the PENS treatment. However, all of these outcomes measured PENS over the short term (≤ 3 weeks). The remaining 2 RCTs gave longer treatments (4 and 6 weeks) with a follow up to 3 months. Again the results favoured PENS, with the 6 week treatment finding a sustained effect at 3 months, whilst the 4 week treatment did not. The review concluded that whilst the RCTs suggest that PENS has effects that exceed placebo in the short term, the evidence does not permit conclusions about the long-effectiveness of PENS for treating low back pain. We would concur with this. Additionally, we found no trial data that had looked at PENS for the treatment of breast pain and back pain other than low back pain.

Request Carried Out: January 2007

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ARIF Request

Spinal Cord Stimulation
Chronic Pain

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The Problem Submitted For ARIF To Advise Upon

What is the evidence on the effectiveness of spinal cord stimulation in the management of chronic pain?

Comments

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ARIF Request

Intraspinal Drug Delivery Chronic Pain

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of intraspinal drug delivery in the management of chronic pain?

Comments

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ARIF Request

Residential Pain Management Programmes
Chronic Pain
Pain

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of residential pain management programmes (PMPs) for patients with severe chronic pain that has not responded to other therapies?

Comments

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ARIF Request

Early Referral
Chronic Renal Failure

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The Problem Submitted For ARIF To Advise Upon

What is the evidence on the effectiveness of early referral to specialist renal services for people with chronic renal failure?

Comments

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ARIF Request

Chronic Sinusitis

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The Problem Submitted For ARIF To Advise Upon

What is the most effective diagnostic test for chronic sinusitis?

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ARIF Request

Tonsillectomy
Chronic Tonsillitis

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The Problem Submitted For ARIF To Advise Upon

Evidence for the effectiveness of tonsillectomy for chronic tonsillitis and chronic pharyngitis in children and adults.

Comments

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ARIF Request

Chronic Wounds
Ulcers (Diabetic/Pressure)
Topical Negative Pressure Vacuum Assisted Wound Closure Therapy

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This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in December 2005 and Update in March 2007.

The Problem Submitted for ARIF to Advise Upon:

What is the clinical and cost-effectiveness of vacuum assisted wound closure (VAC) therapy for wound management?

VAC therapy is the application of negative pressure across the entire surface of the wound to remove extracellular fluid and exudate, reduce oedema and improve blood flow. The therapy involves packing the wound with foam dressing, embedding an evacuation tube connected to a computer-controlled vacuum pump, and covering the foam, tubing and at least 3-5 centimetres of healthy tissue with an adhesive drape to create a seal. Fluid is then drawn from the wound through the foam into a disposable canister.

Reviews Identified

- Evans D, Land L. Topical negative pressure for treating chronic wounds. The Cochrane Database of Systematic Reviews 2001, Issue 1. Art. No.: CD001898. DOI: 10.1002/14651858.CD001898
- Fisher A, Brady B. Vacuum assisted wound closure therapy. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2003
- Higgins S. The effectiveness of vacuum assisted closure (VAC) in wound healing Clayton, Victoria: Centre for Clinical Effectiveness (CCE); 2003
- Pham C, Middleton P, Maddern G. Vacuum-assisted closure for the management of wounds: an accelerated systematic review. Stepney, SA: Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S); 2003
- Ontario Ministry of Health and Long-Term Care. Vacuum assisted closure therapy for wound care. Toronto: Ontario Ministry of Health and Long-Term Care; 2004
- Samson DJ, Lefevre F, Aronson N. Wound-healing technologies: low-level laser and vacuum-assisted closure. Rockville: Agency for Healthcare Research and Quality (AHRQ); 2004 (Report No 111)
- Costa V, Brophy J, McGregor M. Vacuum assisted wound closure therapy (VAC ®). Montreal: Technology Assessment Unit of the McGill University Health Centre (MUHC), 2005 (Report no 19) http://upload.mcgill.ca/tau/VAC_report_final.pdf

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Comments

Whilst the seven reviews identified all provide good overviews of the topic we would especially recommend the Ontario Health Technology Advisory Committee review. This well conducted systematic review aims to determine if VAC therapy is effective and cost effective in healing wounds including pressure or diabetic ulcers, sternal wounds, and skin grafts. It provides a comprehensive and up-to-date account of the clinical need for therapy, the VAC technology and the available evidence of its effectiveness.

The Ontario reviewers conclude that there is some evidence from small randomised controlled trials (RCTs) which indicates VAC therapy may promote better/faster healing for some patients, but that caution is required because of the RCTs size and openness to bias. In their appraisal of the economic literature the reviewers identify some cost comparisons (with saline, wet-to-moist and wet-to-dry dressings) that indicate VAC therapy may be cheaper due to reduced labour costs (as VAC dressings are changed less frequently). However no unbiased well conducted cost effectiveness analyses were identified.

In overall conclusion, based on the evidence to-date, the clinical effectiveness of VAC therapy in wound management is unclear. More rigorous RCTs assessing the use of VAC therapy on different types of wounds are required along with an independent economic evaluation from an NHS/UK perspective.

Request Carried Out: December 2005

Update: March 2007 - The request was updated in March 2007.

Reviews Identified

- Ontario Ministry of Health and Long-Term Care. Negative pressure wound therapy: health technology literature review. Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care (MAS); 2006
- Pham CT, Middleton PF, Maddern GJ. The safety and efficacy of topical negative pressure in non-healing wounds: a systematic review. Journal of Wound Care 2006;15(6):240-50.

Randomised Controlled Trials

- Stannard JP, Robinson JT, Anderson ER, McGwin G, Volgas DA, Alonso JE. Negative pressure wound therapy to treat hematomas and surgical incisions following high-energy trauma. The Journal of Trauma 2006;60 (6):1301-06
- Braakenburg A, Obdeijn MC, Feitz R, van Rooij IA , van Griethuysen AJ, Klinkenbijl JH. The clinical efficacy and cost effectiveness of the vacuum-assisted closure technique in the management of acute and chronic wounds: a randomized controlled trial. Plastic and Reconstructive Surgery 2006;118 (2):390-7
- Vuerstaek JD, Vainas T, Wuite J, Nelemans P, Neumann MH, Veraart JC. State-of-the-art treatment of chronic leg ulcers: A randomized controlled trial comparing vacuum-assisted closure (V.A.C.) with modern wound dressings. Journal of Vascular Surgery 2006;44(5):1029-37
- Llanos S, Danilla S, Barraza C, Armijo E, Pineros J L, Quintas M, Searle S, Calderon W. Effectiveness of negative pressure closure in the integration of split thickness skin grafts: a randomized, double-masked, controlled trial. Annals of Surgery 2006;244(5):700-5

Comments

We identified two well conducted systematic reviews. The most up-to-date of the two was produced by the Ontario Health Technology Advisory Committee which searched comprehensively to March 2006. Their conclusions were similar to those mentioned in the original request.

However, in addition we identified four very recently published RCTs with a total of 250 participants which would have been included in the systematic reviews had they been available. We have not been

able to systematically review these extra studies, or indeed confirm that these are all the recently published RCTs. The need for a further up-dated systematic review is urgently indicated.

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ARIF Request

Mental Health
Clinical Psychology (Clinical Psychologists)

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The Problem Submitted For ARIF To Advise Upon

Is there any evidence on the effectiveness of clinical psychology in general and whether clinical psychologists are more effective than other professionals, such as counsellors, in certain situations?

Comments

This request was carried out more than four years ago and has not been updated since. The articles identified may no longer be the best available and therefore the commentary may be out of date. As a precaution the information has been removed from this page.

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ARIF Request

Cognitive Behavioural Therapy Depression

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The Problem Submitted For ARIF To Advise Upon

The effectiveness of cognitive behavioural therapy (CBT) in treating depression in non-white communities, particularly South Asian/Pakistani women.

Comments

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ARIF Request

Screening by Colonoscopy in those with Family History Colorectal Cancer

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The Problem Submitted For ARIF To Advise Upon

What is the evidence base of the proposals made for the West Midlands Familial Cancer Initiative, particularly those concerning screening of individuals with a positive family history of colorectal cancer?

Comments

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ARIF Request

Echinacea
Common Cold

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The Problem Submitted For ARIF To Advise Upon

What treatments have been shown to be effective in the treatment of the common cold?

Comments

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ARIF Request

NSAIDS
Common Cold

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The Problem Submitted For ARIF To Advise Upon

What treatments have been shown to be effective in the treatment of the common cold?

Comments

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ARIF Request

"Over the Counter" Remedies
Common Cold

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The Problem Submitted For ARIF To Advise Upon

What treatments have been shown to be effective in the treatment of the common cold?

Comments

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ARIF Request

Steam Inhalation
Common Cold

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The Problem Submitted For ARIF To Advise Upon

What treatments have been shown to be effective in the treatment of the common cold?

Comments

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ARIF Request

Vitamin C
Common Cold

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The Problem Submitted For ARIF To Advise Upon

What treatments have been shown to be effective in the treatment of the common cold?

Comments

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ARIF Request

Zinc
Common Cold

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The Problem Submitted For ARIF To Advise Upon

What treatments have been shown to be effective in the treatment of the common cold?

Comments

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ARIF Request

Communication Disorders in Pre-School Children Screening Tools (WILSTAAR, CHAT) Speech and Language Therapy

Table of Contents

The Problem Submitted For ARIF To Advise Upon

Community Trusts are seeking an effective screening tool for communication disorder in children as part of the pre-school child health surveillance programme. The local Trust was particularly interested in WILSTAAR and CHAT. Are these tools effective?

Comments

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ARIF Request

Health Promotion
Community Development Programmes

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The Problem Submitted For ARIF To Advise Upon

Are Community Development Programmes an effective way of empowering committees?

Comments

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ARIF Request

Community Health Teams
Elderly Physically Frail People

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The Problem Submitted For ARIF To Advise Upon

Is there any evidence that the provision of a community health team for older people with physical health problems and frailty would benefit service users?

Comments

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ARIF Request

Community Hospitals

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The Problem Submitted For ARIF To Advise Upon

Is there any evidence on the effectiveness of community hospitals within the UK for the delivery of services such as rehabilitation, GP beds, and nurse run clinics for chronic conditions such as diabetes and epilepsy?

Comments

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ARIF Request

Conductive Education Rehabilitation Parkinson's Disease

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

How effective is conductive education in the rehabilitation of patients with Parkinson's disease?

Conductive education is an educational approach (developed by Dr Andras Peto in Hungary in 1945) which helps individuals with the skills and motivation they need to overcome every day problems of movement and bodily control.

Reviews Identified

None identified.

Other Evidence

- Bandyopadhyay S, Beynon J, Hallam S, Corne J, O'Mahony MS. Conductive education-based physiotherapy in Parkinson's disease. British Journal of Therapy and Rehabilitation 2002;9(5):176-9
- Brown MR, Pavel A The impact of conductive education on quality of life for people with acquired neurological conditions Parkinson's, Stroke, Multiple Sclerosis. Birmingham: National Institute of Conductive Education; 2007

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Comments

Whilst conductive education (CE) is an established approach to rehabilitation its role in the treatment of patients with Parkinson's disease (PD) appears to be largely un-researched. We did not locate any systematic reviews or RCTs assessing the effectiveness of CE as therapy for patients with PD.

Evidence to-date (based on small scale uncontrolled studies assessing the provision of therapy over approximately 10 weeks) appears insufficient to either conclusively refute or support the effectiveness of CE in the rehabilitation of patients with PD (Bandyopadhyay et al, 2002; Brown & Pavel, 2007). To address this issue a well conducted RCT with adequate statistical power conducted over a longer term is required.

Request Carried Out: October 2007

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ARIF Request

Continuous Hyperfractionated Accelerated Radiotherapy (CHART) Lung Cancer (Non-Small Cell Lung Cancer - NSCLC)

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of Continuous Hyperfractionated Accelerated Radiotherapy (CHART)?

Comments

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ARIF Request

Continuous Positive Airways Pressure (CPAP) Sleep Apnoea

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of continuous positive airways pressure for obstructive sleep apnoea?

Comments

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ARIF Request

Osteo-odonto-keratoprosthesis
Corneal Disease

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of osteo-odonto-keratoprosthesis in the management of severe corneal disease?

Comments

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ARIF Request

Counselling
Mental Health

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of counselling services in general and in the primary care setting in particular?

Comments

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ARIF Request

Counselling
Domestic Violence

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of counselling for the victims of domestic violence?

Comments

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ARIF Request

Street Lighting Crime

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of improved street lighting on reduction in crime?

As part of the West Midlands Crime GRIP initiative, ARIF was asked to appraise the best available systematic review on this topic.

Comments

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ARIF Request

Restorative Justice Crime

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of face-to-face restorative justice on repeat offending and victim satisfaction?

Comments

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Critical Appraisal

Teaching
Critical Appraisal

Table of Contents

The Problem Submitted For ARIF To Advise Upon

Is there any evidence of the effectiveness of teaching critical appraisal?

Comments

This page does not represent a response to a formal request to ARIF.

It is however, a frequently asked question and one of ARIF's members of staff was involved in undertaking a systematic review of effectiveness on this subject.

This page provides a means for persons interested in this topic to access the full report of this systematic review. It is also available on the sites of the institutions where the other authors of the report work.

Click here for a PDF version of this article.
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ARIF Request

Cyclo-oxygenase-2 (COX-2) Inhibitors
Naproxen
Ischaemic Heart Disease (IHD)

Table of Contents

The Problem Submitted For ARIF To Advise Upon

Is naproxen associated with reduced numbers of fatal and non-fatal ischaemic heart disease (IHD) events relative to no use of naproxen?

Comments

Rofecoxib has now been withdrawn. Therefore, as a precaution all information has been removed from this page.

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ARIF Request

Immunoreactive Trypsin Screening (IRT) Cystic Fibrosis

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The Problem Submitted For ARIF To Advise Upon

What is the evidence base of a proposal to introduce regionwide neonate screening for cystic fibrosis using immunoreactive trypsin?

ARIF was asked to examine the evidence-base of a document submitted to support this proposal.

Comments

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ARIF Request

Day Hospitals
Mental Illness
Psychiatric Disorders

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The Problem Submitted For ARIF To Advise Upon

What is the evidence on the effectiveness/cost effectiveness of day hospitals in the treatment of people with mental illness in comparison with other NHS or social services models of provision?

Comments

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ARIF Request

Day Hospitals
Elderly Patients

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The Problem Submitted For ARIF To Advise Upon

What is the evidence on the effectiveness/cost effectiveness of day hospitals in the treatment of the elderly in comparison with other NHS or social services models of provision?

Comments

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ARIF Request

D-Dimer Test
Pulmonary Embolism (PE)
Deep Venous Thrombosis (DVT)

Table of Contents

The Problem Submitted For ARIF To Advise Upon

In the diagnosis of DVT and PE, what is the effectiveness and cost-effectiveness of undertaking serum D-Dimer tests and, based on the result, progressing to ultrasound or V/Q scan for the final diagnosis?

Comments

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ARIF Request

Deep Brain Stimulation
Pallidotomy
Parkinson's Disease

Table of Contents

The Problem Submitted For ARIF To Advise Upon

What are the effects of:

- thermocoagulation (pallidotomy)
- deep brain stimulation

in the treatment of movement disorders, especially Parkinson's Disease?

Comments

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ARIF Request

Deep Brain Stimulation Dystonia

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of deep brain stimulation for dystonia?

Comments

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ARIF Request

Low Molecular Weight Heparin
Deep Vein Thrombosis

Table of Contents

The Problem Submitted For ARIF To Advise Upon

What evidence is there that low molecular weight heparin for the treatment of deep vein thrombosis/ venous thrombo embolism can safely and successfully be used in a community setting?

Comments

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ARIF Request

Low Molecular Weight Heparin (LMWH) Deep Venous Thrombosis (DVT)

Table of Contents

The Problem Submitted For ARIF To Advise Upon

How effective and cost-effective is LMWH relative to other treatments, particularly unfractionated heparin, in the prevention of deep venous thrombosis (DVT)?

Comments

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ARIF Request

Physical Prophylaxis
Deep Venous Thrombosis

Table of Contents

The Problem Submitted For ARIF To Advise Upon

How effective are foot pumps and other physical devices for preventing thromboembolism following elective hip and knee surgery?

Comments

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ARIF Request

Screening Tests
Subjective Cognitive Impairment
Mild Cognitive Impairment
Dementia

Table of Contents

WARNING
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The Problem Submitted for ARIF to Advise Upon:

Is there evidence indicating the best diagnostic tool for identifying mild cognitive impairment in patients presenting with subjective cognitive impairment?

Some patients with mild cognitive impairment (MCI) are likely to progress to Alzheimer's disease (AD). Screening tests which could identify those patients with MCI, particularly those who are likely to progress to AD, may allow assessment of interventions which could potentially prevent or attenuate progression to severe AD.

Reviews Identified

- Holsinger T, Deveau J, Boustani M, Williams JW, Jr. Does this patient have dementia? JAMA 2007; 297(21):2391-2404
- Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA. A review of screening tests for cognitive impairment. J Neurol Neurosurg Psychiatry 2007; 78(8):790-799
- Wild K, Howieson D, Webbe F, Seelye A, Kaye J. Status of computerized cognitive testing in aging: a systematic review. Alzheimers Dement 2008; 4(6):428-437
- Howe E. Update on Alzheimers: Initial screening of patients for Alzheimer's Disease and Minimal Cognitive Impairment. Psychiatry 2007 http://www.psychiatrymmc.com/initial-screening-of-patients-for-alzheimer%E2%80%99s-disease-and-minimal-cognitive-impairment/

Other Evidence

- Luck T, Luppa M, Briel S, Riedel-Heller SG. Incidence of mild cognitive impairment: a systematic review. Dementia and Geriatric Cognitive Disorders 2010;29(2):164-175
- Relkin N. Screening and early diagnosis of dementia. American Journal of Managed Care 2000; 6(22 Suppl):S1111-S1118.
- National Institute for Health and Clinical Excellence CG42 Dementia: full guidance. London:NICE;2006 http://guidance.nice.org.uk/CG42/Guidance/pdf/English

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Comments

Four reviews were identified describing a number of tests that could be used to detect people with MCI. The tests included: Computer Administered Neuropsychological Screen for MCI (CANS-MCI); MicroCog; Modified Mini Mental State Examination (3MS); Cognitive Abilities Screening Instrument (CASI); the Hopkins Verbal Learning Test; Word List Acquisition Test; The WORLD Test; The One Minute Naming Test; The Mini-Cog Test; and The Montreal Cognitive Assessment Test (MoCA). However, to identify the 'best' test for use in clinical practice, a more detailed assessment of each test to determine test accuracy and external validity is required. The information in the reviews is a useful starting point for further research.

Request Carried Out: July 2010

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ARIF Request

Mental Health Planning - Older People
Dementia
Depression
Mental Health

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

ARIF were asked to investigate the literature on models of care which can have a positive impact on mental health outcomes in persons over 65 years, particularly outcomes relating to dementia and/or depression.

Reviews Identified

- Ahuriri-Driscoll A, Rasmussen P, Day P. Mental health services for older people: a critical appraisal of the literature. Christchurch: New Zealand Health Technology Assessment (NZHTA) 2004
- Doughty C. Effective models of mental health service provision and workforce configuration in the primary care setting. Christchurch: New Zealand Health Technology Assessment (NZHTA) 2006
- Gilbody S, Whitty P, Grimshaw J et al. Educational and organizational interventions to improve the management of depression in primary care: a systematic review. JAMA 2003; 289: 3145 – 3151

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Comments

Reviews looking at organisational issues, have to attempt to assess studies that are fundamentally difficult to undertake and evaluate. When assessing this type of research, the aim is to identify trends within the data.

Three systematic reviews were identified, all were well conducted. They included a large number of studies (Ahuriri-Driscoll, Doughty, Gilbody), although there may be a degree of overlap between the reviews.

There appear to be consistent trends within the three reviews appraised that suggested that older people with mental health problems can benefit from collaborative care models, that have incorporated a case manager approach. Most of the primary studies underpinning this research were conducted in the USA, which may affect the generalisability of these findings to the UK population.

Request Carried Out: October 2009

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ARIF Request

Elderly Mentally Infirm Dementia

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The Problem Submitted For ARIF To Advise Upon

What is the evidence concerning treatment of the elderly mentally infirm, in particular with regard to dementia?

Comments

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ARIF Request

Memory Clinics
Dementia

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The Problem Submitted For ARIF To Advise Upon

Is there any evidence that memory clinics are more effective than routine OPD appointments in the management of people with dementia?

Comments

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ARIF Request

Professions Complimentary to Dentistry Dental Care

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness and cost-effectiveness of providing dental care by people from professions complimentary to dentistry (PCD's)?

Comments

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ARIF Request

Physical Activity
Exercise
Depression
Post-natal Depression

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence that increased physical activity improves depression in adults?

Reviews Identified

- Mead GE, Morley W, Campbell P, Greig CA, McMurdo M. Lawlor DA. Exercise for depression. Cochrane Database of Systematic Reviews. (3):CD004366, 2009.
- Daley A, Jolly K, MacArthur C. The effectiveness of exercise in the management of post-natal depression: systematic review and meta-analysis. Family Practice 2009; 26: 154–162.

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Comments

Two systematic reviews were identified, one assessed the evidence on the effect of exercise in depressed adults (Mead 2009) and the other (Daley 2009) the effect on post-natal depression.

Exercise seems to reduce symptom severity of depression in adults compared to no treatment or placebo when based on all available RCT data, but no significant effect is seen when based on the more methodologically sound trials only, although this might be due to lack of power. Of the findings, measured as standardised mean differences, it is unclear how clinically meaningful the changes in the overall effect sizes are. Furthermore, most of the primary studies had low methodological quality, and between the trials there was wide variation in terms of the severity of depression, type, level and duration of exercise intervention, type of comparator and outcome measurement. The data came from outcomes measured close to the end of the treatment period. Although there is data from studies that measured outcome several months after the end of the intervention and also indicated a significant benefit of exercise, the review, however did not indicate whether there was any modulation in the effect of exercise on depression the longer the follow-up.

The effect of exercise on symptom score of post-natal depression is unclear.

Overall, there is some uncertainty in the effect of physical activity for the treatment of depression in adults or post-natal depression.

Request Carried Out: September 2010

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ARIF Request

Prevention
Depression in Adults

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The Problem Submitted For ARIF To Advise Upon

Can depression be prevented in adults?

Comments

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ARIF Request

Prevention
Depression in Children and Adolescents

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The Problem Submitted For ARIF To Advise Upon

Can depression be prevented in children and adolescents?

Comments

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ARIF Request

Dextropopoxyphene Detoxification Opiate Addiction

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The Problem Submitted For ARIF To Advise Upon

Is there any evidence on the effectiveness of dextropopoxyphene in the management of detoxification for opiate addiction?

Comments

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ARIF Request

Population Registers
Diabetes Mellitus

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The Problem Submitted For ARIF To Advise Upon

What is the evidence that population registers for diabetes at a district level are effective in improving patient care and disease outcomes?

Comments

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ARIF Request

Pioglitazone
Diabetes (Type 2)

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The Problem Submitted for ARIF to Advise Upon:

Is there evidence that pioglitazone (a glitazone) is a more effective second line therapy than newer drugs e.g. Incretin enhancers (DPP-4 inhibitors) and Incretin mimics (GLP-1 analogues) in controlling HbA1c in adults with type 2 diabetes?

Reviews Identified

- National Collaborating Centre for Chronic Conditions. Type 2 diabetes: national clinical guideline for management in primary and secondary care (update). London: Royal College of Physicians, 2008. http://www.nice.org.uk/nicemedia/live/11983/40803/40803.pdf

Other Evidence

- Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes. NICE short clinical guideline 87. London: NICE; 2009. http://www.nice.org.uk/nicemedia/live/12165/44318/44318.pdf
- Type 2 diabetes: the management of type 2 diabetes. NICE clinical guideline 66. London: NICE; 2009 .http://www.nice.org.uk/nicemedia/pdf/CG66NICEGuideline.pdf
- Type 2 diabetes: newer agents (partial update of CG66). London: NICE; 2010 http://www.nice.org.uk/CG87
- European Medicines Agency. Recommends suspension of Avandia, Avandamet and Avaglim. Press release. 23 September 2010 EMA/585784. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/09/WC500096996.pdf
- MHRA Press statement: Europe-wide suspension of marketing authorisation for Avanda, Avandamet and Avaglim (rosiglitazone). 23rd September 2010. http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON094121
- Phung OJ, Scholle JM, Talwar M, Coleman CI. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycaemia in Type 2 diabetes. JAMA 2010;303(14):1410-1418

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Comments

The NICE review that informed guideline 87 regarding the use of these drugs in the patient pathway is

the most recent and relevant review at the present time. Of the two trials identified that compared a glitazone against the more recent drugs (incretin enhancers and incretin mimics), only one trial involved pioglitazone. Powered to detect non-inferiority, the mean change difference of HbA1c between the groups was -0.10% (95%CI-0.05, -0.26). More head to head comparisons are required to give a more accurate assessment of the place of pioglitazone in the patient pathway of type 2 diabetes compared to incretin enhancers and incretin mimics.

Request Carried Out: September 2010

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ARIF Request

Screening Programme
Diabetic Eye Disease

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The Problem Submitted For ARIF To Advise Upon

What are the effects/effectiveness of alternative arrangements for the screening (or early diagnosis) of diabetic retinopathy?

Comments

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ARIF Request

Sevelamer Hyperphosphataemia Dialysis

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of sevelamer (Renagel®) for the treatment of hyperphosphataemia in patients on haemodialysis?

Of particular interest in this request was the effectiveness of sevelamer in avoiding the adverse effect of hypercalcaemia observed when hyperphosphataemia is treated with calcium binders

Comments

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ARIF Request

Dietician Advice
Dietary Change
Gallstones - Symptomatic

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Is dietician advice and dietary change for symptomatic gallstones effective in reducing or abolishing symptoms and in eliminating the need for surgery?

Reviews Identified

No systematic reviews or health technology assessments were identified. One review was identified.

- Is there any evidence that gallstones can be encouraged to dissolve spontaneously providing the patient adheres to a strict diet. Have you any information on the chance of spontaneous remission of symptoms associated with gallstones? http://www.tripanswers.org/Answer.aspx?qid=2789

Randomised Controlled Trials

- Hood KA, Gleeson D, Ruppin DC, Dowling RH. Gall stone recurrence and its prevention: the British/Belgian Gall Stone Study Group's post-dissolution trial. Gut 1993;34(9):1277-88
- Frenkiel PG, Lee DW, Cohen H, Gilmore CJ, Resser K, Bonorris GG et al. The effect of diet on bile acid kinetics and biliary lipid secretion in gallstone patients treated with ursodeoxycholic acid. American Journal of Clinical Nutrition 1986;43(2):239-50
- Thornton JR, Emmett PM, Heaton KW. Diet and gall stones: effects of refined and unrefined carbohydrate diets on bile cholesterol saturation and bile acid metabolism. Gut 1983;24(1):2-6

Other Evidence

- Kurbanov SK. Optimization of diet therapy in patients with gallstones complicated with obesity and impaired glucose tolerance. [Russian] Voprosy Pitaniia 2003;72(5):22-4

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Comments

No systematic reviews or health technology assessments were identified.

One review was identified, which was a piece of question-answering information for the question 'Is there any evidence that gallstones can be encouraged to dissolve spontaneously providing the patient adheres to a strict diet. Have you any information on the changes of spontaneous remission of symptoms associated with gallstones?'. Five references were cited but little information on diet therapy to treat patients with gallstones was found.

Four primary studies were identified which were somewhat relevant. Three were small randomised controlled trials (RCTs): one looked at the effect of diet on recurrence of treated gallstones, and two looked at the effect of diet on bile acid kinetics in patients with gallstones. The fourth was a Russian study with limited information about its study design, population, intervention and outcome in its English abstract. As such, none of these appear to address the specific question of this report.

In conclusion, current evidence on the effectiveness of dietician advice and dietary change for symptomatic gallstones in reducing or abolishing symptoms and in eliminating the need for surgery is very limited.

Request Carried Out: May 2010

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ARIF Request

Diphosphonates
Osteoporosis

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The Problem Submitted For ARIF To Advise Upon

A policy for treating osteoporosis is to be developed, therefore: Which patients should be treated with diphosphonates for verified osteoporosis and what role does bone densitometry have in assessment?

Comments

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ARIF Request

Domestic Violence

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The Problem Submitted For ARIF To Advise Upon

How effective is routine screening for domestic violence by healthcare professionals?

Comments

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ARIF Request

Doppler Ultrasound Scanning
Low Birth Weight Babies (Poor Foetal Growth)

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The Problem Submitted For ARIF To Advise Upon

Is there any evidence of the effectiveness and safety of Doppler scanning for the detection of foetal abnormalities?

Comments

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ARIF Request

Drama Techniques Health Promotion

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of drama techniques for imparting health promotion messages and bringing about changes in behaviour?

Comments

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ARIF Request

Drotrecogin alfa (Activated)
Protein C (Recombinant Human Activated)
Sepsis (Severe)

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of drotrecogin alfa (activated) in the treatment of patients with severe sepsis?

Comments

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ARIF Request

Psychological Interventions combined with Drug Therapy
Drug Therapy combined with Pyschological Interventions
Severe Mental Illness (Depression and Schizophrenia)

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The Problem Submitted For ARIF To Advise Upon

Is there any research evidence on the effects/effectiveness of combined psychological and conventional medical care (pharmacotherapy) to improve outcomes in severe mental illness?

Comments

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ARIF Request

DVT
Flying

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The Problem Submitted For ARIF To Advise Upon

1. Does inactivity when in a cramped seating position (such as during long-haul air travel) increase the risk of the development of DVT in airline passengers?
2. Is there evidence that interventions such as the use of compression stockings, hydration, exercise and aspirin prevent DVT?

Comments

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ARIF Request

Guidelines, Policies, Treatment
Dyspepsia - Upper Gastrointestinal Symptoms

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The Problem Submitted For ARIF To Advise Upon

Is there any information which will assist with the development of local policies and processes for the investigation and referral of patients with upper GI symptoms, outside those for urgent cancer referrals?

Comments

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ARIF Request

External Beam Radiotherapy (EBRT)
Radical Prostatectomy
"Watch and Wait" Strategy
Localised Prostate Cancer
Early Prostate Cancer

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Evidence on the effectiveness of brachytherapy uses comparisons with existing standard treatments like EBRT and radical prostatectomy. Following on from this, what is the evidence for the effectiveness of these standard treatments themselves?

Prostate cancer is the second most common cancer in men. However in many men it progresses slowly and may not be the ultimate cause of death. As most cancer treatments have side-effects, it is thus essential that the benefits associated with treatment of early prostate cancer outweigh any side-effects.

See also requests "high dose rate brachytherapy in localised prostate cancer" and "low dose rate brachytherapy in localised prostate cancer"

Reviews Identified

- Alibhai SMH, Klotz LH. A systematic review of randomized controlled trials in localized prostate cancer. The Canadian Journal of Urology 2004;11(1):2110-2117

Randomised Controlled Trials

None identified other than those included in the review above.

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Comments

Although not completely systematic, the review suggested provides a simple summary of the existing RCT evidence, and also highlights additional important RCTs in progress.

The RCT evidence base for the effectiveness of EBRT for localised prostate cancer is limited, restricted to comparisons of EBRT with surgery and needs to be interpreted cautiously. There are no

RCTs comparing EBRT with “watch and wait” strategies.

The RCT evidence base for the effectiveness of radical prostatectomy is more convincing, and in favour of surgery relative to “watch and wait” strategies. There are important trade-offs between benefits and side-effects for patients however.

Request Carried Out: December 2006

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ARIF Request

Early Detection and Treatment Mental Illness

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of the early detection and treatment of severe mental illness in children and adolescents?

Comments

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ARIF Request

Prevention
Eating Disorders

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The Problem Submitted For ARIF To Advise Upon

Can eating disorders be prevented?

Comments

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ARIF Request

Echocardiography/Heart Failure (LVF) ACE Inhibitors

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The Problem Submitted For ARIF To Advise Upon

Is GP open access to echocardiography for the diagnosis of heart failure (LVF - Left Ventricular Failure) likely to be effective in maximising the proven benefits of ACE inhibition?

Comments

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ARIF Request

Elderly Health Promotion, Disease Prevention and Rehabilitation

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The Problem Submitted For ARIF To Advise Upon

What are the effects/effectiveness of interventions to promote health, prevent disease and rehabilitate older patients?

Comments

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ARIF Request

Eye Movement Desensitisation and Reprocessing (EMDR) Post Traumatic Stress Disorder

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of EMDR in the management of post traumatic stress disorder (PTSD) arising from sexual abuse?

Comments

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ARIF Request

Emergency Admissions

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The Problem Submitted For ARIF To Advise Upon

What research evidence is there on the reasons for and interventions to reduce rising numbers of emergency admissions?

ARIF was asked to help assist in the commission of further research by the West Midlands Department of R&D, by identifying whether there were any systematic reviews on this topic.

Comments

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ARIF Request

Lung Reduction Surgery
Emphysema

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The Problem Submitted For ARIF To Advise Upon

What are the effects/effectiveness of lung reduction surgery in severe emphysema?

Comments

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ARIF Request

Endoscopic Laser Foraminoplasty
Lumbar Disc Prolapse

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The Problem Submitted For ARIF To Advise Upon

What is the evidence base for Endoscopic Laser Foraminoplasty?

Comments

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ARIF Request

GP (General Practitoner), Haemodialysis, Renal Services End Stage Renal Failure

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the evidence around cost-effectiveness of GP led renal centres versus hospital based or other models?

There are several options regarding location in which haemodialysis is carried out. In the UK these consist of hospital based settings, usually provided in a specialist unit in a large district or teaching hospital, satellite haemodialysis units based in smaller district general hospitals or home based care. We were asked to investigate evidence regarding effectiveness and cost-effectiveness of a new service of care – GP led haemodialysis units.

Reviews Identified

None identified.

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Comments

No literature was identified that investigated GP led haemodialysis.

Request Carried Out: October 2007

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ARIF Request

Endoscopy
Gastrointestinal Disease

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The Problem Submitted For ARIF To Advise Upon

What would be the evidence base to inform the development of guidelines for a local open access endoscopy service to diagnose upper gastrointestinal problems?

Comments

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ARIF Request

Endovascular Laser Therapy
Venous Leg Ulcers

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of Endovascular Laser Therapy (EVLT) on healing venous leg ulcers, compared to other treatments (such as other surgical procedures) or conservative management (such as compression bandaging)?

Venous leg ulcers arise from high venous pressures within the leg, the consequences of either or both superficial or deep venous malfunction. Venous leg ulcers are the most serious consequence of this malfunction and cause substantial physical and psychological morbidity. Costs of health care are also substantial for this relatively common disorder. (Howard DP et al 2008).

Reviews Identified

- Interventional Procedure Guidance 52. Endovenous laser treatment of thelLong saphenous vein. NICE 2003 http://www.nice.org.uk/nicemedia/pdf/IPG052guidance.pdf
- Howard DP, Howard A, Kothari A, Wales L, Guest M,Davies AH. The role of superficial venous surgery in the management of venous ulcers: A systematic review. European Journal of Vascular and Endovascular Surgery 2008;36(4):458-465

Randomised Controlled Trials

- Viarengo LM, Poterio-Filho J, Poterio GM, Menezes FH, Meirelles GV. Endovenous laser treatment for varicose veins in patients with active ulcers: measurement of intravenous and perivenous temperatures during the procedure. Dermatological Surgery 2007;33(10):1234-1242

Other Evidence

- Huang Y, Jiang M, Li W, Lu X, Huang X, Lu M. Endovenous laser treatment combined with a surgical strategy for treatment of venous insufficiency in lower extremity: a report of 208 cases. Journal of Vascular Surgery 2005;42(3):494-501
- Perkowski P, Ravi R, Gowda RC, Olsen D, Ramaiah V, Rodriguez-Lopez JA, et al. Endovenous laser ablation of the saphenous vein for treatment of venous insufficiency and varicose veins: early results from a large single-center experience. Journal of Endovascular Therapy 2004; 11(2):132-138
- Sharif MA, Lau LL, Lee B, Hannon RJ, Soong CV. Role of endovenous laser treatment in the management of chronic venous insufficiency. Annals of Vascular Surgery 2007; 21(5):551-555

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Comments

Does EVLT work?
Data presented in the studies identified suggests that EVLT for patients with venous ulcers looks like a hopeful treatment. For example, data from the RCT showed that 22 (81%) of patients in the EVLT group had healed ulcers at 12 months compared to 6 (24%) in the control group - elastic or inelastic compression therapy (p=0.0001). However, it must be borne in mind that the size of the data set is very small and incomplete. Only one study was a randomised comparison and this was very small (n=52 patients). The remaining studies were case series therefore without a control group it is difficult to compare the effectiveness of EVLT with other treatments for venous ulcers, or indeed the natural history of the disease.

Is it suitable for all patients with ulcers or just a subgroup?
The patients within the studies may have been highly selected, indeed, the age range given in the study by Huang 2005, suggests that the population was much younger than a typical patient with chronic venous ulcers. Exclusion criteria also indicate that not all patients with venous ulcers are suitable for example in the RCT, patients who are unable to walk were excluded.

Do a proportion continue to require surgery?
Few patients required additional surgery. In Perkowski 2004, six (3%) of target veins were recanalized of which four were only partially open and all were successfully treated with sclerosis.

Can we assess the impact on nursing and tissue viability and surgical options?
All four studies had different routines for the post operation period. In the RCT study patients followed their pre-op treatment of compression bandaging, with no description regarding the degree of compression or length of time the bandaging were applied post op. In contrast Huang and colleagues applied compression bandaging for the first 14 days post op, but did not report the pressure at which the bandaging was applied, whereas Sharif and colleagues did not use compression bandaging post op and Perkowski 2004 did not give details of post operative compression treatment.

Conclusions
From the studies identified, EVLT looks like a hopeful technique to improve healing of chronic venous ulcers and reduce the rate of recurrence. Its effectiveness looks comparable with other surgical techniques also in use. (Howard 2008). It must be borne in mind that an ARIF request is not a full systematic review, therefore, there may be other primary studies that could contribute data but were not identified in this work. Aside from the size of the research base, there are also many clinical questions still to be answered, such as identifying the correct patient population, comparison with other effective treatments, and the effects on patients' quality of life and costs to the health service. Given the prevalence and costs to society and the NHS, it is an area where more research should be undertaken so that the full spectrum of the disease process (i.e. venous incompetence) and the full range of treatment options can be assessed.

Request Carried Out: September 2008

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ARIF Request

Enzyme Potentiated Desensitisation
Multiple Allergies
Gulf War Syndrome

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of enzyme potentiated desensitisation (EPD) for treating patients with severe allergies?

Comments

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ARIF Request

Specialist Epilepsy Clinics
Epilepsy

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The Problem Submitted For ARIF To Advise Upon

Do specialist epilepsy clinics offer advantages over general neurology clinics?

Comments

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ARIF Request

Vagal Nerve Stimulation
Epilepsy

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The Problem Submitted For ARIF To Advise Upon

How effective is vagal nerve stimulation (VNS) for intractable epilepsy?

Comments

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ARIF Request

Esomeprazole
Omeprazole
Lansoprazole
Peptic Ulcer
Erosive Oesophagitis

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence that esomeprazole is more effective and cost-effective than omeprazole or lansoprazole for peptic ulcer disease in adults?

Reviews Identified

- Edwards SJ, Lind T, Lundell L, Das R. Systematic review: standard- and double-dose proton pump inhibitors for the healing of severe erosive oesophagitis - a mixed treatment comparison of randomized controlled trials. Alimentary Pharmacology and Therapeutics 2009;30(6):547-56

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Comments

One systematic review was identified. The review evidence suggests that esomeprazole 40mg has better endoscopic healing rates than omeprazole 20mg for severe erosive oesophagitis at both four weeks and eight weeks of treatment. Compared with lansoprazole 30mg, esomeprazole 40mg also seems more effective at four weeks, and tends to be but is not significantly better at eight weeks. Esomeprazole appeared to be the most effective treatment among licensed PPIs for the healing of severe erosive oesophagitis. However, the reliability of the finding is uncertain due to limited data being presented about the quality of the trials and/or patient/study characteristics.

No relevant evidence was found regarding symptom control of peptic ulcer disease and cost of treatment.

Request Carried Out: October 2010

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ARIF Request

Influenza Vaccinations, Home Heating and Insulation, Keeping Warm
Excess Winter Deaths

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The Problem Submitted for ARIF to Advise Upon:

Are there any interventions or strategies that have been successful in reducing excess winter deaths?

The elderly account for a large proportion of excess winter deaths, but contrary to popular belief it is not hypothermia that is the leading cause of death. For example, during the winter periods between 1976-83, in people over 45 years of age, it was estimated that around 55% of excess winter deaths were attributed to circulatory disease and 33% to respiratory diseases including influenza. There are many factors that have been implicated in causing excess winter death, such as influenza or a change in lifestyle such as diet and exercise, but it is cold temperature exposure that has been frequently implicated in cardiovascular disease and respiratory diseases.

Reviews Identified

- Wilson JS, Fry-Smith A, Goodwin J, Hawker J, Taylor R. A Systematic Review of the Biological and Health Effects of Exposure to Cold Temperature in Healthy and Diseased Adults including the Elderly. University of Birmingham , 2001
- Thomson H, Petticrew M, Morrison D. Health effects of housing improvement: systematic review of intervention studies. BMJ 2001;323(7306):187-190
- West Midlands Public Health Observatory (Contributors : Anne Hartley). Fuel poverty and older people. http://www.wmpho.org.uk/information/fuelpoverty.pdf
- Anonymous. Health Impact Evaluation of Warm Front. http://www.est.org.uk/uploads/documents/aboutest/HIE_of_WF_Summary_Dec_04.pdf

Other Evidence

- Gilbertson J, Stevens M, Stiell B, Thorogood N. Home is where the hearth is: grant recipients' views of England 's home energy efficiency scheme (Warm Front). Social Science and Medicine 2006;63(4):946-956
- Howden-Chapman P, Crane J, Matheson A, Viggers H, Cunningham M, Blakely T, et al. Retrofitting houses with insulation to reduce health inequalities: aims and methods of a clustered, randomised community-based trial. Soc Sci Med 2005; 61(12):2600-2610
- Richardson G, Barton A, Basham M, Foy C, Eick SA, Somerville M. The Watcombe housing

study: the short-term effect of improving housing conditions on the indoor environment. Sci Total Environ 2006;361(1-3):73-80

- Simonsen L, Reichert TA, Viboud C, Blackwelder WC, Taylor RJ, Miller MA. Impact of influenza vaccination on seasonal mortality in the US elderly population. Arch Intern Med 2005;165(3):265-272
- Chalabi Z, Raine R, Stevens M, Wilkinson P. Evaluation of the Met Office Forecasting Project for Primary Care and NHS Trusts. http://www.dh.gov.uk/assetRoot/04/13/64/94/04136494.pdf

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Comments

Exposure to cold temperature has been suggested as the cause of excess winter mortality (Wilson 2001). We investigated the following to see if they reported interventions which could reduce excess winter mortality.

One systematic review on the health effects of housing improvements was identified. (Thompson 2001). It was well conducted and included experimental and non-experimental housing intervention studies that measured quantitative health outcomes. None of the studies measured mortality.

A good overview about Fuel Poverty and Older People produced by the West Midlands Public Health Observatory was identified as a useful resource. As well as providing a description of fuel poverty and who is affected by it, the document also lists Energy Company Schemes aimed at tackling fuel poverty.

Several ongoing evaluations were identified. The Warm Front programme, which is a government funded scheme where vulnerable people can obtain grants to improve home heating and install insulation, has an evaluation which intends to look at the effects of this initiative on the risk of cold related deaths and utilization of health care services. The predicted time of publication was 2005/6, but we only identified one component of the evaluation (Gilbertson 2006) published to date, which reports user satisfaction with the scheme. Two ongoing trials on home heating not related to the Warm Front scheme were also identified (Howden-Chapman 2005, Richardson 2006) but these are in early stages with no results so far.

Regarding respiratory outcomes, a COPD initiative coordinated by the Met Office, has one published evaluation (Gilbertson 2006) which describes 32 patients with COPD who were given information and extra care during December 2004 to March 2005. An audit of eleven health targets was undertaken and these were achieved for influenza vaccination, keeping warm on outdoor excursions and keeping living and bedroom spaces warm. These are factors predicted to reduce excess winter mortality. Additionally, there is a description of the first year of the entire COPD scheme (Chalabi 2004). This evaluation concludes that the pilot phase of the scheme overall has had a positive benefit for COPD management but that it requires further refining and development and ultimately a more formal analysis of costs and benefits.

The impact of influenza vaccination on excess winter deaths was examined by Simonsen 2005. Using data from the USA national multiple cause of death database and by taking age and virus strain into account, they found that over a 30 year period (1968 to 2001) excess winter mortality due to influenza did not exceed 10% of all winter deaths for people over 65 years. The authors concluded that because fewer than 10% of all excess winter deaths are due to influenza, observational studies that claimed a substantial decrease in excess winter deaths due to vaccination (up to 50% in some cases) are substantially overestimating the effect of vaccination.

In summary there appear to be very few studies, which have looked at interventions to reduce excess winter mortality. The absence of evaluations showing the impact of population programmes to reduce winter deaths is as likely to be due to the difficulties of successfully evaluating this public health intervention, as true absence of an effect at the population level. Any temptation to conclude that existing winter death reduction programmes, which incorporate features where we have some evidence of effectiveness at individual levels i.e. influenza vaccination, keep warm campaigns and improved housing for vulnerable groups, are not working at a population level, should be resisted at present.

Request Carried Out: February 2007

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ARIF Request

Exercise Referral Schemes
Exercise

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The Problem Submitted For ARIF To Advise Upon

Is there any evidence that participants in exercise referral schemes sustain increased levels of physical activity?

Comments

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ARIF Request

a - Galactosidase A
Fabrys Disease

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of a-galactosidase A in the treatment of Fabry's Disease.

Comments

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ARIF Request

Sympathectomy
Facial Blushing

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of sympathectomy for facial blushing?

Comments

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ARIF Request

Facilitating Introduction Gay Men

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of facilitating the introduction of gay men into the gay community on reducing risk-taking behaviour and HIV/AIDS infection or transmission?

Comments

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ARIF Request

Tension Free Vaginal Tape
Female Urinary Incontinence

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness and cost effectiveness of tension free vaginal tape compared to standard vaginal hysterectomy or colposuspension for female urinary incontinence?

Comments

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ARIF Request

Uterine Arterial Embolisation
Uterine Fibroids
Fibroids

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of uterine arterial embolisation (UAE) in the treatment uterine fibroids?

Comments

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ARIF Request

Financial Incentives
Physical Activity
Weight Loss

Table of Contents

WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness and cost-effectiveness of providing financial incentive schemes to motivate increasing levels of physical activity?

See related requests: Provision of incentives to motivate smokers to quit and Provision of incentives to motivate reduced alcohol consumption

Reviews Identified

- Paul-Ebhohimhen V, Avenell A. Systematic review of the use of financial incentives in treatments for obesity and overweight. Obesity Reviews 2008;9(4):355-367
- Kavanagh J, Trouton A, Oakley A, Powell C. A systematic review of the evidence for incentive schemes to encourage positive health and other social behaviours in young people. London: EPPI-Centre, Social Science Research Unit, Institute of Education, University of London. 2006
- Kavanagh J, Stansfield C, Thomas J. Incentives to improve smoking, physical activity, dietary and weight management behaviours: a scoping review of the research evidence Social Science Research Unit, Institute of Education, University of London. London: EPPI Centre; 2009 http://eppi.ioe.ac.uk/cms/Default.aspx?tabid=2468&language=en-US

Other Evidence

- NICE. Should incentives be used to encourage healthy living? Newsletter of meeting of NICE Citizens Council May 2010 http://www.nice.org.uk/newsroom/features/HealthyLivingIncentives.jsp

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Comments

Two systematic reviews, and one scoping review were identified that provided relevant information. No studies on cost-effectiveness were identified.

One systematic review (Paul-Ebhohimhen, 2008) focused on trials of behavioural obesity treatments

involving the use of financial incentives to bring about weight loss. Nine RCTs were included, all published between 1974 and 1998 and none were UK based. The interventions were various obesity treatment strategies (e.g. diet, exercise, monitoring of caloric intake, group discussion, providing information, etc.) with or without the use of financial incentives; none of the studies used physical activity as a single intervention. Only two studies measured physical activity level as an outcome, in one of these financial incentives were used as the motivation for attendance at exercise sessions and in the other for weight loss. No analyses specifically for physical activity level change were conducted. Meta-analysis of weight change showed no statistically significant difference between the groups with and without the use of financial incentives.

The other systematic review (Kavanagh, 2006) aimed to assess evidence of the effectiveness of incentive schemes to improve health and other social behaviours in young people aged 11-19 years. Searches were up to 2005. Only four of the included studies focused on the impact of incentives on physical activity. No further detailed information about the four studies was reported, and it is unclear whether the incentives in the studies were financial or other tangible incentives.

The scoping review (Kavanagh, 2009) aimed to identify the nature and extent of the literature on the effectiveness of incentives to motivate healthy behaviours. Searches were between1999-2009. Twenty-six of the included studies focused on physical activity, however, details of the study design, population, country where the study was conducted, and the nature of the incentives (e.g. financial or other tangible) were not reported.

In conclusion, reviewed evidence on the effectiveness of financial incentive schemes to motivate increasing levels of physical activity is sparse. There is no reviewed evidence on the cost effectiveness regarding this issue. Very limited data suggested that behavioural treatments involving the use of financial incentives for obesity and over weight have no significant effect on weight loss; however, the behavioural treatments were multi-faceted and physical activity was neither the only component of the interventions nor necessarily the component the financial incentives focused on.

Request Carried Out: July 2010

To see full report - click here

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ARIF Request

Follicle Stimulating Hormone infertile Women

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of recombinant follicle stimulating hormone (rFSH) compared to human-derived urinary follicle stimulating hormone (uFSH) in assisted conception in infertile women?

Comments

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ARIF Request

Gastric Bypass
Gastric Banding
Obesity

Table of Contents

WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the evidence that gastric bypass is better than gastric banding in reducing obesity related co-morbidities?

Reviews Identified

- Picot J, Jones J, Colquitt JL, Gospodarevskaya E, Loveman E, Baxter L, Clegg AJ. The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation. Health Technology Assessment. 2009;13(41)
- Colquitt JL, Picot J, Loveman E, Clegg AJ. Surgery for obesity. Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD003641. DOI: 10.1002/14651858.CD003641.pub3.

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Comments

The health technology report by Picot was the most relevant to the question. It was well-conducted and published in 2009. Its aim was to assess the clinical effectiveness and cost-effectiveness of bariatric surgery for obesity. Searches were up to 2008.

Of the trials included in the review, only one randomised controlled trial (RCT), which compared laparoscopic Roux-en-Y gastric bypass (LRYGBP) with laparoscopic adjustable gastric binding (LAGB) and reported co-morbidities, is relevant to the question posed above.

This trial targeted participants with a body mass index (BMI) between 35 and 50 and aged between 16 years and 50 years. Twenty-seven participants were recruited to the LRYGBP group and 24 to the LAGB. Follow-up was 60 months. There were a number of similarities at baseline between the the two groups in terms of age, gender, BMI and co-morbidity. However, it was unclear whether the similarity was due to the small sample size.

The review authors assessed the quality of the study and highlighted that there was uncertain risk of bias regarding allocation sequence generation, allocation concealment, whether the trial was free of

selective reporting and free of other bias. As to the study results, at a five year follow up diabetes and hyperlipaemia in the LRYGBP group and sleep apnoea in the LAGB group resolved. The review authors concluded that this small study showed that co-morbidities were few and similar in the comparison groups; the risk of bias for this study is uncertain, although the risk of bias for co-morbidities is likely to be low.

A further ARIF search for primary studies from 2008 to date was conducted but identified no relevant studies.

Overall, there is a paucity of evidence on the effectiveness of gastric bypass in reducing co-morbidities, compared with gastric banding.

Request Carried Out: September 2010

To see full report - click here

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ARIF Request

Gastrointestinal Infections
Respiratory Infections
School Children

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The Problem Submitted For ARIF To Advise Upon

What is the evidence on the effectiveness of interventions to prevent or reduce transmission of gastrointestinal and respiratory infections in schools in young children?

Comments

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ARIF Request

Imatinib
Gastrointestinal Stromal Tumours

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of imatinib (Glivec®) in the treatment of patients with gastrointestinal stromal tumours?

Comments

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ARIF Request

Gastroplasty
Morbid Obesity

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The Problem Submitted For ARIF To Advise Upon

Is banded gastroplasty a safe, effective and cost effective treatment for morbid obesity?

Comments

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ARIF Request

Gender Reassignment

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The Problem Submitted For ARIF To Advise Upon

What are the effects of gender reassignment surgery, and does the balance of positive and negative effects suggest that this procedure is clinically effective overall?

Comments

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ARIF Request

General Management
Oesophageal Cancer

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The Problem Submitted For ARIF To Advise Upon

Is there any evidence on the effectiveness of different interventions for cancer of the oesophagus?

Comments

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ARIF Request

Imiquimod
Genital Warts

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of imiquimod in the treatment of genital warts?

Comments

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ARIF Request

Mucolytic Agents
Glue Ear

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The Problem Submitted For ARIF To Advise Upon

What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Comments

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ARIF Request

Prevention
Glue Ear

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The Problem Submitted For ARIF To Advise Upon

What interventions are effective for the prevention of glue ear (otitis media with effusion)?

Comments

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ARIF Request

Steroids
Glue Ear

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The Problem Submitted For ARIF To Advise Upon

What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Comments

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ARIF Request

Growth Hormone
Growth Hormone Deficiency

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness/cost effectiveness of growth hormone treatment of growth hormone deficient adults?

Comments

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ARIF Request

Recombinant Factor VIII (rFVIII)
Haemophilia A

Table of Contents

The Problem Submitted For ARIF To Advise Upon

What are the effects/effectiveness of rFVIII in individuals with Haemophilia A, relative to existing plasma derived FVIII (pdFVIII) preparations?

Comments

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ARIF Request

Prophylactic versus Intermittent FVIII Haemophilia

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The Problem Submitted For ARIF To Advise Upon

What are the effects/effectiveness of continuous versus intermittent FVIII in treatment of Haemophilia A - including the effect of different prophylactic dosage regimes?

Comments

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ARIF Request

Vitamin K
Haemorrhagic Disease of the Newborn (HDNB)

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The Problem Submitted For ARIF To Advise Upon

What is the evidence for the effectiveness and safety of giving vitamin K to newborns to prevent Haemorrhagic Disease of the Newborn (HDNB), and what is the best means of administration?

Comments

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ARIF Request

Stapling Haemorrhoidectomy Haemorrhoids

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of the stapling technique versus conventional surgery for grade III haemorrhoids not suitable for non-resective surgery?

Comments

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ARIF Request

Immigration Health Checks

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The Problem Submitted For ARIF To Advise Upon

What is the evidence base for asking GPs to carry out health checks on new immigrants, in particular full blood count, Malaria blood film and stool microbiology?

Comments

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ARIF Request

Health Risk Assessment
Lifecheck
Health Promotion

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The Problem Submitted for ARIF to Advise Upon:

What is the validity, reliability and effectiveness of health risk appraisal tools, particularly in the workplace setting and in people with chronic diseases?

Health risk appraisal (HRA – also called health hazard appraisal (HHA) or health risk assessment (HRA) was first introduced in the early 1970's. Its rationale was to enable medical practitioners to incorporate strategies for the prevention of disease into their practice as well as simply being focused on treating existing illness. [Schoenback VJ 1987]. HRA involves comparing an individual's health related behaviours and personal characteristics, elicited by a series of questions, with mortality statistics and epidemiological data with the aim of estimating risk of future medical events and offering a strategy to minimize adverse predictions.

Reviews Identified

- Anderson DR, Staufacker MJ. The impact of worksite-based health risk appraisal on health-related outcomes: a review of the literature. American Journal of Health Promotion 1996;10(6):499-508
- Brindle P, Beswick A, Fahey T, Ebrahim S. Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review. Heart 2006;92(12):1752-1759
- Beswick A, Brindle P, Ebrahim S, Fahey T. Risk scoring for the primary prevention of cardiovascular disease (Protocol). Cochrane Library Issue 1, 2008.
- Schoenbach VJ, Wagner EH, Beery WL. Health risk appraisal: review of evidence for effectiveness. Health Services Research 1987;22(4):553-580
- Wagner EH, Beery WL, Schoenbach WJ, Graham RM. An assessment of health hazard/health risk appraisal. American Journa of Public Health 1982;72(4):347-352

Other Evidence

- Department of Health. NHS Lifecheck. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/Browsable/DH_5663568

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Comments

Five reviews were identified from our standard ARIF search. All were conducted using systematic methodology.

Unfortunantely, only one review by Brindle and colleagues is up-to-date and this concentrates on cardiovascular outcomes only. Findings from this review were that the validity and reliability of HRA varied according to population characteristics, with general trends showing that there was an under-prediction of cardiovascular risk in people with concurrent morbidities such as diabetes and an over-prediction of risk in non-diseased populations. The findings are unequivocal regarding the effectiveness of HRA in cardiovascular disease prevention. It may be that a new systematic review is warranted which looks at HRA in a variety of settings, within a variety of populations for a wider range of health outcomes.

Work and evaluation is also ongoing in this area as part of the NHS LifeCheck initiative, but results from pilot projects are not yet available.

Request Carried Out: February 2008

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ARIF Request

MEND
Weight Management - Children
Healthy Lifestyle - Children
Obesity - Children
Overweight - Children

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in January 2008.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of the MEND programme in treating overweight and obese children?

MEND is a multi-component (encompassing nutrition, exercise and behavioural modification), community based healthy lifestyle programme for overweight and obese children (aged 7-13 years) and their families. It aims to prevent overweight children becoming obese and treat children with obesity.

Reviews Identified

- Sacher PM, Kolotourou M, Chadwick P, Singhal A, Cole TJ, Lawson M. Is the MEND programme effective in improving health outcomes in obese children? International Journal of Obesity 2006;30(2):S41
- Sacher PM, Kolotourou M, Chadwick P, Singhal A, Cole TJ, Lawson M. The MEND programme: effectiveness on health outcomes in obese children. The International Association for the Study of Obesity- obesity reviews 2006;7(Suppl. 2):89
- Sacher PM, Kolotourou M, Chadwick P, Singhal A, Cole TJ, Lawson MS. The MEND Programme: effects on waist circumference and BMI in moderately obese children. The International Association for the Study of Obesity- obesity reviews 2007;8(Suppl. 3):12-13
- Sacher P, Chadwick P, Kolotourou M, Cole T, Lawson M, Singhal A. The MEND RCT: Effectiveness on Health Outcomes in Obese Children. International Journal of Obesity 2007;31
- Sacher PM, Chadwick P, Kolotourou M, Cole TJ, Lawson MS, Singhal A. The MEND Study: Sustained improvements on health outcomes in obese children at one year. North American Association for the Study of Obesity Annual Scientific Meeting 2007; MEND [online], Available from: http://www.mendprogramme.org/cmsfiles/60068/61022/NAASO_Poster_final_fow_web.pdf

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Comments

The most rigorous appraisal of the programme conducted to-date is the randomised controlled trial (RCT) by Sacher. However whilst we understand the author hopes to publish full details of trial later this year, available information is presently limited to a series of conference abstracts.

The MEND programme appears to provide a valid response to a clear public health need. The RCT by Sacher assesses outcomes relevant to the population of interest (primary outcome: waist circumference at 6 months; secondary outcomes: BMI, cardiovascular fitness, physical activity levels and self esteem) and the results reported indicate significant improvements in the intervention group vs. controls at 6 months. Additionally within subject assessments of changes from baseline to 6 and 12 months show the benefits (in primary and secondary outcomes) apparent at 6 months are sustained at one year. The results, published to-date, indicate MEND may be an effective and workable scheme to help combat childhood obesity. However at present these results should be interpreted with some degree of caution as, without access to a full report of the RCT, an assessment of study quality/possible bias cannot be made.

Request Carried Out: January 2008

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ARIF Request

Lamivudine
Hepatitis B

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of lamivudine in the treatment of chronic hepatitis B?

Comments

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ARIF Request

Surgery
Hernia
Inguinal Hernia

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

To assess the clinical and cost-effectiveness of surgical inguinal hernia repair versus watchful waiting in asymptomatic or minimally symptomatic men.

Reviews Identified

No systematic reviews were identified.

Randomised Controlled Trials

- Fitzgibbons RJ Jr, Giobbie-Hurder A, Gibbs JO, Dunlop DD, Reda DJ, McCarthy M Jr et al. Watchful waiting vs. repair of inguinal hernia in minimally symptomatic men: a randomized clinical trial. JAMA 2006;295(3):285-292
- O'Dwyer PJ, Norrie J, Alani A, Walker A, Duffy F, Horgan P et al. Observation or operation for patients with an asymptomatic inguinal hernia: a randomized clinical trial. Annals of Surgery 2006;244(2):167-173

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Comments

Two RCTs were identified and both have similar findings i.e. that in men who present with an asymptomatic hernia (one that is not painful), there is no difference in outcome of pain and quality of life scores between the strategy of watchful waiting and surgery. Surgery is the more expensive option, but the differences between the two strategies may reduce over time as patients following a watchful waiting strategy may eventually require surgery.

Request Carried Out: July 2010

To see full report - click here

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ARIF Request

Hernia Repair Laparascopic

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The Problem Submitted For ARIF To Advise Upon

Should laparoscopic treatment of inguinal hernias be purchased in the light of the evidence on its effectiveness?

Comments

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ARIF Request

Hernia Repair
Mesh (partially absorbable or non-absorbable)
Inguinal Hernias

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The Problem Submitted For ARIF To Advise Upon

What is the relative effectiveness of partially absorbable mesh in comparison with non-absorbable mesh in the repair of inguinal hernias?

Comments

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ARIF Request

Measurement Tool Referral Hip Replacement

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The Problem Submitted for ARIF to Advise Upon:

Which clinical measurement tools that measure referral threshold for hip replacement are evidence based and of these, which is the best?

See related requests - Clinical tools that measure referral threshold for knee replacement; Clinical tools that measure referral threshold for hysterectomy; Clinical tools that measure referral threshold for meniscectomy.

Reviews Identified

- National Collaborating Centre for Chronic Conditions. Osteoarthritis. National clinical guideline for care and management in adults. London: Royal College of Physicians; 2008. [NICE Clinical Guideline CG59]. Available at http://www.nice.org.uk/nicemedia/pdf/CG059FullGuideline.pdf
- Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis and Cartilage 2008;16:137-162. Available at http://www.oarsi.org/pdfs/oarsi_recommendations_for_management_of_hip_and_knee_oa.pdf
- Barbieri A, Vanhaecht K, Van Herck P, Sermeus W, Faggiano F, Marchisio S, et al. Effects of clinical pathways in the joint replacement: a meta-analysis. BMC Medicine 2009, 7:32

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Comments

No systematic reviews or health technology assessments were identified that directly answered the question. Two clinical guidelines and one systematic review were described to inform debate around the question.

In the NICE guidline (NICE 2008) the authors conducted a systematic review with literature searches up to 2007. There was a paucity of good quality evidence, therefore the recommendations on referral criteria for hip and knee joint replacements were mainly informed by expert opinion. The recommendations were based on the holistic assessment of a patient rather than an assessment using

specific clinical measurement tools.

The other guideline reviewed existing guidelines for the management of hip and knee osteoarthritis (OA) (Zhang 2008). Literature searches were up to 2006. The recommendation for joint replacement was based on existing treatment guidelines that used evidence from observational studies, and was presented within a clinical pathway framework rather than an assessment using specific disease measurement tools.

The systematic review (Barbieri 2009) evaluated the effectiveness of clinical pathways for hip and knee joint replacements when compared with standard medical care. Literature searches were from 1975 to 2007. Most of the included studies were cohort studies. The clinical pathway groups showed some benefit over standard medical care. However, recommendations regarding when patients should be offered replacement surgery were not given.

In conclusion, no systematic reviews or health technology assessments had investigated clinical measurement tools to help treatment decisions regarding hip replacement. Two national guidelines that make recommendations on referral for hip replacement surgery were identified but neither was based on patient assessments using clinical measurement tools.

Request Carried Out: April 2010

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ARIF Request

Laser Therapy Unwanted Hair Hirsutism

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of laser therapy for unwanted hair?

Comments

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ARIF Request

Sperm Washing
HIV Discordant Couples

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The Problem Submitted For ARIF To Advise Upon

What is the evidence of effectiveness of sperm washing in reducing the risk of HIV transmission in couples where the man is HIV+ve and the woman HIV-ve?

Comments

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ARIF Request

Home Births
Low Obstetric Risk Women

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The Problem Submitted For ARIF To Advise Upon

What is the comparative safety of home births compared to hospital births for women classified as being of low obstetric risk?

Comments

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ARIF Request

Hormone Replacement Therapy
Osteoporosis

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The Problem Submitted For ARIF To Advise Upon

A policy for treating osteoporosis is to be developed, therefore: Is there a defined group of women who should receive prolonged Hormone Replacement Therapy (HRT) and what role does bone density scanning have in assessing these women?

Comments

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ARIF Request

Rehousing
Housing Clearances
Psychological and Physical Health Impact

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The Problem Submitted For ARIF To Advise Upon

What is the health impact of housing clearances, and in particular the psychological and physical health impact on those people who have been rehoused following housing clearance?

Comments

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ARIF Request

Human Givens Approach REWIND Technique
Mental Health Problems
Post Traumatic Stress Disorder

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in May 2007.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of the Human Givens approach applied to mental health care?

Human Givens suggests that mental ill-health arises from an individual's inability to meet their emotional needs and that therapeutic attempts to supply the deficient needs will lead to improvement.

Reviews Identified

No systematic reviews identified.

Randomised Controlled Trials

No randomised controlled trials identified.

Other Evidence

- Guy K, Guy N. The fast cure for phobia and trauma: evidence that it works. Human Givens 2003;9(4):31-35

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Comments

We identified just one published evaluation of the effect of this new approach. It is a case-series of 30 patients treated with "REWIND" therapy who were assessed by a pre and post general well-being questionnaire rating well-being from 0-50. Well-being was claimed to improve from an average of 12 before treatment to 32 3-6 months after treatment.

Although this is an encouraging early evaluation, the results are highly susceptible to bias and confounding and the results should be interpreted extremely cautiously. Important questions remain about the unique features of this treatment and how the Human Givens approach is actually applied in practice. Considerable further evaluation would seem to be required before this is approach is offered routinely.

Request Carried Out: May 2007

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ARIF Request

Hyaluronic Acid Viscosupplements
Osteoarthritis
Knee

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness the hyaluronic acid viscosupplements (Synvisc® (Hylan G-F20) and Hyalgan®) in the treatment of osteoarthritis (OA) of the knee?

Comments

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ARIF Request

Hydrotherapy

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The Problem Submitted For ARIF To Advise Upon

What are the effects/effectiveness of hydrotherapy?

Comments

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ARIF Request

Hyperbaric Oxygen Osteoradionecrosis

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of hyperbaric oxygen for the prevention and treatment of osteoradionecrosis?

Comments

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Archived ARIF Request

Sapropterin dihydrochloride
Phenylketonuria
Hyperphenylalaninaemia

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

An opinion on the evidence base (reporting of trials and peer reviewed publications) with regard to the use of sapropterin dihydrochloride in phenylketonuria.

Sapropterin dihydrochloride (Kuvan®, Phenoptin) is a synthetic form of tetra-hydrobiopterin, the natural cofactor for the enzyme phenylalanine hydroxylase (PAH).

The discovery of sapropterin-responsive PAH deficiency identifies a potential new treatment option for a subgroup of patients with hyperphenylalaninaemia and phenylketonuria. In theory, this variant of PAH deficiency is treatable with sapropterin, with a possibility that a complicated PKU diet will no longer be required, so that the quality of life of patients can be improved. Thus, the use of sapropterin in addition to the low phenylalanine diet would enable patients to liberalize their diet and maintain blood phenylalanine concentrations within the recommended goal.

Reviews Identified

- National Horizon Scanning Centre. Sapropterin dihydrochloride for Phenylketonuria. Birmingham: NHSC, University of Birmingham; 2006

Trials Identified

- Burton BK, Grange DK, Milanowski A, Vockley G, Feillet F, Crombez EA et al. The response of patients with phenylketonuria and elevated serum phenylalanine to treatment with oral sapropterin dihydrochloride (6R-tetrahydrobiopterin): a phase II, multicentre, open-label, screening study. Journal of Inherited Metabolic Disease 2008;30(5)700-707
- Lee P, Treacy EP, Crombez E, Wasserstein M, Waber L, Wolff,J et al. Safety and efficacy of 22 weeks of treatment with sapropterin dihydrochloride in patients with phenylketonuria. American Journal of Medical Genetics 2008;146A(22):2851-2859
- Levy HL, Milanowski A, Chakrapani A, Cleary M, Lee P, Trefz FK et al. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study. Lancet 2008;70(9586):504-510

Other Evidence

- ClinicalTrials.gov. Study to Evaluate the Response to and Safety of an 8-Day Course of Phenoptin Treatment in Subjects With Phenylketonuria. http://clinicaltrials.gov/ct2/show?term=phenylketonuria&rank=7&flds=Xcdefikn [Accessed 16 Dec 2008]
- ClinicalTrials.gov. Study of Phenoptin to Increase Phenylalanine Tolerance in Phenylketonuric Children on a Phenylalanine-Restricted Diet. http://clinicaltrials.gov/ct2/show/NCT00272792?term=phenylketonuria&rank=11 [Accessed 18 Dec 2008]
- ClinicalTrials.gov. Safety and Efficacy Study of Phenoptin in Subjects With Hyperphenylalaninemia Due to BH4 Deficiency. http://clinicaltrials.gov/ct2/show/NCT00355264?term=phenylketonuria&rank=21 [Accessed 18 Dec 2008]
- ClinicalTrials.gov. Study of Phenoptin in Subjects With Phenylketonuria Who Participated in Protocols PKU-004 or PKU-006. http://clinicaltrials.gov/ct2/show/NCT00332189?term=phenylketonuria&rank=5 [Accessed 18 Dec 2008]
- Burnett JR. Sapropterin dihydrochloride (Kuvan/phenoptin), an orally active synthetic form of BH4 for the treatment of phenylketonuria. IDrugs 2007;10(11):803-813
- Michals-Matalon K. Sapropterin dihydrochloride, 6-R-L-erythro-5,6,7,8-tetrahydrobiopterin, in the treatment of phenylketonuria. Expert Opinion on Investigational Drugs 2008;17(2):245-251

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Comments

We identified three primary studies and two background reviews. Overall, the results of the studies have indicated a substantial decline in blood phenylalanine levels in subjects classified as responders to sapropterin. However, it is interesting to note that reductions are stated as percentages (e.g. a ≥30% reduction in baseline phenylalanine level) rather than on recommended target values. Thus, it is difficult to ascertain the true significance of these falls in phenylalanine levels in terms of whether they merely reduce the levels of phenylalanine, or they do so to a desirable level as well.

However, the peer-reviewed publications were essentially all describing one cohort of patients that underwent three different trials. Thus, subsequent studies utilized an enriched population sample. This is a form of selection bias, which may have influenced the results in favour of the intervention arm. Without detailed information from the other primary studies, which are yet to be published, the effect of such design features remains to be determined.

Request Carried Out: January 2009

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ARIF Request

Measurement Tool Referral Hysterectomy

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The Problem Submitted for ARIF to Advise Upon:

Which clinical measurement tools that measure referral threshold for hysterectomy are evidence based and of these, which is the best?

See related requests - Clinical tools that measure referral threshold for hip replacement; Clinical tools that measure referral threshold for knee replacement; Clinical tools that measure referral threshold for meniscectomy.

Reviews Identified

None identified.

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Comments

No systematic reviews or health technology assessments were identified that had investigated clinical measurement tools to help treatment decisions regarding hysterectomy.One NICE guideline that contained recommendations on referral of women with heavy menstrual bleeding for hysterectomy was identified, however, the recommendations were not based on patient assessments using clinical measurement tools.

Request Carried Out: May 2010

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ARIF Request

Hysterectomy and Sub Total Hysterectomy

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The Problem Submitted For ARIF To Advise Upon

For non-malignant cases, which produces the best outcomes; hysterectomy or sub-total hysterectomy?

Comments

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ARIF Request

Photodynamic Therapy
Idiopathic Sub-Foveal Choroidal Neovascularisation

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of photodynamic therapy for idiopathic sub-foveal choroidal neovascularisation?

Photodynamic therapy (PDT) is a newly developed type of treatment combining
- injection of a light-sensitive dye which concentrates in areas of “abnormality”
- low power laser

The rationale is that abnormal cells can be destroyed without damage to nearby normal cells.

Comments

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ARIF Request

Laronidase
a - L - iduronidase
Mucopolysaccharidosis Type 1

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence on the effectiveness of the recombinant enzyme replacement laronidase in the treatment of the lysosomal storage disorder mucopolysaccharidosis type 1 (MPS 1)?

Background

- MPS 1 is an inherited disorder caused by a deficiency in an enzyme called a - L - iduronidase.
- This enzyme is found in the lysosomes of all cells and is essential for breaking down long sugar molecules called dermatan sulphate and heparan sulphate. These sugars are also known as mucopolysaccharides or glycosaminoglycans.
- Deficiency of this enzyme disrupts the normal recycling process of these sugars leading to storage of the partially broken mucopolysaccharide inside the cell.
- Symptoms of MPS 1 include enlargement of the liver and/or spleen, neurological impairment, stunted growth, skeletal deformities, enlargement of facial features and tongue, joint stiffness, impaired hearing and vision, sleep disorders, general malaise and reduced stamina. More severe complications include cardiac complications, obstructive airways disease and respiratory infection.
  MPS 1 is classified into 3 groups, depending on the severity of the symptoms:
  - Severe - Hurler Syndrome
  - Moderate - Hurler/Scheie Syndrome
  - Mild - Scheie Syndrome
- Laronidase is a recombinant form of human a - L - iduronidase and is the only treatment currently available that directly addresses the cause of the disease.

Reviews Identified

No systematic reviews were identified.

Primary Studies Identified

- Aldurazyme® (laronidase) - Solution for intravenous infusion only. Prescribing Information Leaflet. Genzyme Corporation, Cambridge, MA, USA. URL: http://www.genzyme.com/corp/AZpi.pdf [Accessed 8 May 2003]

- Kakkis ED et al. Enzyme replacement therapy in mucopolysaccharidosis I. New England Journal of Medicine 2001; 344:182-188
- Kakavanos R, Turner CT, Hopwood JJ, Kakkis ED, Brook DA. Immune tolerance after long-term enzyme-replacement therapy among patients who have mucopolysaccharidosis I. Lancet 2003; 361:1608-1613

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Comments

Our searches did not identify any systematic review on this topic, nor did we identify any fully published reports of any randomised controlled trials.

It appears that evidence of the effectiveness of laronidase in the treatment of MPS1 comes from two studies. A prospective uncontrolled 'before and after' study that enrolled 10 patients (Kakkis et al 2001, Kakavanos et al 2003) and a part published randomised placebo-controlled trial that enrolled 45 patients (Aldurazyme Leaflet). Both studies indicate that laronidase may be a promising treatment for MPS1, however the findings of these studies should be treated with caution due to limitations of the methodology employed in the first study and absence of a full publication on which to appraise the validity of the second study. Therefore, robust information on the degree and sustainability of improvement in the characteristics of patients with MPS1 and the frequency and severity of adverse events is required.

As new information is likely to become available on this topic, care should be taken if this advice is accessed more than 6 months after this request was carried out.

Request Carried Out: May 2003

Update: June 2006 - A recent health technology assessment undertaken by WMHTAC/ARIF for the NHS HTA programme has been published on this topic.

- Connock M, Juarez-Garcia A, Frew E, Mans A, Dretzke J, Fry-Smith A, et al. A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1. Health Technology Assessment 2006;10(20)

We recommend reading this report as it is the most current and robust review of the clinical and cost-effectiveness of enzyme replacement therapy for patients with Fabry's disease.

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ARIF Request

Immunoglobulin Replacement Therapy
Immunodeficiency - Primary

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness and cost-effectiveness of immunoglobulin replacement therapy for common variable immunodeficiency (CVID)?

Comments

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ARIF Request

Revision Total Hip Arthroplasty
Impacted Cancellous Allografts and Cement

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The Problem Submitted For ARIF To Advise Upon

What is the strength of evidence in favour of this technique over existing total hip revision in terms of quality and cost-effectiveness?

Is there any information whether these should be carried out at tertiary centres? Is there a minimal level of activity/experience of operator needed to ensure good quality surgery?

Comments

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ARIF Request

Impotence

The Problem Submitted For ARIF To Advise Upon

What is the research evidence on the epidemiology, diagnosis and treatment of male impotence?

Comments

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ARIF Request

Incentives 'Quit and Win' Smoking Cessation Smokers

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the clinical and cost-effectiveness of providing incentives to motivate smokers to quit?

Financial and material incentives are used in many smoking cessation programmes in support of the quitting process. They are used to encourage programme recruitment or reward cessation achieved at predefined stages. Rewards may be provided for attendance, irrespective of subsequent performance (i.e. guaranteed), or paid relative to the participant's success within a programme (i.e. contingent).

'Quit and Win' contests were developed in the 1980s by the Minnesota Heart Health Programme and have since been widely used as population-based smoking interventions at local, national and international levels. Key features include the offer of a large prize, a pledge by smokers to quit for a set period of time (generally around 30 days) on the target quit date, validation of smoking status prior to entry, and biochemical validation of quitting amongst potential winners.

See related requests: Provision of incentives to motivate reduced alcohol consumption and Provision of financial incentive schemes to motivate increasing levels of physical activity

Reviews Identified

- Cahill K, Perera R. Competitions and incentives for smoking cessation. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD004307. DOI: 10.1002/14651858.CD004307.pub3.
- Lumley J, Chamberlain C, Dowswell T, Oliver S, Oakley L, Watson L. Interventions for promoting smoking cessation during pregnancy. Cochrane Database of Systematic Reviews 2009, Issue 3, Art. No.: CD001055. DOI: 10.1002/14651858.CD001055.pub3.
- Cahill K, Perera R. Quit and Win contests for smoking cessation. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD004986. DOI: 10.1002/14651858.CD004986.pub3.

Other Evidence

- O'Connor R, Fix B, Celestino P, Carlin-Menter S, Hyland A, Cummings KM. Financial incentives to promote smoking cessation: evidence from 11 quit and win contests. Journal of Public Health

Management and Practice 2006;12(1):44-51

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Comments

Cahill and Perera's generally well-conducted review of competitions and incentives for smoking cessation identified 17 RCTs and controlled studies. Results indicated material and financial incentives were effective in motivating smokers to quit in the shorter term (around 6 months). However these early successes seemed to dissipate when rewards ceased. It seemed incentives might encourage smokers to take part in cessation programmes. Although, once recruited, cessations amongst those offered rewards in comparison with those not appeared similar. Cost-effectiveness was not assessed.

Focusing on smoking cessation during pregnancy, Lumley et al's generally well-conducted review indicated that, of the different types of smoking interventions assessed, the provision of incentives appeared the most effective. A meta-analysis of four generally small controlled studies of variable quality indicated there was a significant reduction in smoking amongst groups offered incentives in comparison with those not. The intervention was notably restricted to pregnancy and its effectiveness in the longer term in the absence of incentives was not considered. Cost-effectiveness was not assessed.

Focusing on 'Quit and Win' contests, evidence from Cahill & Perera's review indicated contests may help some smokers quit, but their impact on community smoking rates was low. These conclusions, based on five studies targeting relatively local populations (city/county) in which selection bias seemed likely, should be interpreted cautiously. Also it appeared the contests may have been subject to levels of deception which could undermine their validity. Evidence from O'Connor et al's plausible cost-effectiveness study of 11 'Quit and Win' contests in the USA concluded that for a relatively modest investment of resources thousands of smokers can be recruited to make a serious quit attempt and many will remain non-smokers months later. However programme impact in the longer term was not assessed.

Evidence to-date indicates incentives may enhance recruitment to smoking cessation programmes and support the quitting process whilst on offer. However the longer term impact on preventing relapse, when payments cease, does not appear to have been established.

Request Carried Out: July 2010

To see full report - click here

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ARIF Request

Incentives - Rewards (Smoking Cessation)
Text Messaging
Smoking Cessation
Pregnancy

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the evidence for:

a) the effectiveness of incentives for smoking cessation in pregnancy and
b) the use of SMS texting for motivational purposes

to support a smoking cessation programme?

Reviews Identified

- Lumley J, Oliver S, Chamberlain C, Oakley L. Interventions for promoting smoking cessation during pregnancy (Review) Cochrane Database of Systematic Reviews 2004, Issue 4
- Cahill K, Perera R. Competitions and incentives for smoking cessation (Review) Cochrane Database of Systematic Reviews 2008, Issue 3
- Cahill K, Perera R. Quit and Win contests for smoking cessation (Review) Cochrane Database of Systematic Reviews 2008, Issue 4

Primary Studies

- Heil SH, Higgins ST, Bernstein IM, Solomon LJ, Rogers RE, Thomas CS et al. Effects of voucher-based incentives on abstinence from cigarette smoking and fetal growth among pregnant women. Addiction 2008;103:1009-1018
- Brendryen H, Drozd F, Kraft P. A digital smoking cessation program delivered through internet and cell phone without nicotine replacement (happy ending): randomised controlled trial. Journal of Medical Internet Research 2008;10(5):e51
- Brendryen H, Kraft P. Happy Ending: a randomised controlled trial of a digital multi-media smoking cessation intervention. Addiction 2008;103:478-484
- Rodgers A, Corbett T, Bramley D, Riddell T, Wills M, Lin R-B, Jones M. Do u smoke after txt? Results of a randomised trial of smoking cessation using mobile phone text messaging. Tobacco Control 2005;14(4):255-261

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Comments

Incentives

Three relevant systematic reviews were identified one of which, Lumley et al, evaluated various smoking cessation interventions aimed at reducing smoking in pregnancy. The other two reviews assessed competitions and incentives (Cahill 2008), and quit and win contests (Cahill 2008) for smoking cessation in the general population. One trial relating to pregnancy (Heil 2008) was included in the Cahill review.

In the review by Lumley only three of the 70 included trials evaluated rewards as part of a multi-component smoking cessation programme (Donatelle 2000, Sexton 1984, Walsh 1997). The data from the Donatelle and Sexton studies were pooled in a meta-analysis and showed that a combination of rewards plus social support was significantly more effective at reducing numbers smoking in late pregnancy compared to other strategies. The result for the Walsh study was similar.

The aim of the randomised controlled trial (Heil 2008) was to assess whether vouchers contingent upon smoking abstinence during pregnancy were effective at reducing smoking. The comparator group earned vouchers independent of smoking status. Contingent vouchers significantly increased smoking abstinence at the end of pregnancy and at 12 weeks postpartum. At 24 weeks postpartum, three months after the end of the voucher programme, there was no significant difference.

To summarise, the evidence on the use of incentives for smoking cessation in pregnancy suggests that the provision of a reward or incentive can be an effective way of helping women quit smoking during pregnancy compared to usual care alone (or being given a reward regardless of smoking status). This abstinence did not continue into the long-term postpartum. Issues surrounding the design and conduct of trials for interventions for smoking cessation during pregnancy have limited the availability of good quality evidence.

Text Messaging

No systematic reviews evaluating SMS technology for smoking cessation were identified. Two primary studies were identified relating to general adult popoulations.

The trial by Brendryen aimed to test the hypothesis that a digital smoking cessation intervention, which included SMS texting (up to three per day), would produce an increased 12 month abstinence rate compared with the control condition of a self help booklet. Significantly higher repeated abstinence rates were achieved for the intervention group compared to the comparator group at one, three and six months but not at 12 months post cessation.

In the randomised controlled trial by Rodgers, the intervention group received up to five personalised text messages per day containing smoking cessation advice, support and distraction, in addition to a quit buddy. At six and 12 weeks follow-up significantly more subjects had stopped smoking in the intervention group compared to the comparator group. By 26 weeks smoking cessation rates were no different in the two groups. The results of both trials may be affected by the use of self-reported abstinence and the timing of rewards and assessments.

To summarise, evidence to support the effectiveness of SMS texting as an intervention for smoking cessation in pregnancy is lacking. Trials in the general adult population suggested texting could lead to higher quit rates than those achieved with usual practice alone but were not covincing due to limitations arising from the trial design and conduct.

Request Carried Out: July 2009

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ARIF Request

Peri-Urethral Injection Incontinence

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The Problem Submitted For ARIF To Advise Upon

What is the cost effectiveness of peri-urethal collagen injections in the treatment of stress incontinence? Are there short or long term complications that need to be considered?

Comments

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ARIF Request

Infant Mortality Rates (IMR)
Perinatal Mortality Rates (PMR)

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The Problem Submitted For ARIF To Advise Upon

Suggest an approach to devise an evidence based strategy to reduce high rates of perinatal and infant mortality.

The main role of ARIF in this request was to assist and facilitate a worker from the commissioning authority in question, identify interventions which had been demonstrated to have an effect on perinatal and infant mortality.

Comments

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ARIF Request

IVF and GIFT
Infertility

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The Problem Submitted For ARIF To Advise Upon

Are there any reviews on IVF and GIFT that have been produced since the 1992 Effective Health Care Bulletin, The Management of Subfertility? (Leeds: School of Public Health, University of Leeds, 1992. pp24. No 3).

Comments

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ARIF Request

Intra-Cytoplasmic Sperm Injection (ICSI) Infertility

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The Problem Submitted For ARIF To Advise Upon

What is the evidence for the effectiveness of intra-cytoplasmic sperm injection for assisted conception?

Comments

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ARIF Request

Vaccination
Influenza

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The Problem Submitted For ARIF To Advise Upon

What are the effects/effectiveness of different policies on the use of influenza vaccination?

Comments

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ARIF Request

Vaccination of Health Care Workers
Prevention of Influenza

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The Problem Submitted For ARIF To Advise Upon

Is there any evidence that annual vaccination of health care workers against influenza has health benefits for individuals, patients or organisations?

Comments

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ARIF Request

Integrated Care Pathways

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The Problem Submitted For ARIF To Advise Upon

Are Integrated Care Pathways (ICPs) effective and cost effective, particularly in terms of getting research evidence into practice?

Comments

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ARIF Request

Intravenous Gammaglobulin Kawasaki Disease

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The Problem Submitted For ARIF To Advise Upon

What is the evidence that intravenous gammaglobulin prevents the formation of coronary artery aneurysms in children with Kawasaki Disease?

Comments

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ARIF Request

Intravenous Immunoglobulin
Neurological Movement Disorders
Sydenham's Chorea
PANDAS

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of intravenous immunoglobulin (IVIG) in the treatment of neurological movement disorders of probable autoimmune origin following infection, given the presence of antibasal ganglia antibodies (ABGAs)?

Our main focus was on conditions in which basal ganglia dysfunction appears to have resulted from post-streptococcal autoimmunity, principally Sydenham's chorea and PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections).

Reviews Identified

- Fergusson D, Hutton B, Sharma M, Tinmouth A, Wilson K, Cameron DW et al. Use of intravenous immunoglobulin for treatment of neurological conditions: a systematic review. Transfusion 2005; 45 (10): 1640-57

Randomised Controlled Trials

- Perlmutter SJ, Leitman SF, Garvey MA, Hamburger S, Feldman E, Leonard HL, Swedo SE. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. Lancet 1999;354 (9185):1153-8
- Garvey MA, Snider LA, Leitman SF, Werden R, Swedo SE. Treatment of Sydenham's chorea with intravenous immunoglobulin, plasma exchange, or prednisone. Journal of Child Neurology 2005;20(5):424-29

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Comments

High quality evidence on this topic is sparse. A well conducted and relatively up-to-date systematic review of RCTs evaluating the use of IVIG regardless of clinical condition identified one trial of relevance to our question (Perlmutter, 1999). Our own searches identified one further RCT (Garvey,

2005).

The results of these two small RCTs (n≤30) indicate IVIG can be effective in lessening symptom severity for children with infection triggered obsessive-compulsive disorder and tic disorders, and in reducing the choreatic symptoms of Sydenham's chorea. However the relative effectiveness of IVIG in comparison with plasma exchange is unclear.

To-date available evidence on the effectiveness of IVIG appears insufficient to either fully support or refute its choice as an immunomodulatory regimen for patients with movement disorders of probable autoimmune origin. Further larger RCTs are needed, with sufficient power to establish whether or not the trends noted in small trials are statistically significant.

Request Carried Out: October 2007

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ARIF Request

Irlen Lenses, Coloured Lenses, Tinted Lenses
Irlen Syndrome, Scotopic Sentivitity

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence for Irlen syndrome and if it exists, what evidence is there for the advised therapy?

Irlen syndrome or scotopic sensitivity, was first recognised in 1983 by Helen Irlen, who observed that some people with poor reading improved when coloured overlays were put onto pages of text. The main symptoms include, light sensitivity, contrast problems, restricted field of clear vision, poor depth perception and poor attention and concentration http://www.hale.ndo.co.uk. Usual symptoms include “perceptual distortions of the text such as apparent movement of the letters, blurring or coloured halos”. [Wilkins AJ]

Reviews Identified

- Dohnert M, Englert ED. The Irlen syndrome--are there pathophysiologic correlates and scientific evidence for reading with colors Z Kinder Jugendpsychiatr Psychother 2003;31(4):305-309

Randomised Controlled Trials

- Robinson GL, Foreman PJ. Scotopic sensitivity/Irlen syndrome and the use of coloured filters: a long-term placebo-controlled study of reading strategies using analysis of miscue. Perceptual and Motor Skills 1999;88(1):35-52
- Robinson GL, Foreman PJ. Scotopic sensitivity/Irlen syndrome and the use of coloured filters: a long-term placebo controlled and masked study of reading achievement and perception of ability. Perceptual and Motor Skills 1999;89(1):83-113
- Blaskey P, Scheiman M, Parisi M, Ciner EB, Gallaway M, Selznick R. The effectiveness of Irlen filters for improving reading performance: a pilot study. Journal of Learning Disabilities 1990;23(10):604-612
- O'Connor PD, Sofo F, Kendall L, Olsen G. Reading disabilities and the effects of colored filters. Journal of Learning Disabilities 1990;23(10):597-603, 620
- Christenson GN, Griffin JR, Taylor M. Failure of blue-tinted lenses to change reading scores of dyslexic individuals. Optometry 2001;72(10):627-633

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Comments

Overall, the Dohnert and Englert review concludes that there “does not appear to be conclusive evidence of the effectiveness of coloured lenses in the treatment of dyslexia: the most we can say is that there appears to be an unspecified placebo effect”.

However, the Dohnert and Englert review was not a systematic review, and some of the RCTs identified do suggest an effect. A systematic review of the effectiveness of the use of Irlen lenses and coloured overlays in dyslexia, autism and reading disabilities is thus a priority for further research.

Request Carried Out: July 2006

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ARIF Request

Isolated Limb Infusion
Isolated Limb Perfusion
Melanoma
Skin Cancer

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The Problem Submitted for ARIF to Advise Upon:

To compare the clinical effectiveness of isolated limb infusion with isolated limb perfusion in the treatment of melanoma.

Reviews Identified

None identified.

Studies assessing the effectiveness of ILI

- Bonenkamp JJ, Thompson JF, de Wilt JH, Doubrovsky A, de Faria Lima R, Kam PCA. Isolated limb infusion with fotemustine after dacarbazine chemosensitisation for inoperable loco-regional melanoma recurrence. European Journal of Surgical Oncology 2004;30(10):1107-12
- Brady MS, Brown K, Patel A, Fisher C, Marx W. A Phase II Trial of Isolated Limb Infusion With Melphalan and Dactinomycin for Regional Melanoma and Soft Tissue Sarcoma of the Extremity. Annals of Surgical Oncology 2006;13(8):1123-9
- Lindner P, Doubrovsky A, Kam PCA, Thompson JF. Prognostic Factors After Limb Infusion With Cytotoxic Agents for Melanoma. Annals of Surgical Oncology 2002;9(2):127-36
- Lindner P, Thompson JF, de Wilt JHW, Colman M, Kam PCA. Double isolated limb infusion with cytotoxic agents for recurrent and metastatic limb melanoma. European Journal of Surgical Oncology 2004;30(4):433-9
- Mian R, Henderson MA, Speakman D, Finkelde D, Ainslie J, McKenzie A. Isolated limb infusion for melanoma: a simple alternative to isolated limb perfusion. Canadian Journal of Surgery 2001;44(3):189-92

Other Evidence

- Noorda EM, Vrouenraets BC, Nieweg OE, van Coevorden F, Kroon BBR. Isolated Limb Perfusion: What Is the Evidence for Its Use? Annals Surgical Oncology 2004;11(9):937-45

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Comments

No systematic reviews addressing this question were identified and no direct comparisons of the effectiveness of ILI with ILP were located. However five studies (one phase II trial and four case series) that assessed the effectiveness of ILI in the treatment of melanoma were identified. To help facilitate an, albeit, indirect comparison of ILI and ILP additional searches were undertaken for papers assessing the effectiveness of ILP, an established procedure which has been studied quite extensively. The research identified indicated ILI can provide a similar frequency and duration of response to that achieved with conventional ILP, with fewer complications. The results should however be interpreted with some caution. Any observed similarity, or difference, in treatment effect could have been influenced by small, apparently inconsequential, differences between the patients in one set of studies relative to the other (confounding). Furthermore the case series for ILI or ILP, individually, are open to bias, particularly selection bias.

Request Carried Out: October 2006

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ARIF Request

Joint Replacement Surgery

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The Problem Submitted For ARIF To Advise Upon

How effective is simultaneous bilateral joint replacement surgery?

Comments

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ARIF Request

Joint Surgery
Obesity

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The Problem Submitted for ARIF to Advise Upon:

Surgery in obese patients:

1. What is the evidence that obesity impacts adversely on patients who have surgery, particularly joint surgery?
2. If there is poor outcome, what interventions have been shown to reduce BMI prior to surgery?
3. Are there any trials which have investigated the effect of weight reduction prior to surgery?

In the UK two thirds of adults are now considered to be overweight or obese. Of these, 22% of men and 23% of women are obese. Obesity is generally defined as a body mass index (BMI) greater than 30, where BMI is defined as weight (kg)/height2 (m2).

Reviews Identified

- Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC et al. Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. Health Technology Assessment 2004;8(21):iii-182
- Choban PS, Flancbaum L. The impact of obesity on surgical outcomes: a review. Journal of the American College of Surgeons 1997;185(6):593-603.
- Kane RL, Saleh KJ, Wilt TJ, Bershadsky B, Cross WW, III, MacDonald RM, et al. Total knee replacement. Evidence Report Technology Assessment (Summary) 2003;(86):1-8.
- Ontario Ministry of Health and Long-Term Care. Total knee replacement. Toronto: Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care (MAS), 2005:51.
- Stukenborg-Colsman C, Ostermeier S, Windhagen H. [What effect does of obesity have on the outcome of total hip and knee arthroplasty. Review of the literature. Orthopade 2005;34(7):664-667.
- White RH, Henderson MC. Risk factors for venous thromboembolism after total hip and knee replacement surgery. Current Opinion in Pulmonary Medicine 2002;8(5):365-371.

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Comments

1. Impact of obesity on surgical patients:

Two systematic reviews (Ontario Ministry 2005, Kane 2003) were identified and the three were narrative reviews (Stukenborg-Colsman 2005, White 2002, Choban 1997). Both systematic reviews and one narrative review (Stukenborg-Colsman 2005) investigated total knee replacement surgery concentrating on functional outcomes post- operative. All three reviews concluded that obesity did not impact on post-operative functional outcomes. A further narrative review (White 2002) investigated total hip and knee replacement, concentrating on thromboembolic complications. It concluded that hip replacement and a BMI of over 30 is associated with increased risk of symptomatic venous thrombotic embolism (VTE) but not in patients undergoing knee replacement. The remaining narrative review (Choban 1997), looked at the effect of obesity on a range of intra and short term post surgical outcomes. It concluded that patients who are obese are theoretically at an increased risk of complications, but these risks have not uniformly translated into increased or prohibitive morbidity or mortality. They suggest that "with appropriate perioperative precautions and monitoring obese patients can be treated as safely and effectively as their normal weight counterparts in most circumstances and should not be denied surgical treatment when surgery constitutes the most appropriate therapy". When considering the conclusions of the narrative reviews, one must consider aspects of selection bias, and that the type and quality of the studies are not formally assessed.

2. Interventions to reduce BMI prior to surgery:
   Only one systematic review was identified (Avenell A 2004). This review had a wider brief and investigated the long-term effects of obesity treatments on body weight, risk factors for disease and disease contracted. The review also searched for studies on weight loss prior to surgery, but were unable to identify any RCTs on this subject.

3. Trials investigating weight reduction prior to surgery:
   No relevant studies identified.

Few studies have investigated the impact of obesity on intra-operative and post-operative outcomes in patients undergoing lower body joint surgery. The information identified for this ARIF request suggests that obesity does not adversely affect long-term outcomes. No RCTs were identified which compared a programme of weight loss prior to surgery with standard pre-operative care. This is an area where there is a major primary research gap.

Request Carried Out: August 2006

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ARIF Request

Radiofrequency Ablation (RFA) Kidney, Liver and Lung Cancer

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The Problem Submitted for ARIF to Advise Upon:

Is there data to support the use of Radiofrequency Ablation of the kidney, liver and lung as an alternative to surgical resection?

RFA is a minimally invasive method of destroying cancerous tumours. It works by the insertion of an electrode into the tumour through which radiofrequency energy is passed producing heat. The electrodes can be inserted through the skin (percutaneous) or during surgical procedures. It can also be performed under local, regional or general anaesthetic.

Reviews Identified

Kidney Cancer

- National Institute for Clinical Excellence, Interventional Procedures Programme. Interventional procedures overview of percutaneous radiofrequency ablation of renal tumours; 2003 http://www.nice.org.uk/page.aspx?o=ip215overview
- Hailey D. Radiofrequency ablation in the treatment of kidney cancer. Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2006
- Gervais DA, Arellano RS, Mueller P. Percutaneous ablation of kidney tumors in nonsurgical candidates. Oncology (Huntington) 2005; 19(11 Suppl 4):6-11
- Wagner AA, Solomon SB, Su LM. Treatment of renal tumors with radiofrequency ablation. Journal of Endourology 2005;19(6):643-52
- Zagoria RJ. Imaging-guided radiofrequency ablation of renal masses. Radiographics 2004;24(Suppl 1):S59-71

Liver Cancer

- National Institute for Clinical Excellence. Interventional Procedures Programme. Interventional procedure overview of radiofrequency ablation for the treatment of liver tumours. http://guidance.nice.org.uk/page.aspx?o=ip127overview
- Sutherland LM, Williams JAR, Padbury RTS, Gotley DGA. A systematic review of radiofrequency ablation for the treatment of liver tumours. North Adelaide, S. Australia. ASERNIP; 2002 Report No.28

- Galandi D, Antes G.Radiofrequeny thermal ablation versus other interventions for hepatocellular carcinoma. Cochrane Database of Systematic Reviews 2004. Issue 2: CD003046
- Lopez PM, Villanueva A, Llovet JM. Systematic review: evidence-based management of hepatocellular carcinoma - an updated analysis of randomised controlled trials. Alimentary Pharmacology and Therapeutics 2006;23:1535-47

Colorectal Metastases

- National Institute for Clinical Excellence. Interventional Procedures Programme. Interventional procedure overview of radiofrequency ablation for the treatment of colorectal liver metastases. http://guidance.nice.org.uk/page.aspx?o=ip248overview
- Medical Services Advisory Committee. Radiofrequency ablation of liver tumours. Canberra: MSAC, 2003:108
- Marlow NE. Radiofrequency ablation for the treatment of liver tumours: a systematic review. North Adelaide, S. Australia. ASERNIP; 2006 Report No. 56

Lung Cancer

- Zhu JC, Yan TD, Black D, Morris DL. Ct18p radiofrequency ablation of lung tumours: a systematic review. Australian and New Zealand Journal of Surgery 2007;77(Suppl 1):A11-2
- National Institute for Health and Clinical Excellence. Interventional Procedures Programme. Interventional procedure overview of percutaneous radiofrequency ablation for primary and secondary lung cancers. February 2005 http://guidance.nice.org.uk/page.aspx?o=ip316overview

Randomised Controlled Trials (Ongoing)

- Kidney -Protocol ID 9359-03, NCT00221728, 2003-006. Investigating RFA versus conservative surgical treatment in patients who are at risk of renal insufficiency.
- Liver -ISRCTN58458258 - investigating RFA combined with chemotherapy versus chemotherapy alone in patients with unresectable colorectal liver metastases.

Other Evidence

- Liver - hepatocellular carcinoma. National Institute for Clinical Excellence. Radiofrequency ablation of hepatocellular carcinoma. London: National Institute for Clinical Excellence (NICE) 2003. (Interventional Procedure Guidance 2) http://guidance.nice.org.uk/IPG2/guidance/pdf/English
- Liver - colorectal metastases. National Institute for Clinical Excellence. Radiofrequency ablation for the treatment of colorectal metastases in the liver. London: National Institute for Clinical Excellence (NICE) 2004. (Interventional Procedure Guidance 92) http://www.nice.org.uk/page.aspx?o=220829
- Lung cancer - National Institute for Health and Clinical Excellence. Percutaneous radiofrequency ablation for primary and secondary lung cancers. Interventional Procedure Guidance 185. July 2006 http://guidance.nice.org.uk/ipg185/guidance/pdf/English

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Comments

From the evidence presented in the reviews identified at this time, there is no data to support the use of RFA in kidney, liver and lung as an alternative to surgical resection. Surgical resection for all three organs appears to be the gold standard. However, many patients are unable to undergo surgery, due to poor functioning of the diseased organs, the nature of the disease, and comorbidities prohibiting surgery. It is in these types of patients that the majority of RFA studies have been conducted. The use of RFA in treating kidney, liver and lung cancer still has many unknowns. More research is needed to answer whether the treatment is effective in the long-term and to give answers to the optimal delivery of the treatment, the type of patient who could benefit and how it compares to other treatments available. However, the safety profile seems good. It should still be regarded as an experimental treatment, and

patients who are undergoing it should be aware of the uncertainties surrounding it. NICE guidance is available and reflects the current evidence base.

Request Carried Out: August 2007

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ARIF Request

Measurement Tool Referral Knee Replacement

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The Problem Submitted for ARIF to Advise Upon:

Which clinical measurement tools that measure referral threshold for knee replacement are evidence based and of these, which is the best?

See related requests- Clinical tools that measure referral threshold for hip replacement; Clinical tools that measure referral threshold for hysterectomy; Clinical tools that measure referral for meniscectomy.

Reviews Identified

- National Collaborating Centre for Chronic Conditions. Osteoarthritis. National clinical guideline for care and management in adults. London: Royal College of Physicians; 2008. [NICE Clinical Guideline CG59]. Available at http://www.nice.org.uk/nicemedia/pdf/CG059FullGuideline.pdf
- Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis and Cartilage 2008;16:137-162. Available at http://www.oarsi.org/pdfs/oarsi_recommendations_for_management_of_hip_and_knee_oa.pdf
- Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P et al. Standing committee for international clinical studies including therapeutic trials ESCISIT. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a task force of the standing committee for international clinical studies including therapeutic trials (ESCISIT). Annals of the Rheumatic Diseases 2003,62(12):1145-55
- Barbieri A, Vanhaecht K, Van Herck P, Sermeus W, Faggiano F, Marchisio S, et al. Effects of clinical pathways in the joint replacement: a meta-analysis. BMC Medicine 2009, 7:32

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Comments

No systematic reviews or health technology assessments were identified that directly answered the question. Three clinical guidelines and one systematic review were described to inform debate around the question.

Of the guidelines, one was issued by the National Institute for Health and Clinical Excellence (NICE). The second was produced by the Osteoarticular Research Group at University of Edinburgh, UK. They, together with the systematic review (Zhang W 2008) included both knee and hip pathology and are described in the ARIF feedback - Clinical measurement tools that measure referral threshold for hip replacement.

The third guideline (Jordan 2003) aimed to update the existing recommendations for management (including all treatments) of knee osteoarthritis (OA) using evidence based medicine and expert opinion. Literature searches were up to 2002. Thirty-five studies on total knee replacement were identified, which were all descriptive, with overall quality of the studies ranked using a quality score. However, no further details of the studies were reported. The authors recommended that joint replacement has to be considered in patients with radiographic evidence of knee OA who have refractory pain and disability. However, it was not based on patient assessments using clinical measurement tools.

Request Carried Out: April 2010

To see full report - click here

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ARIF Request

Laser Therapy
Port Wine Stain

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of laser therapy for port wine stains?

Comments

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ARIF Request

Laser Therapy (Intralesion)
Port Wine Stain

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of laser therapy for port wine stains and other subcutaneous vascular disorders (haemangioma and arterio-venous malformations)?

Comments

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ARIF Request

Routine Health Checks - Primary Care Learning Disabilities

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of regular health checks in the primary care setting for people with learning disability?

Comments

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ARIF Request

Learning Disability

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The Problem Submitted For ARIF To Advise Upon

Is there evidence of any health promotion interventions that ameliorate the effects of learning disabilities?

Comments

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ARIF Request

Link Worker

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The Problem Submitted For ARIF To Advise Upon

Research bids have been received to fund "link workers". Is there any research on the effects and effectiveness of these?

Comments

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ARIF Request

Low Molecular Weight Heparin
Unstable Angina

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The Problem Submitted For ARIF To Advise Upon

How effective and cost-effective is LMWH relative to other treatments, particularly unfractionated heparin, in the management of unstable angina?

Comments

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ARIF Request

Low Molecular Weight Heparin Treatment of Thromboembolic Disease

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness and cost effectiveness of LMWH relative to other interventions for the treatment of existing thromboembolic disease?

Comments

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ARIF Request

Low Molecular Weight Heparin (LMWH) Treatment of Thromboembolic Disease Management of Unstable Angina

Table of Contents

The Problem Submitted For ARIF To Advise Upon

What is known about the relative effectiveness and cost-effectiveness of different LMWH products in the prevention of deep venous thrombosis in orthopaedics; the management of unstable angina; and the treatment of existing thromboembolic disease?

Comments

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ARIF Request

Lung Cancer - Non-Small Cell

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The Problem Submitted For ARIF To Advise Upon

Is there evidence that lung cancer mortality could be substantially reduced by carrying out more surgery?

Comments

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ARIF Request

Trauma Centres/Services/Systems Major Trauma

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The Problem Submitted for ARIF to Advise Upon:

Is there any review evidence relating to the most effective delivery of care to patients who have suffered severe trauma?

Reviews Identified

- Celso B, Tepas J, Langland-Orban B, Pracht E, Papa L, Lottenberg L et al. A systematic review and meta-analysis comparing outcome of severely injured patients treated in trauma centers following the establishment of trauma systems. Journal of Trauma 2006;60:371-8
- Mann NC, Mullins RJ, MacKenzie EJ, Jurkovich GJ, Mock CN. Systematic review of published evidence regarding trauma system effectiveness. Journal of Trauma 1999;47:S25-S33
- Mullins RJ,.Mann NC. Population-based research assessing the effectiveness of trauma systems. Journal of Trauma 1999;47:S59-S66

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Comments

Two systematic reviews were identified and the review by Celso et al aimed to investigate whether the outcomes of patients with severe trauma are improved for patients treated at trauma centres within trauma systems, defined as having the following components: injury prevention, pre-hospital care, services at trauma centres and other acute care facilities and post-hospital care.

Searches were up to August 2006 and were restricted to published literature in peer-reviewed journals, English language and North American publications, therefore there is a risk of publication bias and generalisability to the UK is a problem. All the studies were population-based.

Eight studies demonstrated improvement in favour of the trauma interventions. Of these, four assessed trauma systems and four assessed trauma centres. Effect sizes ranged from Odds Ratio 0.50 (95% CI 0. 0.42, 0.61) to OR 0.80 (95% CI 0.70, 0.91). Three studies demonstrated an effect in favour of the control groups. Two of these were assessments of trauma systems. All the effect sizes are quite large, with OR ranging from 1.69 to 3.25. Three studies found no difference, with all of these studies using the before and after design.

The narrative and data given in Table 3 provide information on what components contribute to an effective major trauma intervention. For example, the study by Mullins, which investigated trauma systems in Oregon, found that the case mix altered through time, with an increase in more seriously injured patients being sent to the trauma centres over time. They suggested that some of the improvement was due to improved training of staff, as well as advancements of technology. However, when the Oregon trauma systems were compared to Washington state, which did not have a trauma system, they found that the Oregon trauma system was the most effective with OR for mortality 0.80 (95% CI 0.70, 0.91).

The review by Mann NC et al was well-conducted but there are limitations of generalisability with similar problems to the Celso review regarding the search. The main findings were that:

- Panel studies “demonstrate a reduction in the number of preventable deaths with increasing commitment to trauma care resources and expertise.
- Trauma registry data from designated trauma centres uniformly demonstrate a 15% reduction in mortality when compared to Major Trauma Outcome Study (MTOS) norms.
- Population based studies incorporating multivariate modelling to control for covariates demonstrate a 15% to 20% reduction in the risk of death after a trauma centre/system is in place”.

Overall conclusion

Both the reviews found that trauma systems offer a survival advantage for injured patients. However, the data on which this is based is old and there are some problems with the methodology of many of the studies. All of the studies included in the reviews are from North America therefore the generalisability of the findings are debatable. There is clinical and statistical heterogeneity present between the studies, probably the most important being whether the study was looking at a trauma system or a trauma centre.

With regard to planning trauma services the reviews recommend adequate funding of trauma systems should be available and trauma centres should have a good throughput of patients to enable staff to keep/develop their skills. Protocols should be developed to optimise triage of major trauma patients in the pre-hospital stage with processes to ensure that the trauma centres are informed of potential admissions in advance of their arrival.

Request Carried Out: January 2009

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ARIF Request

Testosterone Replacement Therapy
Male Menopause

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The Problem Submitted For ARIF To Advise Upon

Is there any evidence as to the effects of testosterone supplementation in middle aged males suffering "andropausal symptoms"?

Comments

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ARIF Request

Social Marketing
Mass Media
Alcohol Misuse
Young People

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in May 2008.

The Problem Submitted for ARIF to Advise Upon:

What is the evidence on the effectiveness of marketing/publicity/media campaigns aimed at reducing alcohol use amongst young people (aged 16-25 years)?

Reviews Identified

- Gordon R, McDermott L, Stead M, Angus K. The effectiveness of social marketing interventions for health improvement: what's the evidence? Public Health 2006;120(12):1133-9
- Stead M, McDermott L, Gordon R, Angus K, Hastings G. A review of the effectiveness of social marketing alcohol, tobacco and substance misuse interventions. Report prepared for the National Social Marketing Strategy for Health. Stirling: Institute for Social Marketing; 2006
- De Jong W. The role of mass media campaigns in reducing high risk drinking among college students. Journal of Studies on Alcohol 2002; Suppl 14:182-92

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Comments

Three papers were identified. Two, Gordon 2006 and Stead 2006, reviewed the effectiveness of social marketing interventions on health improvement. The Gordon paper provided a general overview of social marketing interventions designed to improve diet, increase physical activity, and tackle substance misuse – drawing on evidence from three reviews. The Stead paper reviewed the effectiveness of social marketing in alcohol, tobacco and substance misuse – this was one of three key sources of the Gordon review. The other paper, De Jong 2002, described current media campaigns to reduce college student drinking (in the USA), reviewed the key principles of campaign design and outlined recommendations for future campaigns.

The essence of the social marketing/media campaigns identified appears to be their adoption of ‘commercial’ principles in the planning, execution and evaluation of programmes designed to influence the voluntary behaviour of target audiences, thereby improving their personal welfare and that of society.

The effectiveness of mass media campaigns in reducing high-risk drinking amongst young people appears unclear. However there is evidence to suggest campaigns utilizing the principles of social marketing may be beneficial in reducing alcohol misuse, principally amongst young people of school age.

Request Carried Out: May 2008

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ARIF Request

Measurement Tool Referral Meniscectomy

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The Problem Submitted for ARIF to Advise Upon:

Which clinical measurement tools that measure referral threshold for meniscectomy are evidence based and of these, which is the best?

See related requests - Clinical tools that measure referral threshold for hysterectomy; Clinical tools that measure referral threshold for knee replacement; Clinical tools that measure referral threshold for hip replacement.

Reviews Identified

No systematic reviews or health technology assessments were identified.

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Comments

Currently, it appears that there are no systematic reviews, health technology assessments or clinical guidelines that focus on clinical measurement tools that measure referral threshold for meniscectomy.

Request Carried Out: July 2010

To see full report - click here

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ARIF Request

Monitoring Measurement Tools Outcome Hand Surgery

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Is there any systematically reviewed evidence on the validity, reliability and responsiveness of clinical measurement tools for monitoring outcomes of hand surgery? Does the evidence from these reviews show how the Disabilities of Arm, Shoulder and Hand (DASH) questionnaire compares with other questionnaires for monitoring outcomes of hand surgery?

Reviews Identified

No systematic reviews or health technology assessments were identified

Other Evidence

Three overviews were identified which may provide some useful information:

- Bindra PR, Dias JJ, Heras-Palau C, Amadio PC, Chung KC, Burke FD. Assessing outcome after hand surgery: the current state. Journal of Hand Surgery British and European Volume 2003;28(4):289-294
- Amadio PC. Outcomes assessment in hand surgery. What's new? Clinics in Plastic Surgery 1997;24(1):191-4
- Amadio PC. Outcome assessment in hand surgery and hand therapy: an update. Journal of Hand Therapy 2001;14(2):63-7

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Comments

Three overviews were identified, which showed that a number of questionnaires have been used for monitoring outcomes of hand surgery. However, currently there are no systematic reviews that assessed studies investigating measurement properties or comparing the DASH questionnaire with alternative measurements for hand surgery outcomes.

Request Carried Out: January 2011

To see full report - click here

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ARIF Request

Peer Education
Men Who Have Sex With Men

Table of Contents

The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of peer education interventions aimed at influencing sexual risk-taking behaviour in men who have sex with men?

Comments

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ARIF Request

Menopause

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The Problem Submitted For ARIF To Advise Upon

What treatments have been shown to be effective to treat symptoms of the menopause?

Comments

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ARIF Request

Uterine Thermal Balloon Ablation Menorrhagia

Table of Contents

The Problem Submitted For ARIF To Advise Upon

What research exists on thermal balloon therapy for women with menorrhagia?

Comments

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ARIF Request

Physiotherapy Mental Illness

Table of Contents

The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of interventions provided by physiotherapists in the treatment of the symptoms of mental illness?

Comments

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ARIF Request

Prevention
Mental Illness

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The Problem Submitted For ARIF To Advise Upon

Can mental illness be prevented?

Comments

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ARIF Request

Outcomes Measurement Tools
Mental Illness, Inpatients

Table of Contents

WARNING
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The Problem Submitted for ARIF to Advise Upon:

What validated tools are there to help assess the general functioning of in-patients with mental illness, to follow progress while inpatients and compare discharge with admission state?

There are a great number of outcomes measurement tools to choose from. Falling into three types: standardised measures of psychiatric symptoms, health related quality of life, or standard assessment of patients need, it has been proposed that they can be used to improve patient care in routine clinical settings.

Reviews Identified

- Gilbody SM, House AO, Sheldon TA. Outcome measures and needs assessment tools for schizophrenia and related disorders. Cochrane Database of Systematic Reviews 2003;(1):CD003081
- Gilbody SM, House AO, Sheldon TA. Outcomes Measurement in Psychiatry CRD report 24, 2003, University of York
- Gilbody SM, House AO, Sheldon T. Routine administration of Health Related Quality of Life (HRQoL) and needs assessment instruments to improve psychological outcome--a systematic review. Psychological Medicine 2002; 32(8):1345-1356

Other Evidence

- Gilbody SM, House AO, Sheldon TA. Psychiatrists in the UK do not use outcomes measures. National survey. British Journal of Psychiatry 2002;180:101-103
- National Institute for Mental Health in England. Outcomes Practice Group http://nimhe.csip.org.uk

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Comments

Findings from the systematic reviews, were that no trials had been undertaken that have investigated the value of routine administration of outcomes measurement tools to facilitate clinical decision making

in patients receiving mental health care within the hospital environment. However, the reviews are several years old and there may have been trials undertaken in the interim.

One survey was identified which showed that less than 15% of psychiatrists routinely use some form of outcome measurement in clinical practice.

There is currently work being undertaken at a UK national level which is in the early stages of producing a compendium of outcomes measurement tools for use in mental health services (see National Institute for Mental Health in England - Outcomes Practice Group above).

Request Carried Out: August 2007

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ARIF Request

Mentoring Programmes
Teenage Pregnancy
Vulnerable Teenagers

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of mentoring programmes in reducing teenage pregnancy amongst vulnerable groups?

Reviews Identified

- Fulop M. Youth Mentoring and Pregnancy Prevention. Portland , OR : National Mentoring Centre; 2003
  http://www.nwrel.org/mentoring/pdf/recapp.pdf#search=%fulop%20mentoring%20pregnancy%20prevention%22
- Swann C, Bowe K, McCormack G, Kosmin M. Teenage pregnancy and parenthood: A review of reviews (evidence briefing summary) Health Development Agency; 2003
  http://www.nice.org.uk/page.aspx?0=502489

Other Evidence

- The Social Care Institute for Excellence (SCIE). Preventing teenage pregnancy in looked after children. SCIE Research Briefing No 9 August 2004
  http://www.scie.org.uk/publications/briefings/files/scare09.pdf

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Comments

Whilst the general area of teenage pregnancy prevention has been studied extensively (Swann, 2003), evidence on the effectiveness of mentoring programmes is sparse. One review of youth mentoring and pregnancy prevention was located (Fulop, 2003). However the studies identified all assessed mentoring as a strategy to prevent second pregnancies rather than primary pregnancy prevention. Also the studies appeared to focus on teenagers in general rather than vulnerable groups such as looked after children. Non-the-less Fulop's (2003) paper provides a useful overview of what is known about youth mentoring in the context of pregnancy prevention. The results of two case studies, identified by the review, indicate mentoring may be effective in preventing secondary pregnancy. However the observed reduction in the repeat pregnancy rate amongst teenagers attending mentoring programmes compared with those in the same geographic area should be interpreted cautiously as the possibility of small, apparently inconsequential, differences between the two groups (confounding) cannot be ruled out.

In conclusion the potential of mentoring as a primary pregnancy prevention strategy has not been tested and the extent to which its apparent effectiveness in preventing repeat pregnancies may, or may not, be reflected in primary pregnancy prevention is difficult to gauge.

Request Carried Out: November 2006

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ARIF Request

Total Hip Replacement Metal-to-Metal Resurfacing

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The Problem Submitted For ARIF To Advise Upon

Metal-to-metal hip resurfacing has been suggested as an alternative to performing a standard total hip replacement in selected cases, usually in younger patients. The procedure is intended to prevent future need for revisions. What is the evidence for the effectiveness and safety of this procedure?

Comments

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ARIF Request

Sorafenib
Metastatic Renal Cell Cancer (RCC)

Table of Contents

The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of sorafenib for metastatic renal cell cancer ?

Comments

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ARIF Request

Methicillin-resisitant Staphlococcus Aurenus (MRSA) Ozone Solution

Table of Contents

The Problem Submitted For ARIF To Advise Upon

Are there any reviews of evidence on the effects/effectiveness of ozone solution for treatment of methicillin-resistant staphyloccus aureus (MRSA)

Comments

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ARIF Request

Miglustat
Niemann Pick Disease

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The Problem Submitted For ARIF To Advise Upon

What is the evidence on the effectiveness of miglustat for the treatment of Niemann-Pick disease?

Comments

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ARIF Request

Occipital Nerve Stimulation
Migraine, Chronic

Table of Contents

The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of occipital nerve stimulation (ONS) for someone with chronic migraine?

Comments

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ARIF Request

Rituximab, Monoclonal Antibody Therapy Relapsed Non-Hodgkin's Lymphoma

Table of Contents

The Problem Submitted For ARIF To Advise Upon

What is known about the effectiveness of monoclonal antibody therapy for the treatment of patients with relapsed lymphoma? What is the evidence for the effectiveness of this treatment compared to standard chemotherapy?

Comments

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ARIF Request

MRI

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The Problem Submitted For ARIF To Advise Upon

Is there any good evidence about the effectiveness and cost effectiveness of MRI diagnostic scanning? Is there any evidence about when it is of value and when it is not?

Comments

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ARIF Request

MRI for the Diagnosis of Knee Disorders

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The Problem Submitted For ARIF To Advise Upon

Is GP open access to MRI for the diagnosis of knee disorders cost-effective for the selection of patients to be referred for specialist opinion and care.

Comments

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ARIF Request

MRI for the Diagnosis of Cause of Low Back Pain

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The Problem Submitted For ARIF To Advise Upon

Should GPs have open access to MRI, and should they use it in unselected patients with low back pain that remains unresolved after 6 weeks of conservative management with physiotherapy / exercise etc?

Used in this way, does MRI offer a cost effective way of selecting patients for referral to surgeons and reassuring others that there is no serious disease?

Comments

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ARIF Request

Service Delivery
Multiple Sclerosis (MS)

Table of Contents

The Problem Submitted For ARIF To Advise Upon

Is there any evidence to support the effectiveness of a central multidisciplinary team designated to directly meet the needs of people with multiple sclerosis throughout the country?

Comments

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ARIF Request

Nurse Practitioners

Table of Contents

The Problem Submitted For ARIF To Advise Upon

What is known about the effects of nurse practitioners and what are the implications for commissioned research on this topic?

Comments

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ARIF Request

Nurse Triage
Primary Care

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The Problem Submitted For ARIF To Advise Upon

What is the evidence for the safety and effectiveness of a nurse triage service within the primary care setting?

Comments

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ARIF Request

Obstetric Units

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The Problem Submitted For ARIF To Advise Upon

What is the evidence to support a decision about whether funding for maternity services should be directed at general practitioner or consultant led obstetric units?

Comments

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ARIF Request

Oncology
Positron Emission Tomography
PET Scanning

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The Problem Submitted For ARIF To Advise Upon

What are the current and future prospects of the use of Positron Emission Tomography (PET) in oncology?

Comments

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ARIF Request

Oseltamivir (Tamiflu)
Pandemic Influenza

Table of Contents

The Problem Submitted For ARIF To Advise Upon

Does Oseltamivir reduce mortality in an influenza pendemic situation?

Comments

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ARIF Request

Out of Hours Service (Type and Location) Primary Care

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The Problem Submitted For ARIF To Advise Upon

During 2004 and 2005 ARIF has been approached twice on the effectiveness of different ways of delivering out-of-hours primary care. The most recent request considered the particular merits of co-location with a hospital accident and emergency department.

Comments

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ARIF Request

Telephone Follow-Up
Out-patients - any Clinical Speciality

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of telephone as opposed to face-to-face follow-up of out-patients, particularly with regard to reduction of workload and patient experience?

Reviews Identified

- Currell R, Urquhart C, Wainwright P, Lewis R. Telemedicine versus face to face patient care: effects on professional practice and health care outcomes. Cochrane Database of Systematic Reviews 2000, Issue 2. Art. No.: CD002098. DOI: 10.1002/14651858.CD002098. http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD002098/frame.html

Randomised Controlled Trials

- Wootton R, Bloomer SE, Corbett R, Eedy DJ, Hicks N, Lotery HE et al Multicentre randomised control trial comparing real time teledermatology with conventional outpatient dermatological care: societal cost-benefit analysis. BMJ (Clinical research ed.) 2000;320(7244):1252-6 http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/775/CN-00277775/frame.html
- Welch HG, Johnson DJ, Edson R Telephone care as an adjunct to routine medical follow-up. A negative randomized trial. Effective clinical practice : ECP 2000;3(3):123-30 http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/145/CN-00332145/frame.html
- Beaver K, Tysver-Robinson D, Campbell M, Twomey M, Williamson S, Hindley A et al Comparing hospital and telephone follow-up after treatment for breast cancer: randomised equivalence trial. BMJ 2009;338:a3147
- Murphy E, Mehta S, Gannon D, Bassett JHD, Frank J & Meeran K Telephone follow-up following radioiodine therapy for thyrotoxicosis improves outcome Endocrine Abstracts 3 P301 1999 http://www.endocrine-abstracts.org/ea/0003/ea0003p301.htm
- Williams M, Amin A, Getgood A, Hallam P , Chojnowski AJ, Chapman PG Telephone clinic follow-up following carpal tunnel decompression. Journal of Hand Surgery: European Volume. 2008; 33(5):641-4
- Fallaize RC, Tinline-Purvis C, Dixon AR, Pullyblank AM. Telephone follow-up following office anorectal surgery. Annals of the Royal College of Surgeons of England. 2008; 90(6):464-6

- Hennell S, Spark E, Wood B, George E. An evaluation of nurse-led rheumatology telephone clinics. Musculoskeletal Care. 2005;3(4):233-40

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Comments

One well-conducted Cochrane systematic review was identified. It aimed to investigate the effectiveness of telemedicine as an alternative to face-to-face patient care. Two of the seven included trials were based in the out-patient setting. Searches were conducted up to 1999 so the review is rather dated, particularly given the pace of change of communication technology in recent years. It also predates NHS direct, which may have had an effect on the public's accpetance of telemedicine.

The earliest relevant RCT by Ahring et al 1992, examined glucose self-monitoring in patients who were insulin dependant diabetics. All of the study patients took five daily glucose measurements over a 12-week period. The intervention group transferred their results to the hospital computer once a week, after which patients were given telephone counselling on their diabetic management. The control group took their readings with them to a face-to-face hospital appointment.

The second relevant RCT by Harrison et al 1999, was a pilot study in which patients and their GP jointly consulted hospital consultants via PC based video conferencing equipment.

Ahring et al 1992, reported one statistically significant outcome, namely that HbBA1c levels in the intervention arm showed significant improvement from baseline levels. Harrison et al 1999, reported a higher level of satisfaction in the intervention group but this was not statistically significant. Other outcome measures such as psychological measures were inconclusive and no cost data was identified.

The review authors discussed several biases and confounders that may have influenced the results. They felt that samples within the trials were self-selected, as all required informed consent, therefore participants may have been more willing to try the new technology. Also some patients had more frequent contact with health professionals (for example the Ahring trial) which may have motivated them to manage their condition in a positive way.

Our ARIF search also identified seven relevant primary studies. Of these, three were RCTs, one a CCT and three were observational in nature. Publication dates ranged from 1999 to 2009. Patient populations in the RCTs were dermatology, breast cancer and a range of chronic conditions. None of them found a difference in outcomes between intervention and control groups. The CCT (in patients with thyrotoxicosis who had been treated with radio iodine therapy and were being monitored for hypothyroidism) found that for ‘suitable patients’ telephone follow-up improved patient outcomes. Of the three observational studies, two found that telemedicine was effective (post op carpal tunnel decompression and rheumatology), with one finding no difference (post op minor anorectal conditions).

To conclude, there is some suggestion that telemedicine is feasible, but there is limited data on clinical effectiveness. The confidence that patients have in using the technology, disease expression/severity and social factors such as distance from the hospital, may determine patient satisfaction. Clinical practice would probably also have to adapt to meet the potential and limitations of the communication medium to ensure that workload does not incease. Care should be taken, as observed in some of the trials, that telemedicine replaces face-to-face outpatient consultations rather than becoming an addition to them.

Request Carried Out: May 2009

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ARIF Request

Ovarian Cancer
Screening in those with Family History

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The Problem Submitted For ARIF To Advise Upon

What is the evidence base of the proposals made for the West Midlands Familial Cancer Initiative, particularly those concerning screening of individuals with a positive family history of ovarian cancer?

Comments

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ARIF Request

Pain Management
Post-Polio Syndrome

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The Problem Submitted For ARIF To Advise Upon

What interventions are effective for the treatment of pain associated with Post-Polio Syndrome?

Comments

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ARIF Request

Palivizumab
Respiratory Syncytial Virus

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The Problem Submitted For ARIF To Advise Upon

What is the evidence of effectiveness of palivizumab in preventing respiratory syncytial virus (RSV) infection in infants?

Comments

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ARIF Request

Partner Notification
Sexually Transmitted Infections (STIs)
Sexually Transmitted Diseases (STDs)

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

ARIF were asked to search and appraise systematic reviews on the effectiveness of different methods of partner notification in people with sexually transmitted infections (STIs) who present either to primary care or to more specialist service providers such as genitourinary medicine (GUM) clinics.

Partner notification is a process where sex partners of people with STIs are informed of their potential exposure to infection enabling partners with symptomatic, asymptomatic or incubating infection to be treated. This helps to reduce subsequent sequelae of STIs and also breaks the chains of transmission, so helping to reduce infections within populations. Partner notification can be undertaken by either the patient or health care professional or be a mixture of both (contract tracing).

Reviews Identified

- Trelle S, Shang A, Narty L, Cassell J, Low N. Review. Revised rapid review of the evidence for the effectiveness of partner notification for sexually transmitted infections including HIV. Available from: http://www.nice.org.uk/nicemedia/pdf/Partner_notification_Revised_Review_of_effectiveness.pdf
- NICE Public Health Intervention Guidance One to one interventions to reduce sexually transmitted infections (STIs) including HIV, and to reduce the rate of under 18 conceptions, especially among vulnerable and at risk groups. February Available from: http://www.nice.org.uk/guidance/index.jsp?action =download&o=31899 [accessed 3 June 2008]

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Comments

The most recent and most comprehensive systematic review was undertaken under the auspices of the NICE public health interventions programme. The systematic review was utilised to formulate guidance on interventions to reduce the transmission of STIs. Published in February 2007, recommendations three and four of the guidance document focus on partner notification. The systematic review informing this guidance was well conducted and used appropriate systematic review methodology. Searches were conducted from January 1990 to December 2005. The population under study within the review were both men and women diagnosed with gonorrhoea, chlamydia, non-gonococcal urethritis, syphilis or HIV. Interventions investigated included any type of partner notification strategy including both patient and professional led initiatives.

A total of 59 studies were included, eight were either systematic reviews or guidelines and 41 were primary studies. The information was difficult to synthesize due to the nature of the interventions and heterogeneous populations.

Key findings relating to practice and research are given in the executive summary and were as follows:

- "The current evidence about partner notification does not suggest one single optimal strategy.
- Practical guidance about effective partner notification interventions for gonorrhoea and chlamydia should focus on effective forms of patient referral.
- Whilst there is some evidence to show that labour-intensive methods such as provider and contract referral are better (for intermediate outcomes) than patient referral for index patients with gonorrhoea or chlamydia, these methods are rarely employed in practice for these infections, which are commonly diagnosed outside specialist GUM clinics.
- Good evidence of partner notification is lacking for syphilis and HIV. However, given that infections are usually more serious than gonorrhoea and chlamydia, healthcare professionals should be advised to consider contract referral and provider referral for these patients."

Request Carried Out: June 2008

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ARIF Request

Peer Support Programmes
Peer Led Programmes
Social Behaviours
School-Aged Children
Children

Table of Contents

WARNING
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The Problem Submitted for ARIF to Advise Upon:

Do peer support programmes in school-aged children impact on a range of health and social behaviours, such as smoking, drug taking, safe sex, bullying, educational achievement and criminality?

Reviews Identified

- Simkhada P, van Teijlingen E, Yakubu B, Mandava L, Bhattacharya S, Eboh W et al. Systematic review of sexual health interventions with young people from black and minority ethnic communities Foresterhill; University of Aberdeen; 2006 p28 http://www.healthscotland.com/documents/1800.aspx [accessed 11th July 2008]
- Butler G. Evidence Based Approaches to reducing gang violence A rapid evidence assessment for Aston and Handsworth Operational Group GOWM Research Team July 2004 http://www.gsr.gov.uk/downloads/resources/rea/rea_gang_violence.pdf [accessed 11th July 2008]
- DiCenso A, Guyatt G, Willan A, Griffith L. Interventions to reduce unintended pregnancies among adolescents: systematic review of randomised controlled trials. BMJ 2002;324(735):1426.
- Cuijpers P. Peer-led and adult-led school drug prevention: a meta-analytic comparison. Journal of Drug Education. 2002;32(2):107-19
- Harden A, Weston R, Oakley A. A review of the effectiveness and appropriateness of peer-delivered health promotion interventions for young people London: University of London, Institute of Education, Social Science Research Unit, EPPI-Centre; 1999 http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-20008114/frame.html [accessed 11th July 2008]

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Comments

The review by Simkhada focused specifically on black and minority ethnic (BME) communities in

Scotland. The aim was to identify effective interventions that could support sexual health and well-being of young people from BME communities. Out of 52 included studies only three specifically evaluated the impact of peers as educators or leaders. Of the results presented in the three studies there appears to be a favourable leaning towards peer education, however it is difficult to do a complete evaluation of these studies as details regarding study sizes and size of effects are not reported in the review.

The review by Butler investigated approaches to reducing gang violence. Only one study by Sheehan 1999, used peers in their intervention. The main findings were reported as being "statistically significant differences between the experimental and control group in terms of their support for violence and behaviour problem scores". In addition the intervention was cost-effective. However, without more details it is difficult to assess the size of the effect.

The review by DiCenso investigated the effectiveness of primary prevention strategies aimed at delaying sexual intercourse, improving the use of birth control and reducing incidence of unintended pregnancy in adolescents. Out of 26 included trials, only five involved peer involvement. Just one strategy was found to be statistically significant (Aarons 2000). This was use of birth control in girls in last sexual intercourse. The intervention consisted of three reproductive health classes taught by health professionals, plus five sessions around postponing sexual involvement taught by peer leaders in 10th and 11th grades. The control group received a conventional programme.

The review by Cuijpers investigated the use of peer led drug interventions in prevention of substance misuse in school children. The authors concluded that "peer-led programs may be more or less effective than adult-led programs depending on the contents and target populations"

The review by Harden surveyed the available literature in order to examine whether the peer-delivered approach is a more appropriate and effective model of promoting young peoples health than more traditional approaches. It included young people aged 11 to 24 years and the intervention had to be peer delivered interventions. Twelve studies were included. The authors concluded, "The current evidence base for peer-delivered health promotion is limited. Although the review did find some evidence for the effectiveness of peer-delivered health promotion in producing positive changes in health behaviour, a clear picture of success is still to be determined".

In summary, there is a paucity of evidence regarding the use of peer interventions in the secondary literature. The evidence base included within the reviews appears dated and its relevance to children today is questionable. Therefore the effectiveness of peer support programmes is at present unknown.

Request Carried Out: July 2008

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ARIF Request

Vagal Nerve Stimulation
Persistent Severe Depression

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The Problem Submitted For ARIF To Advise Upon

Aim - to identify the efficacy of vagal nerve stimulation for treatment of severe depression and enduring depression.

Comments

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ARIF Request

Personality Disorder Therapeutic Communities

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The Problem Submitted For ARIF To Advise Upon

What is known about the effectiveness of treating people with severe personality disorders in therapeutic communities?

Comments

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ARIF Request

PET(Positron Emission Tomography)-CT (Computed Tomography) Scanner
Various Cancers

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the accuracy, effectiveness and cost-effectiveness of the combined PET-CT scanner?

In responding to this request ARIF specifically examined:

PET-CT compared to CT scanning alone.

The use of CT in the basket of conditions where there is particular interest in using PET-CT in the first instance – lung cancer; lymphoma; colorectal cancer; thyroid cancer; oesophageal cancer; melanoma; head and neck cancer.

CT scanning uses X-rays to generate cross-sectional images of the body, recording the density of structures. PET scanning uses the emission of positrons from injected markers, especially 2-[18F] fluoro-2-deoxy-D-glucose, to provide images which record how active different parts of the body are. There is thus a strong argument that combining the information from CT scans and PET scans may improve the ability to detect the presence and extent (“staging”) of cancers.

Reviews Identified

- Mundy L, Merlin T. Combined CT and PET scanner for carcinomas Horizon Scanning Report. Canberra: Australia and New Zealand Horizon Scanning Unit; 2005.
- Agency for Health Technology Assessment in Poland. Cost-effectiveness analysis of PET-CT positron emission tomography and the diagnostic technologies financed from public sources in oncological diagnostics in Poland. Clinical and epidemiological aspects. Warsaw: Institute of Public Health and Social Insurance, Wyzsza Szkola Biznesu, National-Louis University; 2006. http://aotm.eu/pliki/bad/hta/PET-CT_clinical_full_ENG.pdf

Randomised Controlled Trials

None identified in ARIF search.

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Comments

These were the two most rigorous, accessible and relevant reviews of research identified. The first of these is more succinct and deals with literature up to 2004; the second is more detailed and consequently less accessible, but reviews literature up to March 2006.

Ostensibly both reviews have identified rigorous research literature which supports the superiority of PET-CT over CT in the key clinical indications of interest in respect of test accuracy. This in turn appears to be reflected in actual changes in patient management decisions.

There is little literature to guide assessment of cost-effectiveness. The Agency for Health Technology Assessment in Poland have attempted to develop an economic model, but the results are probably not generalisable to the UK.

In conclusion although health technology assessments identified provided some reassurance that the benefits promised by PET-CT can be achieved, widespread implementation probably requires even more detailed assessment, particularly taking the circumstances where the technology will be implemented into account.

Request Carried Out: April 2007

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ARIF Request

Phenylketonuria (PKU)

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The Problem Submitted for ARIF to Advise Upon:

To critically appraise the review by Waisbren SE to determine whether the level of phenylalanine (PHe) in the blood is a reliable measure of neurotoxicity in patients with phenylketonuria (PKU).

Reviews Identified

- Waisbren SE et al. Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. Molecular Genetics and Metabolism 2007;92(1-2):63-70

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Comments

There are areas of concern in this review which reduce confidence in the strength of the results and conclusions. There are particular concerns regarding the literature searches, data analysis, heterogeneity and date interpretation, but without undertaking a de novo review, it is not possible to estimate the effect of these reviews on the review's findings.

Request Carried Out: April 2010

To see full report - click here

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ARIF Request

Pulse Dye Laser Treatment
Port Wine Stains

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The Problem Submitted For ARIF To Advise Upon

What is the evidence on the use of pulsed dye lasers to relieve the psychological effects of port wine stains in children and adults?

Comments

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ARIF Request

Prevention
Postnatal Depression

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The Problem Submitted For ARIF To Advise Upon

Can postnatal depression be prevented?

Comments

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ARIF Request

Smoking Cessation (pre-operative)
Pre-Operative Smoking Cessation
Smoking

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of pre-operative smoking cessation interventions?

Comments

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ARIF Request

Prescribing Budgets Resource Allocation

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of manoeuvres to manage prescribing budgets in PCTs?

Comments

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ARIF Request

Prostate Specific Antigen (PSA) to detect Prostate Cancer Prostatism (Symptoms referable to the Prostate)

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The Problem Submitted For ARIF To Advise Upon

What are the effects/effectiveness of PSA testing to detect prostate cancer in those with "prostatic symptoms"?

Comments

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ARIF Request

Stents with Percutaneous Transluminal Renal Artery Angioplasty (PTRA)
Renal Artery Stenosis

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The Problem Submitted For ARIF To Advise Upon

Is stenting for renal artery stenosis an effective procedure especially in terms of life years gained & how many patients are likely to be suitable?

Comments

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ARIF Request

Rituximab
Systemic Lupus Erythematosus (SLE)

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of rituximab for SLE?

Comments

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ARIF Request

Traffic Calming
Road Accidents

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of traffic calming schemes in reducing road accidents?

Comments

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ARIF Request

Schizophrenia

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The Problem Submitted For ARIF To Advise Upon

Request from GRIP Committee to assist in the development of a GRIPKIT advising on evidence based purchasing of services for care of patients suffering schizophrenia.

Comments

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ARIF Request

School Health Services
School Age Children

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The Problem Submitted For ARIF To Advise Upon

School health services generally focus on physical health. Is there any evidence to support a different model encompassing social and mental health and development?

Comments

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ARIF Request

Sexual Behaviour
Sexually Transmitted Infections

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of interventions designed to change sexual behaviour in preventing new or recurrent sexually transmitted infections?

Comments

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ARIF Request

Skin Cancers - Squamous Cell Carcinoma, Basal Cell Carcinoma, Malignant Melanoma
Sunbeds - Sunlamps, Solaria, Sun Tanning Equipment

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The Problem Submitted For ARIF To Advise Upon

What are the health effects of sunbeds, sunlamps, sun tanning equipment & solaria?

Comments

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ARIF Request

Surgery
Sleep Apnoea

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The Problem Submitted For ARIF To Advise Upon

What are the effects/effectiveness of surgery for the treatment of obstructive sleep apnoea/hypoapnoea (OSA)?

Comments

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ARIF Request

Speech Therapy
Special Educational Needs

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The Problem Submitted For ARIF To Advise Upon

What evidence is there that speech therapy for children of school age who have special education needs is effective?

Comments

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ARIF Request

Sterilisation Reversal - Female

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The Problem Submitted For ARIF To Advise Upon

What is the evidence for the effectiveness of female sterilisation reversal?

Comments

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ARIF Request

Sterilisation Reversal - Male Vasectomy Reversal

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The Problem Submitted For ARIF To Advise Upon

Is vasectomy reversal of proven effectiveness with regard to patency and fertility?

Comments

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ARIF Request

Stroke

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The Problem Submitted For ARIF To Advise Upon

Request from GRIP Committee to assist in the development of a GRIPKIT advising on evidence based purchasing of services for care of patients suffering stroke.

Comments

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ARIF Request

Sudden Infant Death Syndrome

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The Problem Submitted For ARIF To Advise Upon

What is the evidence underpinning guidance on the prevention of sudden infant death syndrome?

Comments

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ARIF Request

Surgery
Varicose Veins

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of surgery for CEAP Class 2 varicose veins with significant symptoms?

C - Clinical Signs (Grade 0-6), a= asymptomatic, s = symptomatic
E - Etiology (congenital, primary, secondary)
A - Anatomical distribution (superficial, deep, perforator veins)
P - Pathophysiological dysfunction (reflux + obstruction)

Comments

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ARIF Request

Teaching Hospitals

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The Problem Submitted For ARIF To Advise Upon

What are the effects of teaching hospital status on patient outcomes?

In particular, is there any research looking at the effect of any given hospital changing from a non-teaching hospital to a teaching hospital?

Comments

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ARIF Request

Telemedicine (Video Links)

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The Problem Submitted For ARIF To Advise Upon

What is the evidence that telemedicine is useful in improving quality of care and in what circumstances is it most useful?

Comments

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ARIF Request

Telepathology

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The Problem Submitted For ARIF To Advise Upon

What evidence is there on the effectiveness of telepathology?

Comments

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ARIF Request

Tempero-mandibular Joint Replacements

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The Problem Submitted For ARIF To Advise Upon

What is the effectiveness of Tempero-mandibular Joint (TMJ) replacements (e.g. Christiensen joint replacement system) in conditions causing severe degeneration and scarring (fibrosis)?

Comments

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ARIF Request

Vertebral Balloon Kyphoplasty
Vertebral Compression Fracture

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness and cost-effectiveness of balloon kyphoplasty for patients with vertebral compression fractures (as a result of osteoporosis, chronic steroid use or malignancy) who are refractory to standard medical treatment.

Vertebral compression fractures cause pain and can eventually lead to progressive spinal deformity with abnormal curvature of the spine (known as kyphosis). Conventional treatment consists of the alleviation of symptoms using pain killers and spinal support. However, in a few cases patients do not improve with this treatment and the standard treatment is open back surgery. Balloon kyphoplasty has been recently developed and offers an alternative treatment to standard treatments available.

Reviews Identified

- Gill JB, Kuper M,Chin PC, Zhang Y, Schutt R Jr Comparing pain reduction following kyphoplasty and vertebroplasty for osteoporotic vertebral compression fractures. Pain Physician 2007;10(4):583-590
- Taylor RS, Fritzell P, Taylor RJ. Balloon kyphoplasty in the management of vertebral compression fractures: an updated systematic review and meta-analysis. European Spine Journal 2007;16(8):1085-1000
- Hulme PA, Krebs J, Ferguson SJ, Berlemann U. Vertebroplasty and kyphoplasty: a systematic review of 69 clinical studies. Spine 2006;31(17):1983-2001
- Bouza C, Lopez T, Magro A, Navalpotro L, Amate JM. Efficacy and safety of balloon kyphoplasty in the treatment of vertebral compression fractures: a systematic review. European Spine Journal 2006;15(7):1050-1067
- Vlayen J, Camberlin C, Paulus D, Ramaekers D. Rapid assessment of emerging spine technologies: invertebral disc replacement and vertebro/balloon kyphoplasty. Belgian Health Care Knowledge Centre (KCE reports vol 39A) 2006 http://www.kce.fgov.be/index_en.aspx?SGREF=5223&CREF=7793 [accessed 11th April 2008]
- Percutaneous kyphoplasty for vertebral fractures caused by osteoporosis and malignancy and percutaneous vertebroplasty for vertebral fractures caused by osteoporosis and malignancy. Rockville , MA . 2005 http://www.cms.hhs.gov/mcd/viewtechassess.asp?from2=viewtechassess.asp&whereindex&tid=25&
- Adelaide Health Technology Assessment (AHTA) on behalf of MSAC,UoA. Vertebroplasty and kyphoplasty for the treatment of vertebral compression fracture. 2006 http://www.msac.gov.au/internet/msac/publishing.nsf/Content/AD35ED216E990FC7CA2571420004

A192/$File/MSAC%20Ref%2027%20-%20Vertebroplasty%20and%20Kyphoplasty.pdf [accessed 11th April 2008]

- Balloon kyphoplasty. Health Technology Literature Review Ontario Ministry of Health and Long-Term Care. Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care (MAS) 2004:42 http://www.health.gov.on.ca/english/providers/program/ohtac/tech/reviews/pdf/revkypho_120104.pdf [accessed 11th April 2008]
- SBU. Kyphoplasty in severe back pain from vertebral compression fractures.2008 http://www.sbu.se/en/Ongoing-projects2/Kyphoplasty-in-severe-back-pain-from-vertebral-compression-fractures/ [accessed 11th April 2008]

Randomised Controlled Trials (Ongoing)

- FREE study – NCT00211211
- CAFE study – NCT00211237
- CEEP study – NCT00279877
- KAVIAR study – NCT00323609

Other Evidence

- IPG166 National Institute for Health and Clinical Excellence April 2006. Balloon kyphoplasty for vertebral compression fractures. 2006 http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11111 [Accessed 11th April 2008]
- MHRA. Injectable polymeric cements used in percutaneous vertebroplasty, balloon kyphoplasty and pedicle screw augmentation. MDA/088/2007 http://www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/CON2033182 [accessed 11th April 2008]

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Comments

Nine relevant reports were identified in total. Four were recent systematic reviews, 3 were health technology assessments, one was guidance from NICE, and one was recent medical device alert from the MHRA.. Most of the evidence came from case studies with a handful of non randomised comparative studies none of which compared balloon kyphoplasty with standard surgical treatment. Without good quality RCTs it is open to judgment as to whether the estimates of effectiveness from the studies are free from biases, and therefore valid. There are currently 4 ongoing RCTs being conducted.

For safety, because of the large number of patients enrolled in the case series studies, the adverse events profile is more confirmed. The main adverse event is cement leakage - see MHRA safety warning for further details. Balloon kyphoplasty with a leakage rate of 9% compares favourably with a similar technique called vertebroplasty which showed a leakage rate of 41%. Other potential adverse events such as new vertebral fractures occurred in around 13% of cases, whilst, pulmonary embolism, spinal cord compression nerve root pain and mortality occurred in very small number of cases.

NICE issued guidance on the technique in 2006 and recommended the following: “1.1 Current evidence on the safety and efficacy of balloon kyphoplasty for vertebral compression fractures appears adequate to support the use of this procedure provided that normal arrangements are in place for consent, audit and clinical governance. 1.2 This procedure should only be undertaken with prior discussion by a specialist multidisciplinary team that includes a radiologist and a spinal surgeon, and when there are facilities for good imaging, and arrangements for good access to a spinal surgery service. Clinicians should receive training to reach an appropriate level of expertise before carrying out this procedure. In particular, they must follow the manufacturer’s”

Request Carried Out: May 2008

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ARIF Request

Very Low Birthweight

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The Problem Submitted For ARIF To Advise Upon

What are the outcomes of VLBW infants?

Comments

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ARIF Request

Waiting Lists

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The Problem Submitted For ARIF To Advise Upon

What is the availability of comparative research on the effects/effectiveness of alternative methods of dealing with patients waiting for operations and other procedures ("waiting lists")?

Comments

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Archived ARIF Request

Ischaemic Heart Disease
PCTA (Angioplasty)
Abciximab

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Advice on research on the effects/effectiveness of abciximab (intravenous glycoprotein IIb/IIIa receptor (GPIIb/IIIa) inhibitor).

ARIF was asked to appraise available research on the above new drug.

Reviews Identified

- Genetta TB, Mauro VF. Abciximab: A new anticoagulant used in angioplasty. The Annals of Pharmacotherapy 1996;30:251-7.

Trials Identified

- The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularisation. New England Journal of Medicine 1997;336(24):1689-96
- The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. Lancet 1997;349:1429-35

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Comments

The review cited is not completely systematic. Although the search strategy is stated, it is not completely comprehensive; further there is little or no information on how the results were actually brought together. Essentially, only the results of the one big trial identified - EPIC (NEJM 1994;330:956-61) - were quoted.

The two RCTs given update the information available in the review. With the proviso that these studies may not be representative of all the research available on this topic, and that the three major trials address different applications of the drug, there is clear evidence of potential benefit.

In ARIF's opinion, an important ramification is that abciximab may alter the current preference for CABG as the intervention of first choice for IHD.

Readers interested in this topic may gain valuable further information on this topic from the originator of this request; contact should be via the ARIF office in the first instance.

This is an area particularly prone to need for regular updating as new information is continually becoming available.

Request Carried Out: August 1997

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Archived ARIF Request

Endovascular Stents (EVAR)
Abdominal Aortic Aneurysm (infrarenal)

Table of Contents

WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness and cost-effectiveness of EVARs for infrarenal abdominal aortic aneurysms?

Specifically could ARIF appraise the evidence base of NICE Interventional Procedures Guidance (IPG) 163?

Abdominal aortic aneurysms (AAA) are swellings of the main blood vessel in the abdomen. They cause problems because they are prone to leakage and even catastrophic rupture. The normal method of treatment is by a major operation (“open repair”), in which the aneurysm is opened and an artificial graft sewn in place to replace the weakened section of blood vessel. This is a serious procedure and surgery has a risk particularly in older, frail patients.

In endovascular stent-grafting (EVAR) the equivalent of the graft in the open repair is put in place by threading it through the main blood vessel in the leg, so hopefully obviating the need for major surgery.

See also related requests - Fenestrated Endovascular Stents (EVAR)/Abdominal Aortic Aneurysm, Endovascular Stents (EVAR)/Aneurysm/Abdominal Aortic Aneurysm

Reviews Identified

The following review underpins NICE IPG 163:

- Drury D, Michaels J, Jones L, Ayiku L. A systematic review update of the recent evidence for the safety and efficacy of elective endovascular repair in the management of infrarenal abdominal aortic aneurysms. Sheffield: School of Health and Related Research, June 2005. pp116

Randomised Controlled Trials

The review by Drury et al includes four RCTs, reported in five publications:

- EVAR trial participants. Comparison of endovascular aneurysm repair with open repair of abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. Lancet 2004;364:843-48
- Prinssen M et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. New England Journal of Medicine 2004;351:1607-18
- Blankensteijn JD et al. Two year outcomes after conventional or endovascular repair of

abdominal aortic aneurysms. New England Journal of Medicine 2005;352:2398-405

- Cuypers PWM et al. Randomized study comparing cardiac response in endovascular and open aortic aneurysm repair. British Journal of Surgery 2001;88:1059-1065
- EVAR trial participants. Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial. Lancet 2005;365:2187-92

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Comments

The RCT evidence base of the NICE IPG 163 was appraised (details available on request). The guidance appears generally sound. There does however appear to be a mismatch between the advice and the evidence concerning the effectiveness of endovascular stents in patients at sufficiently high operative risk that open repair would not be contemplated. The RCT, EVAR 2, addressing effectiveness in this patient population suggests that there is no clinical benefit, but much increased cost. These findings are not clearly reflected in the current NICE guidance.

Request Carried Out: June 2006

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Fenestrated endovascular aortic repair for abdominal aortic aneurysm

Synopsis

Question:	What is the evidence of the effectiveness and cost-effectiveness of fenestrated endovascular aortic repair (f-EVAR) for the treatment of abdominal aortic aneurysm (AAA)?
Evidence Identified:	Nordon IM, Hinchliffe RJ, Holt PJ, Loftus IM, Thompson MM. Modern treatment of juxtarenal abdominal aortic aneurysms with fenestrated endografting and open repair: a systematic review. European Journal of Vascular and Endovascular Surgery 2009;38 (1):35-41 Medical Advisory Secretariat. Fenestrated endovascular grafts for the repair of juxtarenal aortic aneurysms: an evidence-based analysis. Ontario Health Technology Assessment Series 2009;9(4).
Comments:	Recently reviewed evidence on the effectiveness of f-EVAR for AAA focused on patients with juxtarenal abdominal aortic aneurysms (JRA), and was based on limited quantity and quality of case series studies of f-EVAR and open surgery repair (OSR). Results from the reviews suggested that for JRA patients f-EVAR was favourable compared with OSR in terms of short-term mortality and duration of operation and hospital stay, but involved a higher rate of early secondary re-intervention. However, the results should be interpreted with caution due to the lack of reliability of the primary studies and the methods employed in the reviews to analysis the findings of these studies. There appeared to be no evidence on the cost-effectiveness of f-EVAR for AAA.
Date Completed:	July 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Fenestrated endovascular aortic repair for abdominal aortic aneurysm

Request completed: July 2010

Question

What is the evidence of the effectiveness and cost-effectiveness of fenestrated endovascular aortic repair (f-EVAR) for the treatment of abdominal aortic aneurysm (AAA)?

Question clarification

In 2005 ARIF was requested to identify and review secondary evidence around the effectiveness of fenestrated endovascular aortic repair (f-EVAR) for the treatment of abdominal aortic aneurysm (AAA). The work undertaken in 2005 was then updated in March 2009[i]. This report updates the previous ARIF work on the topic.

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol (www.arif.bham.ac.uk/strategy.shtml). Text and index terms were used to represent the population and the intervention. Sources were searched from 2009 to June 2010. No language restriction was applied to the searches. As an example the MEDLINE search can be found in Appendix A. The following inclusion criteria were used for study selection:

Population	Patients with abdominal aortic aneurysms. Subgroup: patients with a juxtarenal abdominal aortic aneurysm, or any other subgroups. (Excluding thoracic aortic aneurysms)
Intervention	Fenestrated endovascular stents (excluding branched endovascular stents)
Comparator	Normal endovascular stents; open surgery; no treatment
Outcome	Perioperative, short, medium and long term morbidity and mortality; cost effectiveness (in the medium to long term postoperative)
Study design	Systematic reviews and health technology assessments

Results

Two relevant systematic reviews were identified[1,2]. No economic evaluations on f-EVAR were identified. Full search results can be found in Appendix B.

[i] See the link for the report: http://www.arif.bham.ac.uk/f/fenestrated-endovascular-stents-evar2.shtml

Both reviews assessed evidence on the effectiveness of f-EVAR for juxtarenal abdominal aortic aneurysms (JRAs) compared with open surgery repair (OSR), and both were published in 2009. One,[1] the Nordon review, had slightly wider inclusion criteria for study publication date, study design and sample size. The other by the Medical Advisory Secretariat (MAS) group[2] was conducted from the Canadian perspective, and had narrower inclusion criteria but slightly more updated searches. Outline features of the reviews are listed in Table 1 below.

Characteristics of the reviews

The Nordon review[1] included a total of eight case series studies on f-EVAR and 12 case series studies on OSR. All were published between 2001 and 2008. Two of the f-EVAR studies and one of the OSR studies were conducted in the UK.

The MAS review[2] included one comparative study comparing f-EVAR with OSR (non-randomised controlled trial with contemporaneous controls), five case series on f-EVAR and seven case series studies on OSR, all published from 2004 to 2009. In its inclusion criteria the review intended to include prospective studies only, however, six of the OSR studies were retrospective. For the comparative study it was unclear in which country it was conducted; of the remaining only one f-EVAR study was conducted in the UK (see Table 1 below for details).

The Nordon review included a total of 368 patients in the f-EVAR studies and 1164 in the OSR. The MAS review included in total 274 patients in the f-EVAR case series studies and 858[ii] in the OSR case series studies. The comparative study had a very small sample size with just 16 and 29 in the f-EVAR group and OSR group respectively.

Both reviews focused on patients with juxtarenal abdominal aortic aneurysms (JRAs). However, in the MAS review among patients in the f-EVAR studies some had aortic ulcers (n=3), thoracoabdominal aortic aneurysms (TAAA) (n=8) and one of them underwent a branched graft. Among patients in the OSR studies some had suprarenal aortic aneurysms (SRA) (n=136) and thoracic aortic aneurysms (TAA) (n=45).

The reviews shared three f-EVAR studies and five OSR studies. As a result, in the MAS review, 202 (74%) patients in the f-EVAR studies and 755 (88%) in the OSR studies were also included in the Nordon review. Also, as such, although not stated in the Nordon review it was obvious that the population were not purely patients who had JRAs. See Table 1 below for details.

[ii] The subgroups of JRA, SRA and TAA do not add up to the total in the table 17 (page 35) of the publication. The discrepancy might be due to typo error.

Table 1. Outline features of the two reviews

	Nordon 2009[1]	**MAS 2009[2]**
Country	UK	Canada
Aim	To review the outcomes of f-EVAR for JRA and make a comparison with open repair	To determine whether f-EVAR for JRA can provide better outcomes than OSR
Population	Patients with JRA	Patients with JRA
Intervention	f-EVAR	f-EVAR
Comparator	Standard EVAR, OSR, or no treatment	Standard EVAR, OSR, or no treatment
Outcome	30-day cumulative mortality; renal impairment (defined as an increased in serum creatinine to >2 mg/dl or by >30% compared to baseline in the peri-operative period); target vessel patency; length of stay and secondary re-intervention rate	Primary outcome: 30-day mortality; late mortality (over the period of time that patients have been followed) and permanent dialysis. Secondary outcome: Technical success rate; conversion to repair; temporary dialysis; renal and mesenteric events due to procedure; aneurysm expansion and rupture; target vessels patency; graft migration and component separation; endoleak; post-operational complication; secondary procedures; operating room and hospitalization data.
Inclusion/ exclusion	Inclusion criteria: published studies reporting experience with greater than 10 cases of f-EVAR or open surgical management of juxtarenal abdominal aortic aneurysms. Exclusion criteria: replicate data publication; selective patient subgroup analysis and AAA ruptures.	Inclusion criteria: prospective studies that reported on f-EVAR in patients with JRA; studies reporting primary outcomes and most of the secondary outcomes selected for the review; studies published since 2004; sample size ≥15 patients. Exclusion criteria: retrospective studies; studies reporting technical aspects of the graft implantation; reports that did not contain patient data; sample size <15; other anatomical location of aneurysm.
Data source	PUBMED and EMBASE databases for articles published in the English language between 2001 and 2008	OVID MEDLINE, MEDLINE In-PROCESS & Other Non-Indexed Citations, EMBASE, The Cochrane Library, and the International Agency for Health Technology Assessment database; English-language articles published from 1st January 2004 to 19th December 2008. Searches updated to 23rd March 2009.
Studies included‡	8 f-EVAR series: total N=368 • Prospective - **O'Neill 2006 (USA), N=119** - **Muhs 2006 (Netherlands), N=38** - Bicknell2008 (UK), N=15 - Anderson 2001 (Australia), N=13 • Single centre - Halak 2006 (Australia), N=17 • Retrospective - **Scurr 2008 (UK), N= 45*** - Ziegler 2007 (Germany), N=63 - Semmens 2006 (Australia), N=58 12 OSR series: total N=1164 • Case-control: - **Ockert 2007 (Germany), N=35†** • Prospective: - Bicknell 2003 (UK), N=44 - Sarac 2002 (USA), N=138 • Retrospective: - **Knott 2008 (USA), N=126** - **Pearce 2007 (USA), N=150** - **Chiesa 2006 (Italy), N=119*** - **West 2006 (USA), N=247** - **Back 2005 (USA), N=78** - Ryan 2004 (USA), N=44 - Kudo 2004 (Japan), N=18 - Shortell 2003 (USA), N=112 - Ayari 2001 (France), N=53	1 comparative study: (country unstated); N=45 (all JRA); f-EVAR (n=16) vs. OSR (n=29); 5 f-EVAR case series: total N=274; mean follow up duration 9.4 to 25.8 months. • Prospective - **Scurr 2008 (UK), N=45*** - **O'Neill 2006 (USA), N=119** - **Muhs 2006 (Netherlands), N=38 (includes 8 TAAA and one branched graft)** - Kristmundsson 2009 (Sweden), N=54 (includes 3 aortic ulcer) - Verhoeven 2004 (Netherlands), N=18 7 OSR series **§**: total N=858 (including 677 JRA, 136 SRA and 45 TAA); mean follow up duration 1 to 48 months. • Prospective: - **Chiesa 2006 (Italy), N=119 (JRA=85, SRA=35)*** • Retrospective - **Knott 2008 (USA), N=126 (all JRA)** - **Pearce 2007 (USA), N= 150 (JRA=134, SRA=16)** - **Ockert 2007 (Germany), N=35 (all JRA)†** - **West 2006 (USA), N=247 (JRA=204, SRA=43)** - **Back 2005 (USA), N=158** (**JRA=78**, SRA=35, TAA=45) - Illuminati 2007 (Italy), N=21 (JRA=13, SRA=8) (**TAAA**: thoracoabdominal aortic aneurysms. **JRA**: juxtarenal abdominal aortic aneurysm. **SRA**: suprarenal aortic aneurysm. **TAA**: thoracic aortic aneurysm)
Data analysis	Pooled data for f-EVAR and OSR respectively, with relative risk, 95%CI and p value	Pooled data for f-EVAR and the JRA patients in the OSR series respectively; without relative risk, 95%CI and p value reported

‡ Studies and number of patients in **bold** were included in both reviews.
* The studies were stated as retrospective in the Nordon review while prospective in the Medical Advisory Secretariat review.
† The study was stated as case-control in the Nordon review while retrospective in the Medical Advisory Secretariat review.
§ For the OSR studies the subgroups of JRA, SRA and TAA do not add up to the total in table 17 on page 35 of the publication. This might be due to typo error.

In both reviews the data for the f-EVAR studies and the OSR studies were pooled. However, detailed methods of how the data were combined were not described.

Patient characteristics

In the Nordon review pooled baseline demographic data showed that mean age in the f-EVAR studies was slightly but significantly younger than in the OSR studies (71.8 years vs. 73.8 years; p=0.0001), while there was no significant difference in terms of gender, ischemic heart disease and preoperative renal impairment. Further information regarding the patient population was not reported.

In the MAS review mean patient age in the f-EVAR studies was slightly older than the ORS (74 years vs. 72 years); the authors also stated that all patients in the f-EVAR studies had high risk for open surgery repair and were unfit for infrarenal standard EVAR due to short neck of the aneurysm. Mean follow-up duration was not clearly stated in the Nordon review, while in the MAS review it ranged from 9.4 to 25.8 months in the f-EVAR studies and from 1 to 48 months in the OSR.

Findings of the reviews

In the Nordon review 30-day mortality (measured as cumulative mortality) showed a small but significant benefit with f-EVAR compared to the OSR (1.4 vs. 3.6; relative risk of OSR vs f-EVAR =1.03; 95%CI 1.01 to 1.04; p=0.02). Also, with f-EVAR there were significantly more early re-interventions but less transient renal failures than the OSR cohort, while with no significant difference on postoperative dialysis rate (see Table 2 below for details). The authors stated that the results should be interpreted with caution for the following reasons:

- possible publication bias of the included studies
- insufficient information on patient population
- lack of standard classification of JRAs in the studies
- short-term results
- small case series; no randomised controlled trials that directly compared f-EVAR with OSR, standard management, or no treatment
- uncertainty of applicability of the results

The MAS review stated that for mortality outcomes for the OSR studies data were pooled separately for JRA patients. While for the other data in this review, and for all the data in the Nordon review, presumably the pooled data included also patients with aortic ulcer, TAAA, SRA or TAA. Table 2 below presents the main pooled outcome data in the two reviews.

In the MAS review no relative risks, confidence intervals and p-values were presented. 30-day mortality rate was lower in the f-EVAR studies than in the OSR (1.8 vs. 3.1). The difference between the f-EVAR and OSR appeared smaller than that in the Nordon review. Later mortality and postoperative cardiac, pulmonary and gastrointestinal complications all tended to favour the f-EVAR. Also, operation time and hospital stay days were much shorter in the f-EVAR studies than in the OSR. Mesenteric ischemia, aneurysm expansion and secondary intervention (non-endoleak) rates appeared higher in the f-EVAR than the OSR studies (see Table 2 below for details). In the small comparative study included in this review, it was stated that there was no significant difference between the two groups in 30-day mortality, cardiac or pulmonary complications and duration of surgery, ICU stay or hospital stay. However, no statistical findings were presented to support this (for details see table 2, 3 and 4 on page 20 of the publication); also, patients in the f-EVAR group were generally older than in the OSR group, and had a significantly higher incidence of severe cardiac and pulmonary co-morbidities and diabetes[iii].

The authors also concluded that short- and medium-term (up to 2 years) outcomes were favourable in f-EVAR studies compared with that in the OSR studies but uncertainty remained regarding the long-term results. However, for some of the outcomes the review did not clearly report at which follow-up time they were measured.

Some outcome data for the other subgroups i.e. suprarenal aortic aneurysm (SRA) and thoracic aortic aneurysm (TAA) in the OSR studies were also reported separately but were not statistically pooled and compared with the results in the f-EVAR studies.

The authors stated that the results of the review were based on low quality evidence.

The authors also conducted an economic literature review. No economic analyses on f-EVAR were identified.

Commentary on the findings of the reviews

Overall, there are uncertainties around the results from the two systematic reviews. In both reviews all the studies were case series with the exception of one very small non-randomised comparative study. Both reviews pooled case series studies for each intervention, and then compared the pooled results. However, there is heterogeneity between studies on the same interventions and between the compared interventions. Such heterogeneity includes, but is not limited to, for example: in the MAS review the f-EVAR studies were all prospective while the majority of OSR

[iii] Data on the incidence of severe cardiac and pulmonary co-morbidities and diabetes were not reported; the authors stated that these were significantly higher in the f-EVAR series and $p<0.5$. Thus, presumably the p value was a typo error in the publication.

studies were retrospective; in the Nordon review patients in the f-EVAR studies were slightly but significantly younger than those in the OSR; in both reviews the patient population were mixed with JRA, TAAA, SRA and TAA. As such, there is uncertainty around the appropriateness of pooling data for each intervention and then using those pooled data to compare the interventions. Given that there is a small difference when such pooling and comparison is undertaken for some outcomes, i.e. 30-day mortality, caution should be applied when considering the findings of the studies in the reviews.

Conclusions

Two relevant reviews have been published since the last ARIF report on this topic in 2009. This recently reviewed evidence on the effectiveness of f-EVAR for abdominal aortic aneurysm focused on patients with juxtarenal abdominal aortic aneurysms, and was based on limited quantity and quality of case series studies of f-EVAR and OSR. Results from the reviews suggested that for JRA patients f-EVAR was favourable compared with open surgery in terms of short-term mortality and duration of operation and hospital stay, but involved a higher rate of early secondary re-intervention. However, the results should be interpreted with caution due to the lack of reliability of the primary studies and the methods employed in the reviews to analysis the findings of these studies. There appeared to be no reviews assessing the effectiveness of f-EVAR compared with standard EVAR or no treatment. There also appeared to be no evidence on the cost-effectiveness of f-EVAR for AAA.

Table 2. Main pooled outcomes of the f-EVAR and the OSR case series studies in the two reviews

	Nordon 2009[1]	**MAS 2009[2]**
	f-EVAR vs. OSR	f-EVAR vs. OSR (**all reported as rate**)
30-day mortality (%)	Cumulative mortality: 1.4 (95%CI 0.4 to 3.1) vs. 3.6 (95%CI 2.7 to 4.9); RR (OSR vs. f-EVAR) =1.03 (95%CI 1.01 to 1.04), p =0.02	1.8 vs. 3.1
Cause of mortality	No. of patients:	
• mesenteric ishaemia	2 vs. 18	3.3 vs. 2.9 (not stated as a cause of mortality)
• myocardial infarction	3 vs. 13	-
• mesenteric ishaemia	0 vs. 8	-
• others	0 vs. 4	-
Intra-operative deaths (No. of patients)	0 vs. 2	-
Late mortality	-	12.8 vs. 23.7
Transient renal impairment (%)	14.9 (95%CI 11.5 to 18.7) vs. 20 (95%CI 17.9 to 22.5); RR = 1.06 (95%CI 1.01 to 1.12), p =0.03*	-
Permanent dialysis	-	0 - 2.5 vs. 0 - 3.5
Loss of kidney	-	1.5 vs. 0; incidence of post-operative renal insufficiency in the OSR =14.4%
Postoperative complications (%)		
• dialysis	1.4 (95%CI 0.5 to 3.1) vs. 1.4 (95%CI 0.8 to 2.3); RR = 1.00 (95%CI 0.99 to 1.01), p =1	-
• cardiac	-	1.5 vs. 10.7
• pulmonary	-	0.7 vs. 13.4
• gastrointestinal	-	0.7 vs. 5.9
Target vessel patency	In the f-EVAR: All the studies reported primary technical branch success, and 7/8 reported target vessel patency (TVP) at follow-up. 823/825 (96.6%; 95%CI 95.4 to 97.8) of target vessels were preserved at primary surgery. 6/8 studies reported median follow-up >1 year, of these one study did not report follow-up TVP. In the remaining studies 1-year patency had reduced to 423/469 (92%; 95%CI 90.3 to 94.8). In this period no patient developed new dialysis dependent renal failure. In the OSR: Only one study reported renal artery patency following revascularisation; in those patients attending review (6/14 patients) renal artery patency rate was 85%	-
Primary endoleak (not applicable in the OSR)	Type 1or type 3: n=22	Type 1= 4; type 2 =16.8; type 3 =1.8. Endoleak required treatment: type 1 = 2.9; type 2 = 3.3; type 3 = 1.1
Aortic rupture	-	0 vs. 0

	Nordon 2009[1]	**MAS 2009**[2]
	f-EVAR vs. OSR	f-EVAR vs. OSR (**all reported as rate**)
Patients required secondary re-intervention (%)	15 (95%CI 11.5 to 18.7) vs. 2.6 (95%CI 1.5 to 4.4); RR = 0.87 (95%CI 0.83 to 0.91), p=0.0001*	(Non-endoleak) 8.8 vs. 7.8
Aneurysm expansion	-	1.4 vs. 0
Graft migration (not applicable in the OSR)	-	1.5
Graft separation (not applicable in the OSR)	-	0.7
Operation time (minutes)	-	240 vs. 287
Hospital stay (days)	-	6 vs. 13

* Stated as 'early', presumably referred to up to 30-days follow-up

References

1. Nordon IM, Hinchliffe RJ, Holt PJ, Loftus IM, Thompson MM. Modern treatment of juxtarenal abdominal aortic aneurysms with fenestrated endografting and open repair: a systematic review. European Journal of Vascular and Endovascular Surgery 2009;38 (1):35-41

2. Medical Advisory Secretariat. Fenestrated endovascular grafts for the repair of juxtarenal aortic aneurysms: an evidence-based analysis. Ontario Health Technology Assessment Series 2009;9(4).

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 exp aortic aneurysm/
2 aortic aneurysm$.mp.
3 or/1-2
4 f evar.mp.
5 fevar.mp.
6 fenestrated.mp.
7 4 or 5 or 6
8 3 and 7
9 limit 8 to yr="2009 -Current"

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Appendix B – Literature search results

Systematic reviews

Source – Cochrane Library (Wiley internet) 2010 Issue 2 (DARE)

Medical Advisory Secretariat.
Fenestrated endovascular grafts for the repair of juxtarenal aortic aneurysms: an evidence-based analysis. Ontario Health Technology Assessment Series 2009;9(4).

Nordon IM, Hinchliffe RJ, Holt PJ, Loftus IM, Thompson MM.
Modern treatment of juxtarenal abdominal aortic aneurysms with fenestrated endografting and open repair: a systematic review. European Journal of Vascular and Endovascular Surgery 2009; 38 (1):35-41

Source – ARIF Database

Bakoyiannis CN, Economopoulos KP, Georgopoulos S, Klonaris C, Shialarou M, Kafeza M et al.
Fenestrated and branched endografts for the treatment of thoracocabdominal aortic aneurysms: A systematic review. Journal of Endovascular Therapy 2010; 17(2):201-209.

Primary Study

Source – MEDLINE (Ovid) 2009 - June week 5 2010

Greenberg RK, Sternbergh WC 3rd, Makaroun M, Ohki T, Chuter T, Bharadwaj P, Saunders A. Fenestrated Investigators.
Intermediate results of a United States multicenter trial of fenestrated endograft repair for juxtarenal abdominal aortic aneurysms.
Journal of Vascular Surgery. 50(4):730-737.e1, 2009.

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Endovascular Aortic Aneurysm Repair (EVAR)

Synopsis

Question:	What is the effectiveness of Fenestrated Endovascular Stents (EVAR) in patients who have abdominal aneurysms? (This request updates the previous request completed in 2005).
Reviews Identified:	Sun Z, Mwipatayi BP, Semmens JB, Lawrence-Brown MM. Short to midterm outcomes of fenestrated endovascular grafts in the treatment of abdominal aortic aneurysms: Systematic review. Journal of Endovascular Therapy 2006;13(6):747-53
Comments:	Much more research has been published regarding fenestrated stent implantation in patients who have complex abdominal aortic aneurysms since the ARIF request in 2005. Short term outcomes appear to be good, however, it is difficult to compare this technique with open repair or other options of care due to the non - comparative nature of the research evidence and also of the inadequate description of the study populations particularly regarding co-morbidities and fitness for open repair. Therefore the conclusions made in 2005 still stand, i.e. that this is a promising technology but it is still at a relatively early stage of evaluation, particularly regarding its effectiveness compared to other treatment options and its long term effectiveness.
Date Completed:	March 2009

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Endovascular Aortic Aneurysm Repair (EVAR)

Request completed: March 2009

Question

What is the effectiveness of Fenestrated Endovascular Stents (EVAR) in patients who have abdominal aneurysms?

Population:	Patients with complex abdominal aortic aneurysms
Intervention:	Fenestrated endovascular stents
Control:	Standard care (open repair, observation, or no treatment)
Outcomes:	Survival, morbidity, costs
Study design:	Systematic review.

Question clarification

The objective was to update the previous ARIF request in 2005 (see Appendix A).

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol http://www.arif.bham.ac.uk/strategy.shtml Text and index terms were used to denote the population and the intervention. Sources were searched from 2005 to March 2009. No language restriction was applied to the searches. The MEDLINE search can be found in Appendix B. Studies were selected according to the inclusion criteria stated in the question.

Results

This report is based on evidence from one systematic review. Full search results can be found in Appendix C.

Sun Z, Mwipatayi B P, Semmens J B, Lawrence-Brown M M.
Short to midterm outcomes of fenestrated endovascular grafts in the treatment of abdominal aortic aneurysms: a systematic review. Journal of Endovascular Therapy 2006; 13 (6): 747-53

This was a reasonably well-conducted review. An in depth summary can be found in Appendix D. The review aimed to assess the short to mid - term outcomes of patients with complicated abdominal aortic aneurysms, which had been repaired using a fenestrated endovascular graft. Searches went from 1999 to 2006 and sought only English language studies, which may have introduced some publication bias. The primary studies identified by ARIF in 2005 had been

incorporated into this review. In total six studies were included, four were published in 2006, one in 2005 and one in 2001.

All of the studies were case series, involving in total 317 patients. Patients were mainly men with a mean age of 75 years. The most common fenestrated vessels were the renal artery (575 fenestrated), the superior mesenteric arteries (134 fenestrated) and celiac arteries (6 fenestrated). Follow up ranged from 0 to 48 months, with a greater than 12 month mean follow up reported in four studies.

The results of the studies were pooled in the systematic review and reported as follows:

	Mean % (95% CI)
Mortality <30 days	1.1 (0.4, 2.7)
Mortality > 30 days	8.3 (2.9, 13.6) p<0.01 vs. early mortality
Perfusion of fenestrated arteries (peri-operative)	97 (92, 100)
Perfusion of fenestrated arteries (late follow up)	90 (85, 95)
*Pre-existent renal dysfunction	22.7 (15.7, 61.1)
*Post-procedural renal dysfunction	13.3 (4.1, 22.5) p=0.2 vs. pre-op renal dysfunction
Occluded arteries	5.3 (1.8, 8.8)
Stenosed arteries	2.6 (0.4, 4.8)
Endoleaks <30 days	11.2 (3.2, 22.5)
Endoleaks > 30 days	9.4 (2.6, 16.3)

Overall, the review authors conclude that *"fenestrated endovascular grafting provides an alternative technique to treat patients with complex aneurysm necks, achieving lower mortality than open repair under comparable conditions"* however, *"the techniques for fenestrated stent grafts are still in their infancy and the stability and patency of fenestrated vessels remains to be proven in long-term follow up".*

The main problem of this review is that the patient population has not been adequately described. Whilst the review clearly states that patients had to have a fenestrated stent due to their complicated anatomy, no description was given regarding co-morbidities and more importantly, whether they were eligible for open repair, or were unfit for open repair. This makes it very difficult to generalize the findings of the review.

Conclusion:

Much more work has been published regarding fenestrated stent implantation in patients who have complex abdominal aortic aneurysms since the ARIF request in 2005. Short term outcomes appear

to be good, however, it is difficult to compare this technique with open repair or other options of care due to the non - comparative nature of the research evidence and also of the inadequate description of the study populations particularly regarding co-morbidities and fitness for open repair. Therefore the conclusions made in 2005 still stand, i.e. that this is a promising technology but it is still at a relatively early stage of evaluation, particularly regarding its effectiveness compared to other treatment options and its long term effectiveness.

Appendix A – Previous ARIF request May 2005

RE: Fenestrated endovascular stent-grafting for complex abdominal aortic aneurysms

As we have already indicated a major challenge has been understanding exactly what is involved in this procedure and how it differs from EVAR (endovascular aneurysm repair) on which there is a large amount of information to guide commissioners, not least advice from NICE (Interventional Procedure Guidance 10, June 2003).

Our understanding, is that both technologies are concerned with the treatment of abdominal aortic aneurysms, swellings of the main blood vessel in the abdomen, which cause problems because they are prone to leakage and even catastrophic rupture. The normal method of treatment is by a major operation, in which the aneurysm is opened and an artificial graft sewn in place to replace the weakened section of blood vessel. This is a major procedure, and many older patients are too frail to undergo the surgery. In endovascular stent-grafting (EVAR) the equivalent of the graft in the open operation is introduced through the main blood vessel in the leg, so obviating the need for a major surgery. The evidence suggests that this is indeed successful although, RCTs to confirm this are still ongoing. Fenestrated endovascular stent-grafting in contrast is a response to the main limitation of EVAR, which is that abdominal aortic aneurysms frequently affect not just the aorta but blood vessels that branch off the aorta (especially the renal arteries) and that more complicated grafts with more complicated insertion procedures are required. Fenestrated stents are specially tailored grafts which allow blood to flow down these side branches. An inevitable consequence of the tailoring process is that cost is very much greater than EVAR, which is itself expensive.

Unsurprisingly, given that evaluation of EVAR has only just reached the RCT stage, it is inevitable that as a further development of the EVAR technology, fenestrated endovascular stenting is at an even earlier stage of evaluation. We ran our searches of the main databases for systematic reviews, RCTs and other primary studies. The only directly relevant studies we identified were two case-series (there were certainly no systematic reviews of RCTs or RCTs alone):

- Greenberg RK, Haulon S, O'Neill S, Lyden S, Ouriel K. Primary endovascular repair of juxtarenal aneurysms with fenestrated endovasular grafting. Eur J Vasc Endovasc Surg 2004;27:484-491
- Greenberg RK, Haulon S, Lyden S, Srivastava SD, Turc A, Eagleton MJ, Sarac TP, Ouriel K. Endovascular management of juxtarenal aneurysms with fenestrated endovasular grafting. J Vasc Surg 2004;39:279-87

Unfortunately the latter is a sub-set of the former, so effectively the only available published evidence on effectiveness appears to be one case-series.

The study in question appears to provide complete follow-up of 32 patients for a mean of 9.2 months (range 0 to 24 months). The patients appear likely to be a complete sample of all those on whom the technology was attempted over the 2 year period covered (August 2001 to December 2003). The inclusion criteria were:

- Physiologically high risk for open surgical repair (evidence of non-reconstructable cardiac ischaemia; ejection fraction <25%; significant chronic pulmonary disease; chronic renal insufficiency)
- Unsuitable for traditional infrarenal endovascular grafts
- Aneurysms at risk of rupture (greater than 5.5 cm; grew more than 0.5 cm over past year)

There appeared to be a high level of technical success and there was only one post-operative death at 7 days in the early follow-up period before 30 days. The authors emphasise that although the study demonstrates technical feasibility, "it remains critical to follow the status of stented visceral vessels, and establish the long-term efficacy of this type of repair". The acknowledged need for further rigorous evaluation is in keeping with the known biases (selection, attrition and

outcome assessment) to which case-series are highly prone, lacking as they do a proper control group. The discussion section of the paper also emphasises the importance of careful patient selection, proper graft design and technical expertise in achieving the results reported.

In conclusion fenestrated endovascular stent grafting is a promising technology, but is at an early stage of evaluation of its effectiveness; cost-effectiveness is unknown and important given the very high cost of the grafts. Ideally, at present, this treatment should only be commissioned in the context of a rigorous evaluation. We will feed back the need for such research to the NHS HTA programme. Any patients on whom this technique is applied on a case-by-case basis should be clearly informed that the technique is still experimental.

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Appendix B – Literature Search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 exp Aortic Aneurysm/
2 fenestrated endovascular.mp.
3 endograft$.tw.
4 aortic aneurysm$.mp.
5 1 or 4
6 2 or 3
7 5 and 6
8 limit 7 to "reviews (optimized)")
9 limit 8 to yr="2005 - 2009"

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Appendix C – Literature search results

Systematic review

Source – Cochrane Library (DARE) 2009 Issue 1

Sun Z, Mwipatayi B P, Semmens J B, Lawrence-Brown M M. Short to midterm outcomes of fenestrated endovascular grafts in the treatment of abdominal aortic aneurysms: a systematic review. Journal of Endovascular Therapy 2006; 13 (6): 747-53

Primary studies

Source – MEDLINE (Ovid) 2005 - 2009

Bicknell CD. Cheshire NJ. Riga CV. Bourke P. Wolfe JH. Gibbs RG. Jenkins MP. Hamady M. Treatment of complex aneurysmal disease with fenestrated and branched stent grafts. European Journal of Vascular & Endovascular Surgery. 37(2):175-81, 2009 Feb.

Kawaguchi S. Yokoi Y. Shimazaki T. Koide K. Matsumoto M. Shigematsu H.
Thoracic endovascular aneurysm repair in Japan: Experience with fenestrated stent grafts in the treatment of distal arch aneurysms. Journal of Vascular Surgery. 48(6 Suppl):24S-29S; discussion 29S, 2008 Dec.

Ziegler P. Avgerinos ED. Umscheid T. Perdikides T. Stelter WJ.
Fenestrated endografting for aortic aneurysm repair: a 7-year experience.
Journal of Endovascular Therapy: Official Journal of the International Society of Endovascular Specialists. 14(5):609-18, 2007 Oct.

O'Neill S. Greenberg RK. Haddad F. Resch T. Sereika J. Katz E.
A prospective analysis of fenestrated endovascular grafting: intermediate-term outcomes.
European Journal of Vascular & Endovascular Surgery. 32(2):115-23, 2006 Aug.

Muhs BE. Verhoeven EL. Zeebregts CJ. Tielliu IF. Prins TR. Verhagen HJ. van den Dungen JJ.
Mid-term results of endovascular aneurysm repair with branched and fenestrated endografts.
Journal of Vascular Surgery. 44(1):9-15, 2006 Jul.

Semmens JB. Lawrence-Brown MM. Hartley DE. Allen YB. Green R. Nadkarni S.
Outcomes of fenestrated endografts in the treatment of abdominal aortic aneurysm in Western Australia (1997-2004). Journal of Endovascular Therapy: Official Journal of the International Society of Endovascular Specialists. 13(3):320-9, 2006 Jun.

Adam DJ. Berce M. Hartley DE. Anderson JL. Repair of juxtarenal para-anastomotic aortic aneurysms after previous open repair with fenestrated and branched endovascular stent grafts.
Journal of Vascular Surgery. 42(5):997-1001, 2005 Nov.

Background review

Source – MEDLINE (Ovid) 2005 - 2009

Chuter TA. Fenestrated and branched stent-grafts for thoracoabdominal, pararenal and juxtarenal aortic aneurysm repair. Seminars in Vascular Surgery. 20(2):90-6, 2007 Jun.

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Appendix D – Critical Appraisal of:

Sun Z, Mwipatayi B P, Semmens J B, Lawrence-Brown M M
Short to midterm outcomes of fenestrated endovascular grafts in the treatment of abdominal aortic aneurysms: a systematic review. Journal of Endovascular Therapy 2006; 13 (6): 747-53

Aim	To perform a systematic review of the short to midterm outcomes of fenestrated endovascular grafts in patients with abdominal aortic aneurysms (AAA).
Background	Main reason for using fenestration has been "to treat infrarenal neck <10mm long. The second reason is to preserve a dominant or single renal vessel if it is slightly lower than the other side. The third reason is to preserve mesenteric vessels with the aim of eventually bridging across from the thoracic to the infrarenal aorta"
ARIF comment	Case series contributing to the data. All patients within the studies received a fenestrated stent. Review looks fine, although as they mention in their discussion, limiting studies to 10 patients or more may have underestimated complication rates.
Population	Patients with complicated thoracic or abdominal or thoracoabdominal aneurysms. ***ARIF comment: not stated if these patients were ineligible for open repair.***
Intervention	Fenestrated stent graft.
Control	Not clear. Is it open repair, non fenestrated stent (probably not), observation or no treatment?
Outcome	Clinical outcomes & post-procedural complications.
Other inclusion criteria	1. Patients had to have a thoracic or abdominal or thoracoabdominal aneurysms repaired with a fenestrated stent graft. 2. Studies included at least 10 patients. 3. Number of vessels fenestrated and their status (perfusion, stenosis, or occlusion) following the procedure were addressed. 4. Peri procedural and post procedural outcomes reported in the study.
Quality of Review	Reasonable quality, searched only for English language papers, and only searched PubMed and MEDLINE, which may have missed some studies and given it a North American slant.
Study design	Systematic review, studies = case series with more than 10 patients in them.
Search date/ search strategy	MEDLINE & PubMed searched between 1999 to 2006. English Language only. Excluded conference abstracts, technical or case reports and review articles. ***ARIF comment: excluding conference abstracts may have limited the number of studies included, particularly as this is a fairly new technology. Excluding case reports possibly limited the pool of data, particularly in centres where this procedure is not routine.***
Data analysis	Mean and 95% CI.
Number of studies included	Included 6 studies, involving 317 patients. Four studies were published in 2006, 1 in 2005 and 1 in 2001. Study dates ranged from 1998 to 2005.
Trial characteristics	Patients were mainly men, with a mean age of 75 years where reported. The most common fenestrated vessels were the renal artery (575 fenestrasted), with 134 superior mesenteric arteries and just 6 celiac arteries. In all studies, pre-operative and follow up imaging included computed tomographic angiography, with all but one trial (which used ultrasound) utilising digital subtraction angiography in preoperative imaging. For follow up two studies also used plain radiography with a third study using ultrasound.

<table>
<tr><td>Effectiveness – results/ Adverse events</td><td>Zenith stent-graft = only device used.

<table>
<tr><td></td><td>Mean % (95% CI)</td></tr>
<tr><td>Mortality <30 days</td><td>1.1 (0.4, 2.7)</td></tr>
<tr><td>Mortality > 30 days</td><td>8.3 (2.9, 13.6) P<0.01 vs. early mortality</td></tr>
<tr><td>Perfusion of fenestrated arteries (peri-operative)</td><td>97 (92, 100)</td></tr>
<tr><td>Perfusion of fenestrated arteries (late follow up)</td><td>90 (85, 95)</td></tr>
<tr><td>*Pre-existent renal dysfunction</td><td>22.7 (15.7, 61.1)</td></tr>
<tr><td>*Post-procedural renal dysfunction</td><td>13.3 (4.1, 22.5) p=0.2 vs. pre-op renal dysfunction</td></tr>
<tr><td>Occluded arteries</td><td>5.3 (1.8, 8.8)</td></tr>
<tr><td>Stenosed arteries</td><td>2.6 (0.4, 4.8)</td></tr>
<tr><td>Endoleaks <30 days</td><td>11.2 (3.2, 22.5)</td></tr>
<tr><td>Endoleaks > 30 days</td><td>9.4 (2.6, 16.3)</td></tr>
</table>
* From text “mean values of postprocedural renal dysfunction were 16.8% and 7.4% for groups with and without pre-existing renal impairment, indicating a strong predilection for increase in renal adverse events. **ARIF comment – doesn’t seem to show that in the table of results.**

Follow - up periods ranged from 0 to 48 months with a >12 month mean follow up reported in 4 studies.</td></tr>
<tr><td>Discussion comments.</td><td>Relatively high late mortality (compared to EUROSTAR data where it was 5.5%) possibly related to the higher age of the patients.
Pre-operative renal function is a predictor of poor patient outcome, found in all patient groups who undergo endovascular repair.
The review authors were concerned regarding the incidence of leaks which they describe as “*disturbingly high*”, however they do say that this incidence rate is within the reported range of leaks in patients who have conventional endovascular repair (4% to 44% Armerding MD et al 2000).
Studies were based on two main research groups, one from Australia, and one from America, which they say, “*indicates that this technology is restricted to expert centres*”. They also comment that by excluding single case studies they “*may have underestimated the rate of post procedural complications*”.</td></tr>
<tr><td>Cost effectiveness results</td><td>Not studied.</td></tr>
<tr><td>Conclusions</td><td>“Our systematic review showed that fenestrated endovascular grafting is a feasible technique to treat complex AAAs. It has a relatively low 30 day mortality compared to conventional open AAA repair or conventional stent graft procedure. However, preoperative renal impairment is a strong indicator of postoperative renal dysfunction. Assessment of renal function following fenestrated endovascular grafting deserves to be refined. The techniques for fenestrated stent grafts are still in their infancy and the stability and patency of fenestrated vessels remains to be proven in long term follow-up”.</td></tr>
<tr><td>Further ARIF comments</td><td>Comparison data is not available, therefore, do not know what the patients risks are for mortality.
Case series contribute to the data. All patients within the studies received a fenestrated stent.
Review looks fine, although as the authors mention in the discussion, limiting studies to 10 patients or more may have underestimated complication rates.</td></tr>
</table>

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Archived ARIF Request

Accident and Emergency Triage General Practitioners

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in September 2001.

The Problem Submitted for ARIF to Advise Upon:

Is there any evidence on the effectiveness of general practitioners (GPs) in accident and emergency (A & E) units and are there any additional benefits compared to if he or she was not present on outcomes such as admission rates?

Question Reformulated

We sought to clarify the exact role of the GP within the A & E units. The scenario was that the GP:

- would operate in a triage system
- would assess patients for their suitability for admission to hospital or diversion to other primary care services

The primary outcomes of interest included:

- reductions in waiting times for patients
- reductions in admissions to hospital

Reviews Identified

- Royal College of Physicians of Edinburgh and The Royal College of Physicians and Surgeons of Glasgow. Scottish Intercollegiate Working Party on acute medical admissions and the future of general practice. Edinburgh: Royal College of Physicians of Edinburgh; 1998
- REAP The rise in emergency admissions project. A report to the West Midlands NHS Executive; 1998
- New Zealand Health Technology Assessment Agency. Acute medical admissions: a critical appraisal of the literature. New Zealand Health Technology Assessment Agency Christchurch. New Zealand, NZHTA; 1998. (NZHTA report 6)
- New Zealand Health Technology Assessment Agency. Emergency Department Attendance: a critical appraisal of the literature New Zealand Health Technology Assessment Agency. Christchurch, New Zealand; 1998 (NZHTA report no.8)

Primary Studies

- Gibney D, Murphy A W, Barton D, Byrne C, Smith M, Bury G, Mullan E, Plunkett P K. Randomized controlled trial of general practitioner versus usual medical care in a suburban accident and emergency department using an informal triage system. Br Jnl Gen Practice 1999;49(438):43-44

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Comments

We identified no systematic reviews that specifically address the issue of the effectiveness of GP triage in A&E units.

Several general reviews were identified on the topic of acute hospital admissions and some of these are listed above. However, little in these reports specifically addresses the topic of GPs in a triage role within an A & E unit, as a strategy to decrease hospital admissions.

Three randomised controlled trials included in the NZHTA (1998) report found that GPs working in A & E departments were less expensive than hospital registrars without any difference in outcome. The savings were achieved via admission of fewer patients and less tests being ordered by GPs. However, a more recent randomised controlled trial (Gibney et al 1999) found that sessional GPs working in an A & E environment prescribed more often and referred more patients to hospital.

In conclusion, we cannot at this stage state with any certainty that the use of GPs in a triage setting within the A & E unit will provide greater benefits with respect to decreasing admissions. Although there is a vast breadth of literature relating to the phenomenon of rising medical admissions, little of it relates to specific A & E unit interventions to reduce hospital admissions and increase diversion of prospective patients to other primary care services.

This topic is prone to require updating as new information becomes available.

Request Carried Out: September 2001

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Archived ARIF Request

Laser Therapy
Acne

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in December 2005.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of laser therapy for acne?

Reviews Identified

None Identified.

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Comments

There are no systematic reviews on this topic. One is required as there are a number of recent randomised controlled trials which have conflicting conclusions.

Request Carried Out: December 2005

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Archived ARIF Request

Laser Therapy
Acne Scarring

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in December 2005.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of laser therapy for acne scarring?

Reviews Identified

- Jordan R, Cummins C, Burls A. Laser resurfacing of the skin for the improvement of facial acne scarring. Birmingham : West Midlands Health Technology Assessment Collaboration, Department of Public Health and Epidemiology, University of Birmingham (WMHTAC); 1998:51
- Jordan RE, Cummins CL, Burls AJE, Seukeran DC. Laser resurfacing for facial acne scars. The Cochrane Database of Systematic Reviews 2000, Issue 3. Art. No.: CD001866. DOI: 10.1002/14651858.CD001866.

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Comments

This is a well conducted review which is unfortunately now out-of-date. The review did suggest that CO2 and Nd:YAG lasers were effective, but the evidence was case-series which are open to bias.

The West Midlands Committee which assessed the first report in 1998 felt there was “Insufficient evidence” to support wide implementation outside rigorous evaluations.

Request Carried Out: December 2005

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Archived ARIF Request

Acoustic Neuroma

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in April 1996.

The Problem Submitted for ARIF to Advise Upon:

What is the 'gold standard' investigation of someone presenting with symptoms suggestive of acoustic neuroma?

Question Reformulated:

What is the most cost-effective combination of:
1. MRI with gandolinium
2. CT scanning
3. Electronystagmography,

the most commonly employed tests to confirm diagnosis of acoustic neuroma?

Reviews Identified

- Bance ML et al. Decision and cost analysis in acoustic neuroma diagnosis. Journal of Otolaryngology 1994; 23:109-120.

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Comments

Judged on the criteria suggested for the validity of decision analyses this report appears to offer moderately sound evidence on the optimum combination of tests to identify patients with acoustic neuroma. The most important issue raised is that the optimum combination depends critically on the utility attached to a false negative result as well and prevalence of the disease - there is no right answer!

Request Carried Out: 1996

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Pegvisomant for Acromegaly

Synopsis

Question:	In 2007, the West Midlands Health Technology Assessment Collaboration (WMHTAC) completed a systematic review that assessed the clinical and cost effectiveness of Pegvisomant (PEG) for use in patients with acromegaly. The conclusion was: *"PEG is highly effective for improving patients IGF-I level. Signs and symptoms of disease improve but evidence is lacking about the long term effects on improved signs and symptoms of disease, quality of life, patient compliance and safety".* ARIF were asked to determine if any new research had been published since the completion of the WMHTAC review and whether this alters the above conclusions.
Reviews Identified:	No reviews supersede the WMHTAC review.
Comments:	The ARIF search identified one new randomised controlled trial (RCT), two controlled clinical trials (CCTs), two uncontrolled trials and identified a publication describing the ACROSTUDY which is an international registry of patients being treated with PEG. No cost studies were found. The two new CCTs have very small sample sizes (n=10) therefore do not add substantially to the evidence base. The RCT suggests that PEG and PEG + long acting octreotide (LAR) are equally effective in improving clinical and biological parameters in patients with acromegaly that has not been adequately controlled by first line treatments such as surgery and/or radiotherapy or second line treatments such as LARs as monotherapy. Just one study in the WMHTAC review had tested this modality (Jorgensen 2005). Using PEG as a monotherapy compared to PEG + LAR may have implications regarding cost. The trial again demonstrates that it is feasible to conduct an RCT in this patient population and that it is possible to measure clinical and patient specific outcomes. This includes the EQ-5D quality of life tool which is commonly utilized in economic modelling. Both the registry data and two uncontrolled trials suggest that over the medium term tumour growth only occurs in a relatively small proportion of patients. These findings do not substantially alter the conclusions of the WMHTAC review. Further good quality research is required, so that the uncertainty about the effectiveness of PEG versus other treatments can be diminished.
Date completed:	April 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Pegvisomant for Acromegaly

Request completed: April 2010.

Question:

In 2007, the West Midlands Health Technology Assessment Collaboration (WMHTAC) completed a systematic review that assessed the clinical and cost effectiveness of Pegvisomant (PEG) for use in patients with acromegaly.[1,2]

The conclusion was:

"PEG is highly effective for improving patients IGF-I level. Signs and symptoms of disease improve but evidence is lacking about the long term effects on improved signs and symptoms of disease, quality of life, patient compliance and safety".

ARIF were asked to determine if any new research had been published since the completion of the WMHTAC review and whether this altered the above conclusions.

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol http://www.arif.bham.ac.uk/strategy.shtml and searches for primary studies were also carried out in CENTRAL, MEDLINE and EMBASE. Text and index terms were used to represent the population and the intervention. Sources were searched from 2007 to March 2010. No language restriction was applied to the searches. The MEDLINE search can be found in Appendix A. The following inclusion criteria were used for study search and selection:

Population	People with acromegaly
Intervention	Pegvisomant (Somavert) – any dose
Comparator	Any or no treatment
Outcomes 1	1. Any clinically relevant. 2. Changes in IGF-1 levels and GH levels. 3. Tumour growth – as one of the key concerns with the use of PEG is that there is a paradoxical increase of growth hormone levels with treatment, which has the potential to increase tumour growth.
Study designs	SRs and HTAs. Primary studies – prioritising randomised control trials (RCTs) or controlled clinical trials (CCTs).

This report does not constitute an update of the WMHTAC review, but took a pragmatic approach to identify new research since the review was undertaken. As only published literature was sought the findings of this report may be subject to publication bias.

Results

The WMHTAC review[1,2] was taken as a proxy for baseline knowledge since none of the systematic reviews identified had undertaken searches after 2007.

Full search results can be found in Appendix B. The search identified one new RCT[3], two CCTs[4,5] and two uncontrolled trials.[6,7] The two new CCTs have very small sample sizes (n=10) therefore do not add substantially to the evidence base and will not be discussed further. Details about all the studies can be found in Appendices C, D, E, F and G. Also identified was a publication describing the ACROSTUDY[8] which is an international registry of patients being treated with PEG. No cost studies were identified.

RCT evidence.

No RCTs were identified that compared PEG with standard care treatments.

The new RCT[3] aimed to evaluate safety and efficacy of PEG as a monotherapy compared to PEG and long acting octreotide (LAR) as a dual therapy. A total of 84 patients enrolled in the trial. These patients were given a LAR for four weeks. At the end of that period patients who had had suboptimal disease control were randomised into the two active arms of the trial (PEG = 27, PEG + LAR = 29). Patients who had had an optimal response were used as controls and continued on the LAR as a monotherapy (n=28).

Adverse events were the primary outcomes assessed, patients were monitored every four weeks and had a MRI at the beginning and end of the trial. Secondary outcomes were drug efficacy, measured by percentage with normalised IGF-I, and signs and symptoms (headache, perspiration, arthralgia, fatigue, soft tissue swelling) and quality of life measured by a disease specific tool ACROQoL and a generic tool EQ-5D. The trial lasted 40 weeks.

There were 25 treatment related adverse events reported amongst the PEG monotherapy patients, 30 in the PEG + LAR group and 15 in the control group. Eight patients had serious adverse events four of which occurred in the PEG group consisting of headache, hepatic enzyme increase, epistaxis (nosebleed) and fat tissue increase. In the PEG + LAR group four patients had hepatic enzyme increase, in two of them a high dose LAR (60mg) was thought to be the reason for this increase. No serious adverse events occurred in the control group.

One of the key concerns about PEG treatment has been the potential for tumour enlargement due to the paradoxical increase in growth hormone with this treatment. There were 67 patients with paired before and after MRI scans of which one patient each in the PEG and PEG + LAR showed an increase greater than 20% in pituitary tumour volume at week 40. The tumour in the PEG patient increased from 2.3cm^3 to 4.3cm^3 whilst the PEG + LARs patient had a smaller increase from 0.6cm^3 to 0.9cm^3.

Results for the secondary outcomes assessed were only reported for PEG and PEG + LARs. Overall there seemed little difference between the two therapy regimens. The only parameter to show a difference was in the mean fasting glucose levels, which compared to baseline were clinically significantly lower in the PEG group (mean = -8mmol/l 95%CI -1.16, -0.53mmol/l). PEG + LARs and LARs only did not show any clinically significant changes. There may however, be a reason for this in that there was a large baseline imbalance between the number of diabetics and patients with glucose intolerance in the PEG group (66%) compared with PEG + LAR (24%) and control (28%). This imbalance may simply be due to the small number of patients enrolled in the trial or be caused by poor randomisation techniques (randomisation and concealment of allocation procedures were not described).

Uncontrolled trials.

The two uncontrolled trials, do offer some new data regarding the likelihood of tumour growth. Both studies found that only a handful of patients had pituitary tumour growth. In Buhk et al[6] at 24 month follow up just three patients out of 45, who had been receiving PEG as a third line therapy, had a tumour volume increase greater than 25%, with all three experiencing this increase in the first year of PEG treatment. The second study by Jimenez et al[7] found that out of 304 patients who had been given PEG just nine patients had had tumour growth within at least an 18 month period.

Registry data.

The final paper[8] analysed data from the ACROSTUDY which is an international registry sponsored by Pfizer, the company producing PEG. Its aim is to gather data on the safety and efficacy of PEG and involves 300 centres in 10 countries. Data collection is web-based. The first patient entered the database in 2004, and at the time of the analysis in February 2009 the registry contained data on 792 patients. The mean time on the register at the time of analysis was 1.66 years, however, 83% of the patients on the register were already receiving PEG prior to registration, therefore the mean duration that patients had been on PEG was 3.31 years. PEG was given as a monotherapy in 67% of patients, dual therapy either PEG + dopamine agonist (DOPA) or PEG + a somatostatin

analogue (SSA) in 6% and 23% respectively and as a triple therapy, PEG + SSA + DOPA in 4% of patients. Around 90% of patients received PEG in one daily dose. The mean weekly dose was 106 mg for patients with a normal IGF-I and 113 mg for patients with a raised IGF-I which is well within recommended dosing and not dissimilar to the mean doses reported in some studies in the WMHTAC report. Mean IGF-I prior to starting PEG was 518+/- 296ng/ml, which normalised at one year to 277+/- 180ng/ml. The rate of IGF-I normalisation did not differ in patients taking dual or triple therapy.

Concerning safety, a total of 56 serious adverse events were reported in 46 patients. Thirteen were thought to be due to PEG. Of these nine were elevated liver enzymes, three were pituitary tumour growth and one a subarachnoid haemorrhage. Paired MRI data were available in 411 patients (the longest duration being 8.9 years). A change in tumour size was reported in 70 patients. Thirty one showed a decrease, 22 an increase and in 11 patients the evidence was “contradictory”.

Conclusions

The new studies identified do not substantially alter the conclusions of the WMHTAC report[1,2]. The WMHTAC report did highlight the concern that PEG treatment may promote tumour growth.

Both the registry data[8] and two uncontrolled trials[6,7] do suggest that over the medium term tumour growth only occurs in a relatively small proportion of patients.

The RCT[3] suggests that PEG and PEG + LAR are equally effective in improving clinical and biological parameters in patients with acromegaly that has not been adequately controlled by first line treatments such as surgery and/or radiotherapy or second line treatments such as LARs as monotherapy. Just one study in the WMHTAC review[1,2] had tested this modality (Jorgensen 2005) but this had been on a very small sample n = 11 patients. There may be the potential for saving on the cost of PEG if given in combination with LAR as the median dose of PEG was 15mg/day at 40 weeks compared with 20mg/day for PEG as a monotherapy. However, this would need to be off set by the cost of LAR. A ‘back of the envelope calculation’, using the same drug values as in the WMHTAC report, shows that saving 5mg of PEG amounts to a saving of approximately £9,000 per patient per annum. The cost of LAR at a median dose of 30mg per 28 days as reported in the RCT, costs around £24, 000 per patient per annum. However, the full economic impact would need to be confirmed using more sophisticated economic modelling techniques.

The trial[3] also demonstrates that it is feasible to conduct an RCT in this patient population and that it is possible to measure clinical and patient specific outcomes such as the generic tool EQ-5D

which is commonly utilized in economic modelling. This may encourage future investigators to undertake good quality research so that the uncertainty about the effectiveness of PEG versus other treatments can be diminished. However, ethical issues may need to be considered.

References

1 Connock M, Adi Y, Bayliss S, Moore D. The clinical and cost effectiveness of pegvisomant for the treatment of acromegaly: a systematic review. Birmingham: University of Birmingham, Department of Public Health and Epidemioloy; 2007. Report No. 64.

2 Moore DJ, Adi Y, Connock MJ, Bayliss S. Clinical effectiveness and cost-effectiveness of pegvisomant for the treatment of acromegaly: a systematic review and economic evaluation. *BMC Endocr Disord* 2009; **9**:20.

3 Trainer PJ, Ezzat S, D'Souza GA, Layton G, Strasburger CJ. A randomized, controlled, multicentre trial comparing pegvisomant alone with combination therapy of pegvisomant and long-acting octreotide in patients with acromegaly. *Clin Endocrinol (Oxf)* 2009; **71**(4):549-557.

4 Neggers SJ, van Aken MO, de Herder WW, Feelders RA, Janssen JA, Badia X, *et al*. Quality of life in acromegalic patients during long-term somatostatin analog treatment with and without pegvisomant. *J Clin Endocrinol Metab* 2008; **93**(10):3853-3859.

5 Zgliczynski W, Zdunowski P. [Pegvisomant--growth hormone receptor antagonist in the treatment of acromegaly]. *Endokrynol Pol* 2007; **58**(5):408-416.

6 Buhk JH, Jung S, Psychogios MN, Goricke S, Hartz S, Schulz-Heise S, *et al*. Tumor volume of growth hormone-secreting pituitary adenomas during treatment with pegvisomant: a prospective multicenter study. *J Clin Endocrinol Metab* 2010; **95**(2):552-558.

7 Jimenez C, Burman P, Abs R, Clemmons DR, Drake WM, Hutson KR, *et al*. Follow-up of pituitary tumor volume in patients with acromegaly treated with pegvisomant in clinical trials. *Eur J Endocrinol* 2008; **159**(5):517-523.

8 Trainer PJ. ACROSTUDY: the first 5 years. *Eur J Endocrinol* 2009; **161 Suppl 1**:S19-S24.

Appendix A – Literature search

The following search strategy was used in MEDLINE to identify secondary and primary studies and was adapted for use in the other information sources:

Database: Ovid MEDLINE(R) 1950 to March Week 5 2010
Search Strategy:

1 pegvisomant.mp. or exp PEGVISOMANT/
2 somavert.mp.
3 b2036.mp.
4 growth hormone receptor antagonist$.mp. or exp growth hormone receptor antagonist/
5 or/1-4
6 acromegaly.mp. or exp ACROMEGALY/
7 5 and 6
8 limit 7 to yr="2007 - 2010"

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Appendix B – Literature search results

Systematic Reviews

Source – MEDLINE (Ovid) 1950 to March Week 5 2010

Roelfsema F, Biermasz NR, Pereira AM, Romijn JA. The role of pegvisomant in the treatment of acromegaly. *Expert Opinion on Biological Therapy*. 2008; 8(5) :691-704

Source - EMBASE (Ovid) 1980 to 2010 Week 13

Moore DJ, Adi Y, Connock MJ, Bayliss S Clinical effectiveness and cost-effectiveness of pegvisomant for the treatment of acromegaly: A systematic review and economic evaluation. *BMC Endocrine Disorders* 2009; 9 : 20pp
http://www.biomedcentral.com/1472-6823/9/20

Source – CRD databases (via TRIP)

Maison P, Tropeano A-I, Macquin-Mavier I, Giustina A and Chanson P. Impact of Somatostatin Analogs on the Heart in Acromegaly: A Metaanalysis *J Clin Endocrinol Metab* 2007 ; 92(5): 1743-1747

Source – Cochrane Library (Wiley) 2010 Issue 1 (HTA)

Connock M, Adi Y, Bayliss S, Moore D The clinical effectiveness and cost-effectiveness of pegvisomant for the treatment of acromegaly: a systematic review (Structured abstract) Birmingham: West Midlands Health Technology Assessment Collaboration; 2007
PG: 1-124
http://www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-32008100042/frame.html

Systematic Review in progress

Source – Cochrane Library (Wiley) 2010 Issue 1 (CDSR)

Balti EV, Akwo EA, Fezeu L, Kengne AP, Sobngwi E, Mbanya JC. Somatostatin analogues, dopamine agonists or growth hormone antagonists for pituitary adenoma-induced acromegaly. Protocol for a review Protocols Issue 1 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD008292 ; 2010 No 1
PB: John Wiley & Sons, Ltd
http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD008292/frame.html

Other reviews

Source – TRIP database

Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, *et al*. Guidelines for Acromegaly Management: An Update. *J Clin Endocrinol Metab* 2009; 94(5):1509-1517.

Cook DM. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly *Endocr Pract* 2004 May-Jun;10(3):213-25.

Primary studies

Source – Cochrane Library (Wiley) 2010 Issue 1 (CENTRAL)

Zgliczyski W, Zdunowski P [Pegvisomant--growth hormone receptor antagonist in the treatment of acromegaly] *Endokrynologia Polska* 2007; 58(5): 408-16 US: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/659/CN-00628659/frame.html

Neggers SJ, van Aken MO, de Herder WW, Feelders RA, Janssen JA, Badia X et al Quality of life in acromegalic patients during long-term somatostatin analog treatment with and without pegvisomant. *The Journal of clinical endocrinology and metabolism* 2008; 93 (10): 3853-9 http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/694/CN-00669694/frame.html

Source – MEDLINE (Ovid) 1950 to March Week 5 2010

Trainer P, Ezzat S, D'Souza GA, Layton G, Strasburger CJ. A randomized, controlled, multicentre trial comparing pegvisomant alone with combination therapy of pegvisomant and long-acting octreotide in patients with acromegaly. *Clinical Endocrinology*. 2009; 71(4):549-57.

Source - EMBASE (Ovid) 1980 to 2010 Week 13

Buhk J.-H, Jung S, Psychogios M.N, Goricke S, Hartz S, Schulz-Heise S et al.Tumor volume of growth hormone-secreting pituitary adenomas during treatment with pegvisomant: A prospective multicenter study. *Journal of Clinical Endocrinology and Metabolism*. 2010 :95(2): 552-558.

Jimenez C, Burman P, Abs R, Clemmons D.R, Drake W.M, Hutson K.R et al. Follow-up of pituitary tumor volume in patients with acromegaly treated with pegvisomant in clinical trials. *European Journal of Endocrinology*. 2008;159(5): 517-523.

Background information

Source – Cochrane Library (Wiley) 2010 Issue 1 (HTA)

National Horizon Scanning Centre Pegvisomant for acromegaly - horizon scanning review (Brief record) Birmingham: National Horizon Scanning Centre (NHSC) ; 2002 http://www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-32003000921/frame.html

Source – HTAi Vortal

Somavert (pegvisomant for injection) August 2008 *Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) -- August 2008* http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/ucm123343.htm

Source – TRIP database

The use of pegvisomant in the management of acromegaly Newcastle: NHS Regional Drug and Therapeutics Centre ; January 2006 http://www.nyrdtc.nhs.uk/docs/eva/PEGVISOMANT_a.pdf

Pegvisomant: CEDAC final recommendation on reconsideration and reasons for recommendation Canadian Agency for Drugs and Technologies in Health Ottawa: CADTH; July 2006 http://www.cadth.ca/media/cdr/complete/cdr_complete_Somavert_%20August2_2006.pdf

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Appendix C – Critical appraisal of:

Trainer PJ. Ezzat S. D'Souza GA. Layton G. Strasburger CJ.
A randomized, controlled, multicentre trial comparing pegvisomant alone with combination therapy of pegvisomant and long-acting octreotide in patients with acromegaly. Clinical Endocrinology. 71(4):549-57, 2009 Oct.

Study details – RCT taken from full publication.

Authors: Trainer PJ
Title: A randomized, controlled, multicentre trial comparing pegvisomant (PEG) alone with combination therapy of pegvisomant and long-acting octreotide (LAR) in patients with acromegaly.
Year of publication: 2009
Aim: To evaluate the safety and efficacy of pegvisomant (PEG) to PEG + long-acting octreotide (LAR).
Population: Acromegaly patients receiving long acting octreotide (LAR) but are suboptimally controlled (as indicated by a serum IGF-I>or=1.3x upper limit of normal of the age related reference range).
Intervention 1: PEG
Intervention 2: PEG + LAR
Dose of PEG = 10mg daily SC injection for 8 weeks, adjustments made in 5mg increments at 8 week intervals up to a max of 30mg or min 5mg daily.
Dose of LAR = remained the same as that which they received at the screening visit. Administered intragluteally at 4 week intervals.
Controls: LAR only (group = responsive to LAR at enrolment).
Outcomes assessed: Primary = adverse events. Assessed at 4 week intervals. MRI was undertaken at the start and finish of the trial.
Secondary = efficacy. Measured by sera IGF-I, signs and symptoms (headache, perspiration, arthralgia, fatigue, soft tissue swelling – evaluated on a scale from 0:best to 8: worst. Total severity of signs and symptoms = sum of the scores across all 5 symptoms. Ring finger also measured.
Study design:
N = 27 = PEG only, 28 PEG + LAR, 28 LAR only.
Inclusion into WMHTAC review? Probably.
Quality assessment
Explicit eligibility criteria: Yes – patients had to have previously undergone surgical and/or radiotherapy, and were required to have received long-acting octreotide for at least 6 months prior to study enrolment. Various exclusion criteria related to comorbidities. Patients who had inadequate control of acromegaly during a pre-trial 4 week screening period were randomised.
Randomisation: methods not described. Control group consisted of patients who had been adequately controlled on LAR prior to study enrolment.
Allocation concealment: methods not described.
Baseline similarity: There appear to be a number of baseline imbalances, the biggest and probably the most significant is the number of patients with diabetes and glucose intolerance. PEG only = 66% (Diabetes 37%, glucose intol 29%), PEG + LAR 24% (diabetes 14%, glucose intol 10%) and control LAR only 28% (diabetes 14%, glucose intol 14%).
Patients blinded: presume not given the mode of administration of both drugs.
Physicians blinded: presume not given the mode of administration of both drugs.
Outcome assessors blinded: Not stated.
Losses: Minimal losses – PEG = 2 patients, PEG + LAR = 2 patients, control = 1 patient.
ITT or >10% dropout: ITT

FROM ABSTRACT.
"PEG and P-LAR were well tolerated and there were no differences in the number of AEs. Patients receiving P-LAR tended to be more likely to have clinically significant increases in hepatic transaminase levels, especially those receiving high-dose LAR. Normalization of IGF-I was similar with both regimens (56% and 62% of patients for PM and P-LAR respectively). The change in IGF-I assay resulted in lower rates of IGF-I normalization than expected. Reductions in fasting glucose levels were greater with PM than with P-LAR (-0.8 mmol/l; 95%CI -1.16, 0.53mmol/l)".

FROM BODY TEXT.
Outcomes assessed:
Primary = adverse events. Assessed at 4 week intervals. MRI was undertaken at the start and finish of the trial.

Treatment related AE – PEG = 25, PEG + LAR = 30, LAR = 15.
Eight patients had serious treatment related AE. In PEG 4 patients had serious treatment related AE which were headache, hepatic enzyme increase, epistaxis (nosebleed) and fat tissue increase. In PEG + LAR 4 patients had hepatic enzyme increase, in 2 of them a high dose of LAR (60mg) was thought to be the reason for this increase. No serious treatment related AE were found in LAR only.

Tumour growth
There were 67 patients with paired MRI of which one patient each in the PEG and PEG + LAR showed an increase of ≥20% increase in pituitary tumour volume at week 40. The PEG patient increased from 2.3cm^3 to 4.3cm^3 whilst the PEG + LARs increased from 0.6cm^3 to 0.9cm^3.

Secondary = efficacy. Measured by sera IGF-I, signs and symptoms (headache, perspiration, arthralgia, fatigue, soft tissue swelling – evaluated on a scale from 0:best to 8: worst. Total severity of signs and symptoms = sum of the scores across all 5 symptoms. Ring finger also measured. Fasting glucose levels.

IGF-I normal concentrations	Week 40 No. Patients	Any time in study No. Patients	
PEG	14/25 (56%)	15/25 (60%)	Difference not significant
PEG + LAR	16/26 (62%)	19/26 (73%)	
LAR	NR	NR	

Ring size	Mean reduction in ring size = for both treatments was approx 2 ring sizes. Change from baseline for both groups combined = -1.9 (SD 3.53) 95% CI -2.90, -0.90. Difference between the 2 groups at 40 weeks = -0.2(95% CI -2.3, 1.8).NS
PEG	
PEG + LAR	
LAR	NR

Signs/symptoms Points score	Baseline score (SD)	Total score improvement (SD)	Difference between PEG and PEG + LAR at week 40
PEG	12.0 (7.49)	3.2 (6.78)	-0.7 (95%CI -4.5, 3.1) (NS)
PEG + LAR	14.9 (8.85)	3.8 (7.92)	
LAR	NR	NR	NR

Quality of Life Measured by ACROQoL	Baseline score. (SD)	Score improvement at 40 weeks. (SD)	Difference between PEG and PEG + LARat week 40
PEG	58.9	3.4 (10.12)	NR
PEG + LAR	45.4	2.7 (10.98)	
LAR	NR	NR	NR
EQ-5D	No difference between PEG and PEG + LAR		

Fasting glucose levels - greater in PEG group, than PEG + LAR = 0.8mmol/l (95%CI -1.16, -0.53 mmol/l)

Misc.
Median dose of PEG at week 40 (for those patients who completed the study) was 20mg/day,rather than the median dose in the PEG + LAR at 15mg/day, which was a significant difference of 5mg/day (95% CI 0, 10 mg/day).

FROM ABSTRACT.
"Conclusions: in patients suboptimally controlled on LAR, PM and P-LAR were equally well tolerated and effective in normalizing IGF-I and overall clinical improvement was observed in both regimens. Thus, PEG monotherapy and adjunctive therapy are equally viable options for the treatment of LAR-resistant acromegaly".

ARIF COMMENTS

Areas of concern

Small patient numbers**:** no sample size calculation reported.
Quality of trial: methods of randomisation not described, given the marked differences in baseline of the 3 groups (in particular the PEG group), there may be a chance that selection bias has affected the trial.
Treatment of patient groups: the trial was too short to allow the PEG group to get to the higher doses of PEG as the dose rise was incremental. Uncertain as to the validity of maintaining the LARs dose at baseline levels, does this reflect clinical practice or is the LARs dose titrated according to patient response?

Reporting of results: no result reported regarding the LARs only group, unclear what relevance this group had to the study, a better control group would have been a LARs group of non responders.

Relevance to Answering the ARIF Request Question

- The paper demonstrates that it is feasible to conduct RCTs in this patient population.
- The paper suggests that PEG versus PEG + LAR are equally effective in improving clinical and biological parameters in patients with acromegaly that has not been controlled by first line treatments such as surgery and/or radiotherapy or second line treatments such as LARs as a monotherapy.
- There may be the potential for cost saving for PEG if it is given in combination with LAR as the median dose of PEG was 15mg/day at 40 weeks compared with 20mg/day for PEG as a monotherapy. However, this would need to be confirmed using economic modelling techniques to take into account the additional cost of LAR and the additional benefits.`
- There are quality problems particularly around how randomisation was undertaken, there may be a degree of selection bias, as the groups were not balanced at baseline and the PEG group had more than twice the number of diabetics compared to the PEG + LARs group or the LARs group. However, this may simply be an artefact of the small sample size. There were 14 patients with diabetes in the sample that were randomised and 11 with glucose tolerance. This means that 45% of the randomised sample had problems with glucose intolerance. In the non randomised control group, who had responded to LAR as a monotherapy, there were just 4 patients who were diabetic and 4 patients with glucose intolerance meaning that 28% of the sample had glucose tolerance problems.

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Appendix D Critical appraisal of:

Neggers SJ, van Aken MO, de Herder WW, Feelders RA, Janssen JA, Badia X *et al* .
Quality of life in acromegalic patients during long-term somatostatin analog treatment with and without pegvisomant. *The Journal of clinical endocrinology and metabolism* 2008; 93(10): 3853-9
http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/694/CN-00669694/frame.html

Study details - controlled clinical trial (CCT) - Data taken from abstract only.
Details taken from abstract only. **Authors:** Neggers SJ **Title:** Quality of life in acromegalic patients during long-term somatostatin anolog treatment with and without pegvisomant **Year of publication:** 2008 **Aim:** To assess whether weekly administration of 40 mg pegvisomant (PEG-V) improves quality of life (QoL) and metabolic parameters in acromegalic patients with normal age-adjusted IGF-I concentrations during long-acting somatostatin analog (SSA) treatment. **Population:** Patients with acromegaly with normal age-adjusted IGF-I concentrations during long-acting somatostatin. **Intervention:** PEG **Controls:** Placebo **Outcomes assessed:** Quality of life – measured using the Acromegaly Quality of Life Questionnaire (AcroQoL), and the Patient-Assessed Acromegaly Symptom Questionnaire (PASQ). **Study design:** Prospective, double blind placebo controlled crossover. **N** = 20 **Inclusion into WMHTAC review?** Unsure in that patients were responsive to OCTR (therefore not within licence indications).
Methods This was a prospective, investigator-initiated, double blind, placebo-controlled, crossover study. Twenty acromegalic subjects received either PEG or placebo for two consecutive treatment periods of 16 weeks, separated by a washout period of 4 weeks. Efficacy was assessed as change between baseline and end of each treatment period. QoL was assessed by the Acromegaly Quality of Life Questionnaire (AcroQoL) and the Patient-Assessed Acromegaly Symptom Questionnaire (PASQ).
Results “The AcroQoL (P = 0.008) and AcroQoL physical (P = 0.002) improved significantly after PEG was added. The addition of PEG also significantly improved the PASQ (P = 0.038) and the single PASQ questions, perspiration (P = 0.024), soft tissue swelling (P = 0.036), and overall health status (P = 0.035). No significant change in Z-score of IGF-I (P = 0.34) was observed during addition of PEG. Transient liver enzyme elevations were observed in five subjects (25%)”. **Conclusion** “Improvement in quality of life was observed without significant change in IGF-I after the addition of 40 mg PEG weekly to monthly SSA therapy in acromegalic patients who had normalized IGF-I on SSA monotherapy. These data question the current recommendations on how to assess disease activity in acromegaly. Moreover, the findings question the validity of the current approach of medical treatment in which PEG is used only when SSA therapy has failed to normalize IGF-I”.
ARIF comment: Small study, but suggests a novel way of using PEG therefore included for information.

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Appendix E Critical appraisal of:

Zgliczyński W, Zdunowski P
Pegvisomant-growth hormone receptor antagonist in the treatment of acromegaly.
Endokrynol Pol. 2007 Sep-Oct;58(5):408-16. [Article in Polish]

Study details - controlled clinical trial (CCT) - Data taken from abstract only.
Details taken from abstract only. **First Author:** Zgliczyński W. **Title:** Pegvisomant-growth hormone receptor antagonist in the treatment of acromegaly. **Year of publication:** 2007 **Population:** Pts with persistent acromegaly post surgery and OCTR treatment. **Intervention:** PEG for 12 weeks, PEG + OCTR for 8 weeks. **Controls:** OCTR only **Outcomes assessed:** clinical symptoms, IGF-1 level, fasting glucose, HbA(1c) **Study design:** controlled clinical trial, controls matched for age, sex disease history and GH and IGF-1 levels. **N** = intervention 10, control presume 10. **Inclusion into WMHTAC review?** small study just on the boundary of the WMHTAC review inclusion criteria i.e. number of patients – probably would have been included in WMHTAC review.
Methods "Material consisted of 10 patients (6M, 4F) aged 24 to 48 with active acromegaly, after neurosurgery, in which OCTR was ineffective in disease control. Patients with glucose metabolism disturbances were assigned to the group receiving PEG. Controls were matched for age, sex, disease history, GH and IGF-I level. Patients received PEG throughout 12 weeks, then combined therapy with PEG and OCTR-LAR was started for 8 weeks and then OCTR-LAR was given alone for the next 8 weeks. Controls were medicated with OCTR-LAR 30mg every 4 weeks during the study. Clinical symptoms and IGF-I level, fasting glucose and HbA(1c) was measured to assess treatment efficacy".
Results "Pegvisomant reduced IGF-1 after first week of therapy from 1270+/-229 to 759+/-223 (40% p<0.04). Prolonged therapy led to further IGF-I . After 12 weeks of treatment IGF-I was significantly lower in comparison to initial as well as to controls (604mg/l vs. 1270 and 1330 respectively p<0.02). Combined therapy with PEG and OCTR-LAR was not superior to PEG alone. During treatment with PEG improvement of glucose metabolism was seen, as well as decrease in insulin doses required. No adverse events were recorded". Conclusions "PEG effectively lowers IGF-I concentration and improves disease control in patients with acromegaly after unsuccessful surgery and with octreotide unresponsiveness. Significantly improves glucose metabolism. PEG is indicated in patients with active acromegaly after standard treatment failure, especially in cases of coexistent diabetes mellitus."
ARIF comment. Very small sample size, not quite sure whether the controls were from the original sample of 10. Adding very little to the evidence base.

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Appendix F Critical appraisal of:

Buhk JH, Jung S, Psychogios MN, Göricke S, Hartz S, Schulz-Heise S, *et al.*
Tumor volume of growth hormone-secreting pituitary adenomas during treatment with pegvisomant: a prospective multicenter study.
J Clin Endocrinol Metab. 2010 Feb;95(2):552-8. Epub 2009 Dec 4.

Study details - uncontrolled study - Data taken from abstract only.
Details taken from abstract only. **Authors:** Buhk J H **Title:** Tumour volume of growth hormone-secreting pituitary adenomas during treatment with pegvisomant: a prospective multicentre study. **Year of publication:** 2010 **Population:** Patients receiving PEG (majority using PEG as a 3rd line therapy. **Intervention:** PEG – 24 month follow up. **Controls:** N/A **Outcomes assessed:** tumour volume **Study design:** survey **N** = 45/61 patients completed 24 month follow up. **Inclusion into WMHTAC review?** Relevant to side effects?
Aim "Clinical and biochemical remission in acromegaly can frequently be achieved with the recombinant GH receptor antagonist pegvisomant, even when other treatments fail. However, increases in tumor volume have been reported. Because previous studies suffer from inhomogenous magnetic resonance imaging (MRI) protocols, this prospective study examined the long-term course of adenoma volume during pegvisomant therapy by standardized MRI".
Methods "Five centers in Germany participated. High-resolution MRI was performed at baseline and 6, 12, and 24 months after enrollment. Patients were outpatients, and pegvisomant is third-line therapy in most of the cases. Main Outcome Measures: The primary end point was tumor volume at 24 month follow-up, measured by a single, double-blinded rater".
Results "Forty-five of 61 patients completed 24 months' follow-up (73.8%). Tumor volume increase greater than25%during the study was observed in three of 61 patients (4.9%), all during the first year of enrollment. All three patients had had octreotide treatment before initiation of pegvisomant; none of them had had radiotherapy. All volumetric findings were comparable with clinical radiological interpretations. ANOVA revealed no significant change in tumor volume after 24 months (n = 45)".
Conclusions "This study shows that pegvisomant therapy infrequently coincides with tumor growth during long-term treatment of acromegaly. Because all significant tumor volume increases occurred during the first year, these changes might correlate to the change of medication and thus be the result of a rebound from somatostatin-induced shrinkage".

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Appendix G Critical appraisal of:

Jimenez C, Burman P, Abs R, Clemmons DR, Drake WM, Hutson KR, *et al.*
Follow-up of *pituitary tumor volume in patients with acromegaly treated with pegvisomant in clinical trials.* *Eur J Endocrinol. 2008 Nov;159(5):517-23. Epub 2008 Aug 15.*

Study details - uncontrolled study - Data taken from abstract only.
Details taken from abstract only. **Authors:** Jimenez C **Title:** Follow up of pituity tumor volumes in patients with acromegaly treated with pegvisomant in clinical trials. **Year of publication:** 2008 **Population:** Patients receiving PEG for at least 18 months who additionally had been monitored for at least 3 years. Patients at some time had been treated with radiation therapy and/or somatostatin **Intervention:** PEG **Controls:** N/A **Outcomes assessed:** Tumour growth **Study design:** Observational study **N** = 304 patients of which 9 are highlighted as they experienced tumour growth. **Inclusion into WMHTAC review?** Relevant to side effects?
Aim "We examined pituitary tumor volumes in patients treated with pegvisomant for 18 months or longer, and in whom the tumors were monitored for at least 3 years. We present details on 9 of 304 patients in clinical trials with pegvisomant who experienced tumor growth within the first year of treatment".
Method "Magnetic resonance images prior to start of pegvisomant and at last follow-up were examined in 43 patients (14% of participating patients). Twenty-nine had received prior radiation therapy (18% of irradiated patients) and all but five received somatostatin analogs between periods of pegvisomant treatment".
Results "At follow-up, the median tumor volume was 0.6 cc (range 0.0-19.7 cc), in comparison with 1.6 cc (0.0-19.7 cc) at baseline (P<0.001). Twenty-five patients, of which 23 received radiation therapy, had tumor volume reduction. Seventeen patients had no significant change. One patient, who had not received radiation therapy, had an increase in tumor volume from 1.61 to 1.93 cc. Of the nine patients with tumor growth, six had progressive growth before initiating pegvisomant. Two patients with stable tumors while on octreotide experienced enlargement after octreotide discontinuation but remained stable on long-term pegvisomant therapy".
Conclusion "The present data indicate that pegvisomant does not promote tumor growth and suggest that the nine observed cases of tumor progression, which occurred within 8 months after commencing pegvisomant, are likely rebound expansions after discontinuation of somatostatin analogs and/or the natural history of aggressively growing pituitary tumors. Continued long-term surveillance of tumor volume, particularly in non-irradiated patients, is recommended".

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Archived ARIF Request

Lanreotide Octreotide Acromegaly

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in September 1999.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of lanreotide and octreotide in the treatment of acromegaly?

Reviews Identified

- MTRAC. Octreotide (Sandostatin & Sandostatin LAR). Keele: Dept of Medicines Management, Keele University, 1998
- MTRAC. Lanreotide LA (Somatuline LA). Keele: Dept of Medicines Management, Keele University, 1998

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Comments

Neither of the reviews identified can be described as a systematic review and, because they are published as summary documents, they contain insufficient information to make any judgement on their methodological quality. However, they do give a good indication as to the likely quantity and quality of the available literature on the two drugs.

The bottom line of the two reports is that a substantial body of literature exists on the effects and effectiveness of Octreotide, which appears to be effective as an option for the second-line treatment of acromegaly. Lanreotide, on the other hand, has been less well-evaluated but early indications are that it may be as effective as Octreotide. Any benefits must be carefully considered against the risks of long-term treatment and the financial costs. Important questions around the effectiveness of these drugs as a primary treatment were not addressed by the MTRAC reports.

This topic is one of several currently being reviewed by the West Midlands DEC Programme.

Request Carried Out: September 1999

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Pegvisomant Acromegaly

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of pegvisomant (Somavert) in the treatment of patients with acromegaly whose disease is not controlled by surgery and subsequent medical therapy?

Acromegaly is caused by hypersecretion of growth hormone due in most cases to a pituitary tumour. Many of the effects of elevated circulating growth hormone are mediated by a concomitant rise in circulating insulin like growth factor 1. Normalisation of GH and IGF1 levels is the aim of treatment and surgical excision of the tumour as first line therapy with adjuvant medical treatment using dopamine agonists or somatostatin analogues to try to normalise any remaining elevation GH/IGF-1

Pegvisomant is a growth hormone receptor antagonist, which blocks GH receptors and thus the GH stimulated hepatic production of IGF-1. It is licensed in the EU for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalise insulin like growth factor-1 concentrations or were not tolerated.

Reviews Identified

- Albareda M, Mestrón A, Webb SM Pharmacological treatment for acromegaly (Protocol for a Cochrane Review). Date of most recent substantive amendment 13 July 2002 In: The Cochrane Library, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Primary Studies Identified

- Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, van der Lely AJ, Dimaraki EV, Stewart PM, Friend KE, Vance ML, Besser GM, Scarlett JA, Thorner MO, Parkinson C, Klibanski A, Powell JS, Barkan AL, Sheppard MC, Malsonado M, Rose DR, Clemmons DR, Johannsson G, Bengtsson BA, Stavrou S, Kleinberg DL, Cook DM, Phillips LS, Bidlingmaier M, Strasburger CJ, Hackett S, Zib K, Bennett WF, Davis RJ Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant.[see comment]. New England Journal of Medicine 2000;342(16):1171-7
- Herman-Bonert VS, Zib K, Scarlett JA, Melmed S Growth hormone receptor antagonist therapy in acromegalic patients resistant to somatostatin analogs. Journal of Clinical Endocrinology & Metabolism 2000 ; 85(8) : 2958-61

PJ, DraVan der Lely AJ, Hutson RK, Trainer PJ, Besser GM, Barkan AL, Katznelson L et al Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist Lancet 2001; 358: 1754-1759

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Comments

There are no completed systematic reviews on pegvisomant in the treatment of acromegaly. A protocol for a review has been lodged with the Cochrane library (Albareda et al) but the authors acknowledge that the review is not likely to be completed in the near future.

A number of primary studies were identified, examples of which are given above and include the pivotal trial by Trainer et al. Methodological and reporting limitations to some extent restrict analysis and generalisability of the current evidence base.

Pegvisomant appears to potentially be a useful treatment for acromegaly uncontrolled by other means. However, caution is required as further long-term primary research is required, as is more in-depth appraisal/analysis of the already available research, as there are a number of key issues, which have yet to be resolved. These include:

- long term efficacy
- effect on quality of life
- rates of compliance with daily injections
- the long term effects of elevated growth hormone levels mediated by pegvisomant treatment on the body and in particular tumour growth
- any additional costs and impacts on other services associated with pegvisomant treatment. For example, monitoring over and above that carried out for other medical interventions in acromegaly for liver enzyme problems and additional MRIs to detect tumour growth.

Request Carried Out: January 2005

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Acupuncture

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The Problem Submitted for ARIF to Advise Upon:

Requestor had been approached with proposals for use of acupuncture in primary care for relief of and wide range of conditions e.g. pain, allergic conditions, nausea in pregnancy, stress, menstrual disorders and polysymptomatic relief for terminal illness. For which of these indications is there evidence of effectiveness?

Reviews Identified

Bandolier offers an excellent resource on alternative medicines, including acupuncture
http://www.jr2.ox.ac.uk/bandolier/booth/booths/altmed.html

Useful Resources:
The Cochrane Complimentary Medicines Field Group
The National Library for Health - Complementary and Alternative Medicine Specialist Library
Specialist website such as Acubriefs

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Comments

Many of the indications of interest appear to have little evidence to support or refute the use of acupuncture.

We are currently undertaking a mapping exercise to identify which common applications of acupuncture have RCT evidence which has been systematically reviewed and any where there is a need for a systematic review (see report: http://www.rep.bham.ac.uk/2006/Mapping_Acupunture.pdf). There is evidence for its effectiveness in treating dental pain, some forms of joint pain and in the control of nausea in pregnancy. An area where there is a need for a systematic review is acupuncture for allergic rhinitis. This review is currently being done as a REP report.

Request Carried Out: May 2005

Update: August 2008 - A report on Acupuncture for Allergic Rhinitis was published in 2007
http://www.rep.bham.ac.uk/2006/Allergic_Rhinitis.pdf

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Statins (High Dose)
Intensive Lipid Lowering Therapy
Acute Coronary Syndrome (ACS)
Unstable Angina

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the clinical and cost-effectiveness of early aggressive lipid lowering therapy using very high dose statins (80mg/day) for patients with acute coronary syndrome, patients with crescendo angina, and patients undergoing revascularisation?

The early and continued use of high dose statins is undertaken with the aim of reducing low-density lipoprotein cholesterol (LDL-C) to levels substantially below current targets in an attempt to further reduce atherosclerotic progression and protect against major cardiovascular events.

Reviews Identified

No systematic reviews were identified.

Randomised Controlled Trials

- Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM, for the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE-IT) 22 Investigators. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. New England Journal of Medicine 2004;350:1495-504
- Colivicchi F, Guido V, Tubaro M, Ammirati F, Montefoschi N, Varveri A, Santini M. Effects of atorvastatin 80mg daily after onset of unstable angina pectoris or non-Q-wave myocardial infarction. The American Journal of Cardiology 2002;90(8):872-4
- Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, Crowe T, Howard G, Cooper CJ, Brodie B, Grins CL, DeMaria AN, for the REVERSAL Investigators. Effect of Intensive Compared With Moderate Lipid-Lowering Therapy on Progression of Coronary Atherosclerosis. JAMA 2004;291(9):1071-80

No trials assessing cost-effectiveness were identified.

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Comments

Of the three well-conducted RCTs identified, one (Nissen et al, 2004) assessed the effectiveness of the early administration of high dose statins (80mg/day) in reducing atherosclerotic progression and two (Colivicchi et al, 2002; Cannon et al, 2004) assessed its effectiveness in reducing mortality, cardiac events and hospital admissions.

In summary, these recently conducted trials indicate intensive LDL-C lowering therapy provides a significantly greater reduction in atherosclerotic progression and affords greater protection against major cardiovascular events than standard regimens. However, alongside these benefits a greater incidence of liver related side effects has been reported.

It should be noted that, as the RCTs listed were not identified as part of a systematic review, the possibility of publication bias cannot be ruled out. A systematic review of the clinical and cost effectiveness of high dose statins for high risk patients would therefore be beneficial.

Request Carried Out: June 2005

Updated: March 2006 - NICE has issued guidance on the use of statins in CVD but not on the very high risk conditions considered here.

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Archived ARIF Request

Recombinant Tissue Plasminogen Activator (rt-PA) Acute Ischaemic Stroke

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The Problem Submitted for ARIF to Advise Upon:

What is known about the effects and effectiveness of tissue plasminogen activator (rt-PA) for acute ischaemic stroke?

Reviews Identified

- Wardlaw JM, del Zoppo G, Yamaguchi T. Thrombolysis for acute ischaemic stroke (Cochrane Review). In: The Cochrane Library, Issue 3, 1999. Oxford: Update Software.

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Comments

The recommended review is a well-conducted systematic review produced by the Cochrane Stroke Group, and its results can probably be trusted. In our view, the main limitation of the review lies not with the methods, but the way the authors draw their conclusions on the basis of the results. They suggest that, overall, rt-PA is an effective treatment because increases in death rates and intra-cranial haemorrhage are offset by reductions in disability in survivors. This position is fundamentally based on a value judgment around the trade-off between death and disability. The authors also suggest that rt-PA may well be more promising than other thrombolytic agents but this conclusion is based on essentially weak evidence.

While this clearly is an important and largely reliable review, we suggest that readers carefully consider its results from a number of different perspectives before drawing conclusions on the overall effectiveness of the treatment.

Request Carried Out: October 1999

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Archived ARIF Request

Media Campaigns
Health Behaviour/Acute Myocardial Infarction

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in January 1999.

The Problem Submitted for ARIF to Advise Upon:

What evidence is there on the effectiveness of media campaigns and other interventions which aim to reduce patient delay factors in pain to needle time in acute myocardial infarction?

Question Reformulated

Because the original question was both broad in terms of the intervention and specific in terms of the outcome it was reformulated to read:

What is the effectiveness of media campaigns in changing health-related behaviour, specifically in the context of reducing patient delay factors in pain to needle time in acute myocardial infarction?

Reviews Identified

- Grilli R, Freemantle N, Minozzi S, Domenighetti G, Finer D. Impact of mass media on health services utilisation (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

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Comments

The review identified was of high external and internal validity. It is a well-conducted systematic review of interrupted time series. The approach taken by the reviewers appears to have been appropriate and gave rise to results which were easily understood and probably reliable. Two included studies that examined the effect of media campaigns on admission delay in acute myocardial infarction yielded positive results although the confidence intervals around these were wide. The authors' overall conclusion that campaigns of this nature "may have an important role in influencing the use of health care interventions" is probably sound.

The main limitations of the review in the context of the question relate to the information it does not provide. This includes: the effectiveness of targeting the intervention towards certain high risk or target groups; the cost-effectiveness of media campaigns; potential adverse effects such as increased inappropriate health service utilisation; and issues around the ethics of promoting health in this way.

Readers should note that a randomised controlled trial on this topic is currently in progress:

Simons-Morton DG, Goff DC, Osganian S et al.

Rapid early action for coronary treatment: rationale, design and baseline characteristics. REACT Research Group.

Academic Emergency Medicine 1998; 5(7): 726-738.

Request Carried Out: January 1999

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Acyclovir
Chicken Pox

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the evidence that treatment of adult chicken pox with acyclovir helps prevent complications and is cost effective?

Reviews Identified

RCTs only

- Wallace MR et al. Treatment of adult varicella with oral acyclovir. A randomized, placebo-controlled trial. Annals of Internal Medicine 1992;117:358-63
- Choo DC et al. Oral acyclovir in the treatment of adult varicella. Annals of Academic Medicine of Singapore 1995;24:316-321
- Andreoni M et al. A double blind, placebo controlled trial of efficacy and safety of oral acyclovir (Zovirax) in the treatment of chickenpox in adults. Rivista European per le Scienze Mediche e Farmacologiche 1992;14:316-21.
- Al Nakib W et al. A randomised controlled study of intravenous acyclovir (Zovirax) against placebo in adults with chickenpox. Journal of Infectious Diseases 1983;6:49-56

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Comments

A number of relevant research articles were identified, none of which was a systematic review. Such a review would be helpful in understanding the importance of the variation between the results of individual trials which will inevitably occur through chance.

Wallace MR et al is suggested as a starting point in examining research in this area as it is a randomized controlled trial of reasonable size which appears to be well conducted.

The rarity of the severest complications of adult chickenpox mitigates against ever achieving an unequivocal answer to the question posed.

Although we have found no formal cost-effectiveness analysis, it is possible to make some judgements about whether the cost of treatment is worth any likely reduction in symptoms. In our opinion it is not.

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Archived ARIF Request

Adefovir Dipivoxil
Lamivudine-resistant Hepatitis B
Hepatitis B

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in November 2003 and Update in March 2006.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of adefovir dipivoxil for the treatment of patients with lamivudine-resistant chronic HBV?

Reviews Identified

No systematic reviews were identified on this topic.

Trials Identified

- Peters M, Hann HW, Martin P, Heathcote E, Buggisch P, Moorat AE, Sullivan M, Kleber K, Ebrahimi R, Xiong S, Brosgart C. Adefovir dipivoxil (ADV) alone and in combination with lamivudine (LAM) suppresses lam-resistant hepatitis B virus (HBV) replication: 16 week interim analysis. Journal of Hepatology 2002; 36(suppl 1): 6.
- Westland C, Gibbs C, Miller M, Sullivan M. Fry J, Brosgart C, Wulfsohn M, Xiong S. Loss of lamivudine resistance mutations after patients switched to adefovir dipivoxil therapy. Journal of Hepatology 2002; 36(suppl 1): 7.
- Yang H, Westland C, Delaney IV, Gibbs C, Miller M, Fry J, Brosgart C, Xiong S. Lack of emerging resistance mutations in 467 HBeAg- and HBeAg+ patients with chronic hepatitis B receiving adefovir dipivoxil for 48 weeks. Journal of Hepatology 2002; 36(suppl 1): 137.

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Comments

There were no systematic reviews on this topic found.
Three reports of randomised controlled trials were identified. However, the only published information found on these was in abstract form. The lack of methodological detail and the potential for misinterpretation by reporting selected outcomes in abstracts make them an unreliable source of evidence.

Adefovir dipivoxil is a new and emerging treatment for patients with chronic hepatitis B. However, there

is very little published evidence regarding the effectiveness of adefovir dipivoxil in the treatment of patients with lamivudine-resistant hepatitis. This topic is currently the subject of several on-going clinical trials of which the results are awaited. Furthermore, it has just been identified by NICE for appraisal, although guidance is unlikely to be published until 2005. Therefore, in advance of NICE guidance, it would be prudent that any lamivudine-resistant hepatitis B patient who receives adefovir dipivoxil does so as part of a robust evaluation of its clinical effectiveness.

As new information is likely to become available on this topic, care should be taken if this advice is accessed more than six months after this request was carried out.

Request Carried Out: November 2003

Updated: March 2006 - NICE has issued guidance on this topic.

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Clinical and cost effectiveness of nicotine replacement therapy for new licensed indications and combination therapy: A summary of best evidence

David Moore, Josie Sandercock, Anne Fry-Smith,
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Department of Public Health and Epidemiology
West Midlands Health Technology Assessment Group

DPHE 2007, Report Number 63

Clinical and cost-effectiveness of nicotine replacement therapy for new licensed indications and combination therapy: A summary of best evidence

ARIF AND WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION REPORT

Report commissioned by: Programme Development Group: Smoking Cessation, Centre for Public Health Excellence, National Institute for Health and Clinical Excellence, UK

Produced by: Aggressive Research Intelligence Facility
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ABOUT ARIF AND THE WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively produce health technology assessments and systematic reviews. The majority of staff are based in the Department of Public Health and Epidemiology at the University of Birmingham. Other collaborators are drawn from a wide field of expertise including economists and mathematical modellers from the Department of Health Economics at the University of Birmingham, pharmacists and methodologists from the Department of Medicines Management at Keele University and clinicians from hospitals and general practices across the West Midlands and wider.

WMHTAC produces systematic reviews, technology assessment reports and economic evaluations for the UK National Health Service's Health Technology Assessment (HTA) programme, the National Institute for Health and Clinical Excellence (NICE). Regional customers include Strategic Health Authorities, Primary Care Trusts and regional specialist units. WMHTAC also undertakes methodological research on evidence synthesis and provides training in systematic reviewing and health technology assessment.

The two core teams within WMHTAC are the Aggressive Research Intelligence Facility (ARIF) and the Birmingham Technology Assessment Group (BTAG)

ARIF provides a rapid on-demand evidence identification and appraisal service primarily to commissioners of health care. Its mission is to advance the use of evidence on the effects of health care and so improve public health. The rapid response is achieved by primarily relying on existing systematic reviews of research, such as those produced by the Cochrane Collaboration, the National Institute for Health and Clinical Excellence (NICE), the NHS Centre for Reviews and Dissemination, and the NHS Health Technology Assessment (HTA) programme. In some instances, longer answers to questions are required in which case mini rapid reviews of existing systematic reviews and key primary studies are compiled, typically taking 1-2 months to complete.

Occasionally a full systematic review is required and then topics are referred to BTAG who coordinate the production of systematic reviews for several customers under a number of contracts. ARIF is intrinsically involved in the production of these systematic reviews.

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Warning

The information in this report is primarily designed to give approved readers a starting point to consider research evidence in a particular area. Readers should not use the comments made in isolation and should have read the literature suggested. This report stems from a specific request for information; as such utilisation of the report outside of this context should not be undertaken. Readers should also be aware that more appropriate reviews or information might have become available since this report was compiled.

EXECUTIVE SUMMARY

BACKGROUND

In 2005 the Healthcare Regulatory Authority (MHRA) undertook a review of the indications for nicotine replacement therapy (NRT). The MHRA reviewed licensing arrangements for NRT with regard to the wider access to NRT products across the following groups; adolescents, pregnant women, breastfeeding women, cardiovascular disease, and the use of combination NRT. The National Institute for Health and Clinical Excellence (NICE), as part of a wider programme of work on smoking and the NHS in England and Wales, commissioned this report to identify the best evidence on the clinical and cost-effectiveness of NRT for each of the licences.

METHODS

Searches were conducted in key databases such as MEDLINE, EMBASE and the Cochrane Library for evidence relating to the clinical and cost-effectiveness for each of the aims of this report. The main questions addressed in this report were:

- What evidence was cited by the MHRA when reporting the licensing of the specific use of NRT?
- What additional evidence is there of a similar or higher methodological quality than that cited by the MHRA?
- What ongoing research is there?
- What economic evidence is there?
- What are the economic considerations for the specific use of NRT?

RESULTS

Adolescents

Two studies were identified in the MHRA documentation which concluded that there was evidence of efficacy and no indication that NRT if used in this population would raise specific safety issues. A Cochrane review (including one extra study) and two further studies were identified for the current report. These studies do raise some additional questions about whether there is a balance of evidence in favour of NRT being effective to the same degree in adolescents as it is in adults. These studies do not however raise any new safety concerns.

Pregnant Women

The MHRA considered evidence from several studies, of which two placebo-controlled RCTs were identified that investigated NRT patch use in pregnant women. The findings indicated no benefit of NRT with counselling over counselling alone. Although there are a number of short-term utilisation (hours, days) studies of nicotine patch or gum on biomarkers in mother and child and a small pilot RCT, questions regarding the efficacy and safety of NRT in pregnancy still exist. An ongoing UK based RCT may address some of these uncertainties.

Breastfeeding

The MHRA did not identify any studies on the effectiveness and safety of NRT in breastfeeding. One small 'before and after' study was identified for this report. In the absence of more evidence to address the issues surrounding infant safety and given the benefits to mother and baby of not smoking, the recommendation of the MHRA on minimising nicotine dose to the infant via careful scheduling of NRT usage does seem a sensible approach if NRT is used by these women.

Cardiovascular Disease

The primary concern is safety in this group. MHRA recommendation is based on a large population-based study considering the risk of acute MI, stroke and death associated with the use of NRT. We identified one systematic review based on a series of reviews by the Cochrane Tobacco Addiction Review Group. Overall the results of these trials confirm that although there may be some cardiovascular risk associated with NRT this is substantially lower than the risk of continuing to smoke.

Combination NRT + NRT

The MHRA reviewed the evidence on the combination use of NRT, as product information warned against the concurrent use of more than one product. The review recommended that these warnings against combined use be removed based on the findings of five RCTs and a systematic review. We identified another good quality RCT on the use of patch with nasal spray NRT. The results of this trial are comparable to the other trials combining patch and gum or inhaler considered by the MHRA.

Combination NRT + Bupropion

The combination of NRT with bupropion was not covered in the MHRA report. NICE guidance was issued in 2002 and recommends the use of bupropion in smokers over the age of 18. The NICE guidance states there is currently insufficient evidence to recommend a combination therapy of NRT with bupropion. This was based on the evidence of one trial. We identified three new trials, two of which agree with the NICE guidance. The third trial does suggest an advantage in early term twelve week quit rate with the use of combination bupropion and inhaler delivered NRT.

Economic analysis

It was not possible to undertake any *de novo* modelling within the resources available for this report. Searches for existing models did not identify any models for adolescents, pregnancy, breastfeeding, cardiovascular disease or combination NRT. Issues surrounding the cost-effectiveness of NRT for these conditions are discussed, as is a cost-effectiveness model of the combination NRT + bupropion which was identified.

CONCLUSION

The current evidence supports the majority of the conclusions of the MHRA report. There are issues that cannot be adequately addressed with the current evidence base, such as the safety and use of NRT during pregnancy and breastfeeding, as such there is a need for more robust primary research and regular review of the evidence base of the clinical and cost-effectiveness of NRT use.

CONTENTS

TABLES

APPENDCIES

AIMS OF THE REVIEW

- To identify the best evidence on the clinical and cost-effectiveness of NRT for smoking cessation in:
    - Adolescents
    - Breast Feeding
    - Pregnancy
    - Cardiovascular disease

- To identify the best evidence on the clinical and cost-effectiveness of:
    - Combined NRTs (i.e. NRT+NRT)
    - Combined NRT/bupropion therapy

  for smoking cessation.

1. BACKGROUND

In 2005 an Expert Working Group of the Committee for Safety of Medicines/Commission on Human Medicines of the Medicines and Healthcare Regulatory Authority (MHRA) undertook a review of the indications for nicotine replacement therapy.[1] The result of this review was a change to the licensing arrangements for NRT to provide wider access to, and more consistency across, NRT products. The key changes to the licensing were:

1. All forms of NRT can be used in smokers aged 12-17 years
2. NRT can be used by pregnant smokers
3. NRT can be used by breast feeding smokers
4. All forms of NRT can be used by patients with cardiovascular disease
5. More than one form of NRT can be used concurrently
6. NRT can be used in those smokers who are unable to quit abruptly with NRT but want to cut down smoking frequency as a prelude to quitting (e.g. Cut Down to Quit)

The National Institute for Health and Clinical Excellence (NICE), as part of a wider programme of work on smoking and the NHS in England and Wales, commissioned this report to identify the best evidence on the clinical and cost-effectiveness of NRT of each of the licence changes 1-5 above. It also commissioned a similar assessment on the evidence of the combined use of NRT and bupropion (Zyban®; GSK).

The use of NRT for reducing smoking frequency as a prelude to quitting (point 6 above) is the subject of full health technology assessment being conducted for NICE by the National Coordinating Centre for Health Technology Assessment and the West Midlands Health Technology Assessment Collaboration. As such this indication does not constitute part of this report.

2. METHODS

2.1 Searches

Specific searches of electronic bibliographic databases were undertaken to identify the evidence relating to the clinical and cost-effectiveness for each of the aims of this report.

For each aim searches were conducted in

- The Cochrane Library (2006 Issue 3)
- MEDLINE (Ovid - 1966 to August Week 2 2006)
- EMBASE (Ovid - 1980 to 2006 Week 32)

Generic searches were also conducted for cost-effectiveness information to cover all aims in:

- OHE HEED (August 2006)
- MEDLINE (see above)

Searches for ongoing studies were conducted in the National Research Register.

Where possible search strategies employed both MeSH and text terms appropriate to the specific aim and where appropriate terms to limit searches to the most robust study designs (e.g. systematic reviews and controlled trials) were utilised. Although English language terms were utilised, no language restrictions were applied to searches.

Full search strategies are detailed in 0. All searches were carried out by an information specialist.

All search results were entered in to an aim-specific reference management database (Reference Manager, version 11, ISI); a process which automatically removed most duplicate entries. The databases are available on request.

2.2 Identification of relevant studies

Each database was scanned by a research analyst for relevant studies. The algorithm for this process was based on the following:

- Was the study on NRT?
- Was the study on the relevant population/combination?
- For clinical effectiveness –
    - Was the study a systematic review?
    - Was the study an RCT (if a systematic review was identified only more recent RCTs were sought)?
    - If no RCTs were identified what was the best study design available (in order: controlled trials, cohort studies, before and after studies/case series)?
- For cost-effectiveness –
    - Was the study an economic evaluation/economic model?

All decisions were made by a single research analyst.

Hard copies of all relevant articles were obtained. Part translations of articles not in English were undertaken to aid determination of the relevancy.

Articles and studies which were relevant to a specific aim but not considered to be the best study design available were utilised where necessary to inform background and discussion sections of this report.

2.3 Critical appraisal

The methodological strengths and weaknesses of studies identified through the above process were identified using established quality assessment processes.[2]

For clinical effectiveness this was undertaken by a research analyst. For cost-effectiveness this was undertaken by a health economist.

2.4 Analysis/Reporting

For clinical effectiveness evidence, the findings under each aim are reported using the following framework:

- What evidence was cited by the MHRA when reporting the licensing of the specific use of NRT?[1]

- What additional evidence is there of a similar or higher methodological quality than that cited by the MHRA?
- What ongoing research is there?

Where the MHRA had not addressed the specific use of NRT the best available evidence was reported.

Tables detailing characteristics, methodological quality and results of the studies were produced and commented upon.

For economic evidence:

- What economic evidence is there?
- What are the economic considerations for the specific use of NRT?

3. RESULTS

3.1 Clinical Effectiveness

3.1.1 Adolescents

Many adult smokers start their habit in adolescence. The most recent figures for England suggest that 1% of 11 year olds smoke regularly, a figure which rises to 23% of 15 year olds.[3] These levels appear to be similar in other developed countries. Although most of the focus in tobacco control in younger people has been on the prevention of smoking, there are a number of reasons why smoking cessation should also be pursued. Firstly many adolescents who have started smoking want to give up and have made attempts to do so. Second there may be a relationship between the age at which smoking habits are established and ability to give up. In either event, assisting smoking cessation in adolescence would seem an additional goal. The important outstanding question is whether the effectiveness of successful approaches in adults, such as nicotine replacement therapy can be generalised to younger people.

3.1.1.1 MHRA Clinical Effectiveness Evidence

The MHRA identified just two studies providing evidence on effectiveness of NRT in adolescence (see Table 1, Table 2 and Table 3).

The first study by Smith et al[4] was not an RCT and followed 22 girls given NRT for a period of 6 months. Although the claimed smoking rates for the participants fell, the numbers confirmed as not smoking never exceeded 5, and at 3 and 6 months was just 1 non-smoker (4.5% 95% CI 0.1 to 22.8%).

Moolchan et al[5] was a double-blind RCT which compared three arms: NRT patch + placebo gum (N=34) vs NRT gum + placebo patch (N=46) vs placebo patch and placebo gum (N=40). The treatment phase was 12 weeks and all groups had cognitive behavioural therapy. Unfortunately information about method of randomisation and allocation concealment was unclear. However apart from this it was a well conducted study with results analysed on an intention to treat basis. The participants, mostly white and female, had an average age of 15 years, had started smoking at 11 years and had smoked daily

for a mean of 2.65 years, with current smoking levels of 19 cigarettes per day. The proportions abstinent at 3 months after completion of treatment were 18%, 7% and 3% in the patch, gum and placebo groups respectively. The odds ratio (OR) for cessation for NRT patch relative to placebo was 8.4 (95% CI 0.95 to 73.3); in other words the likelihood of quitting was over 8 times more in the NRT group than the placebo group although the certainty about the true value was low as indicated by the wide confidence intervals which included 1.0, the value indicating no difference; for gum the OR was 2.7, again with wide confidence intervals including 1.0, no difference (95% CI 0.27 to 27.3).

There were more adverse events in the NRT groups. However these differences were only statistically significant for pruritus (itching), erythema (reddening of the skin) and shoulder or arm pain for the NRT patch. For gum only the differences in pruritus (itching), sore throat and hiccups could not be accounted for by chance alone. The paper claims the adverse events were similar to those experienced in adults.

Overall the findings from these two studies do indeed provide support for the MHRA's stated view that *"there was evidence of efficacy and no indication that NRT used in this population would raise specific safety issues …."* It must be appreciated that the study by Smith et al is a minor contributor, so essentially the specific evidence base relied on by the MHRA is limited to one relatively small RCT.

Table 1 Adolescents: MHRA Identified Trials: Trial Characteristics

Trial ID	Intervention and control	N *(location; centres)*	Patients	Outcomes	Comments
Smith et al 1996[4] Case-series; not RCT			Not appraised in detail		
Moolchan et al 2005[5] RCT – double blind	Three arms: 1. Nicotine patches * 21 or 14 mg for 12 weeks + placebo gum N=34 2. Nicotine gum * 2 or 4 mg as required for 12 weeks + placebo patch N=46 3. Placebo patch + placebo gum for 12 weeks N=40 All participants received a 45 minute cognitive behavioural therapy session by a trained social worker at the end of each of the 11 treatment sessions over the 12 week treatment period. * GlaxoSmithKline	N=120	120 participants drawn from 1347 adolescents responding to advertisements 329 of these were eligible at a phone screen Only 159 consented to the study 39 of these were ineligible, predominantly because of psychiatric problems (n=22) Characteristics of included patients (approximate averages of the values for each of the three treatment arms) Mean age c 15 years % female c 70% % white c 72% Mean FTND score c 7.0 Mean CPD 19 Mean age started smoking c 11 years Mean years smoked daily c 2.65 75% of included participants had at least 1 current psychiatric diagnosis particularly oppositional defiant and conduct disorder All participants wanted to quit and were able to discuss this with their parent/guardian	Primary: smoke exposure (saliva thiocyanate concentrations) Other: ■ Smoking cessation (point prevalence and prolonged abstinence) ■ Self reported smoking rates (CPD) ■ Adverse events (open questions and questionnaires of specific events)	Smoking cessation point prevalence based on self report that not smoking during 7 days prior to visit + expired air CO 0f < 6ppm Smoking cessation prolonged abstinence based on point prevalence abstinence based throughout the trial

Table 2 Adolescents: MHRA Identified Trials: Trial Quality

Trial ID	Randomisation and concealment	Blinding	Duration, missing data and loss to follow-up	ITT analysis	Comments
Smith et al 1996[4] Case-series; not RCT			Not appraised in detail		
Moolchan et al 2005[5] RCT – double blind	Unclear "…. Adolescents were randomized to 1 of 3 groups according to an algorithm held by the National Institute on Drug Abuse pharmacy, with true replacement of trail-noncompleters"	Stated to be double-blind No further details	Study completion rates: 1. NRT patch 18/34, 53% 2. NRT gum 19/46, 41% 3. Control 16/40, 40% All losses or non-attendance considered to indicate that participant had smoked	ITT principle adopted All losses or non-attendance considered to indicate that participant had smoked of birth weight.	

Table 3 Adolescents: MHRA Identified Trials: Trial Results (main)

Trial ID	Smoking cessation	Safety	Other	Comments
Smith et al 1996[4] Case-series; not RCT		Not appraised in detail		
Moolchan et al 2005[5] RCT – double blind	*Prolonged abstinence at 3 months* post end of treatment: 1. Patch 6/34, 17.7% 2. Gum 3/46, 6.5% 3. Control 1/40, 2.5% Odds ratios: ■ Patch vs control OR 8.36 (95% CI 0.95 to 73.3) ■ Gum vs control OR 2.72 (95% CI 0.27 to 27.3)	*Adverse events*: 19 events reported. Patch – 3 events statistically significantly greater for patch relative to control: pruritus; erythema; shoulder or arm pain Gum – 3 events statistically significantly greater for gum relative to control: pruritus; sore throat; hiccups	*Compliance:* high Patch 78.4% Gum 82.8% Control 80.9% Changes in CPD, CO levels and saliva thiocyanate values between baseline and end of treatment highly affected by losses to follow-up; <50% of randomised patients included.	.

3.1.2 Other Evidence

In general our further searches confirmed the paucity of research evidence.

There was a highly up to date Cochrane review, “Tobacco cessation interventions for young people” published in the Cochrane Library 2006, Issue 4 (i.e. after the end of the search and identified by chance).[6] This addressed not just the effectiveness of NRT but other interventions too, such as the effectiveness of psychosocial interventions. The review was systematic in approach.

There were two included RCTs in the Cochrane review targeting pharmacological interventions: Moolchan et al[5] (see above) and Killen et al[7]. However, the latter apparent additional study relative to those identified by the MHRA, although an RCT, in fact addressed the effectiveness of bupropion SR, the comparison being between NRT patch + bupropion and NRT patch + placebo. This study is thus not considered further. Concerning the results of the study by Moolchan et al, the Cochrane review’s interpretation is possibly more cautious than the MHRA, its conclusion with respect to NRT being, “Medications such as nicotine replacement and buproprion have not been sufficiently tested in adolescents”.

Our own wider searches identified two other RCTs potentially relevant to the effectiveness of NRT (see Table 4, Table 5 and Table 6).

- Hanson et al.[8] This was a double-blind placebo controlled RCT of NRT patch in 100 adolescents with an average age of 17 years and an average cigarette consumption of 16 per day. The treatment phase was 10 weeks and all groups had cognitive behavioural therapy. There were no details about how randomisation was achieved, although there was good balance in the baseline characteristics between the two trial groups. The study was excluded from the Cochrane review on the grounds that the quit rate was only measured up to 10 weeks, at the end of the treatment period. However, given that early reporting of results is likely to bias in favour of NRT, it may be useful to note that Hanson found virtually no differences in quit rates between NRT and placebo. The only significant difference in any of the 15 groups of adverse events considered was an excess of headaches in the placebo group [56% in NRT vs 76% in placebo].

- Stotts et al.[9] This was a further RCT of NRT + behavioural intervention (N=98) vs placebo + behavioural intervention (N=100) vs usual care alone (N=105) for spit tobacco addiction. No mention of this was study was made in the Cochrane review, which may be because spit tobacco use was not considered to meet the inclusion criteria. However, the study did seem sufficiently relevant to be worthy of mention in the context of this report. The RCT was relatively large with 303 randomised between each of the three trial groups. Randomisation was clearly described and allocation appeared to be concealed. Although there were high losses to follow-up, an intention-to-treat analysis strategy was used assuming that those lost to follow-up had relapsed. The study showed that although the behavioural intervention appeared to improve spit tobacco quit rates at 1 year relative to usual care, the addition of NRT provided no further benefit. There were no differences between all tobacco quit rates. The study claimed no serious adverse events among patch users.

We have been alerted to a third RCT additional to the MHRA studies, published since completion of the search but prior to finalisation of the report.[10] As indicated in Table 4, Table 5 and Table 6, this was a well conducted RCT comparing active NRT patch with placebo patch, both arms receiving behavioural counselling. Consistent with the other additional studies was both the very low completion rates of treatment and the absence of difference in quit rates between the trial arms.

In conclusion, concerning other evidence not available to the MHRA report, it does appear that there is additional RCT evidence of relevance. These three studies taken together do raise some additional questions about whether there is truly a balance of evidence in favour of NRT being effective to the same degree in adolescents as it is in adults. These studies do not however raise any new safety concerns.

Table 4 Adolescents: Additional Identified Trials: Trial Characteristics

Trial ID	Intervention and control	N *(location; centres)*	Patients	Outcomes	Comments
Hanson et al 2003[8] RCT – double-blind	Two arms: 1. Nicotine patches * For ≥15 CPD 21mg (6w) then 14mg (2w) then 7mg (2w) For 10-14 CPD 14mg (6w) then 7mg (4w) N=50 2. Placebo patches * N=50 All participants received 10-15 minute cognitive behavioural therapy at the end of each of the weekly treatment sessions over the 10 week treatment period. Also received contingency management procedure (financial incentives for achieving expired air CO readings < 8 ppm) – probably to each trial arm * SmithKlineBeecham	N=100	Eligibility criteria: 1. Smoked 10 CPD for at least 6 months 2. Did not use any other tobacco products more than once per week 3. Were motivated to quit smoking (≥7 on 10 point scale) 4. Not currently using NRT 223 of 375 who phoned clinic met eligibility criteria Characteristics of included adolescents: Mean age 17 years % female 67% % white 87% Mean CPD 16 Mean age started smoking 12 years	Primary outcomes: nicotine withdrawal & salivary cotinine levels Other: ■ Smoking cessation*; 7 day point prevalence ■ Smoking cessation*; 30 day point prevalence ■ Adverse events (15 groups) *Cessation defined as no reported cigarettes during period AND expired air CO ≤ 5ppm	
Stotts et al 2003[9] RCT	Three arms: 1. Nicotine patches (6 weeks) + behavioural intervention classes (6 * 50 minutes) N=98 2. Placebo patches (6 weeks) + behavioural intervention (BI) classes (6 * 50 minutes) N=100 3. Usual care. 5-10 minute counselling followed by a phone call 2 weeks later N=105	N=303	Eligibility criteria: 1. Males aged 14-19 2. Reported regular use of spit tobacco and for the previous year 3. Wanted to quit Of those randomised only the following numbers received intervention: 1. NRT patches + BI, 57 of 98 2. Placebo patches + BI, 54 of 100 3. Usual care, 55 of 105 Characteristics of included adolescents (approximate average across three trial arms): Mean age 17 years % female 0% % white 93% c 73% smoked cigarettes as well as using spit tobacco	Primary outcomes: smoking cessation*; 30 day point prevalence at 1 year *Cessation defined as no reported cigarettes during period AND no cotinine in their saliva samples	

Trial ID	Intervention and control	N *(location; centres)*	Patients	Outcomes	Comments
Roddy et al 2006[10] RCT – double-blind	Two arms: 1. Nicotine patches * (6 weeks) + behavioural counselling (6 * 15 minutes) N=49 2. Placebo patches * (6 weeks) + behavioural counselling (6 * 15 minutes) N=49 Patch schedule: 15mg (2 weeks) then 10mg (2 weeks) then 5 mg (2 weeks) * Specially made by Stowic Resources Ltd, Oxford	N=98	Eligibility criteria: 1. Aged 14-20 and able to consent 2. Aged 12-14 and parental consent obtained 3. Regular smoker 4. Carbon monoxide validation > 5ppm 5. No medical contraindications 145 volunteered for screening (trials nested within a survey of 264 young people) Characteristics of included adolescents (approximate average across three trial arms): Mean age 15 years % female 60%	Primary outcomes: carbon monoxide validated quit rates at four and 13 weeks Other outcomes: adverse events and completion rates	

Table 5 Adolescents: Additional Identified Trials: Trial Quality

Trial ID	Randomisation and concealment	Blinding	Duration, missing data and loss to follow-up	ITT analysis	Comments
Hanson et al 2003[8] RCT – double-blind	Unclear "At the prequit visit participants were randomly assigned in a double-blind manner to receive either the active nicotine patch or the control"	Stated to be double-blind Active and placebo patches stated to be identical in appearance	NRT patch: 25/50, 50% completed treatment Placebo patch: 28/50, 56% completed treatment	ITT model used where drop-outs were considered to be smokers	
Stotts et al 2003[9] RCT	Randomisation described in detail Sequence was random Allocation was concealed	Allocation between active and placebo probably blind Allocation between patch arms and usual care unlikely to be blind	NRT patch + BI: 33/98, 34% completed treatment Placebo patch + BI: 40/10, 40% completed treatment Usual care: 25/105 completed "treatment"	ITT model used where drop-outs were considered to be smokers	
Roddy et al 2006[10] RCT – double-blind	"… and were randomised using computer generated randomisation codes in batches of 10 to either active or placebo nicotine patches." Sequence random; however allocation concealment unclear	Although not stated to be double-blind, probably was Special effort to ensure active and placebo patches were identical "The researchers delivering NRT and counselling were blind to the allocation of subjects"	Completed 6 week treatment: 1. NRT patch + BC 3/49, 6% 2. Placebo patch + BC 5/49,10% BC = behavioural counselling	ITT analysis used; losses to follow-up assumed to be non responders	

Table 6 Adolescents: Additional Identified Trials: Trial Results (main)

Trial ID	Smoking cessation	Safety	Other	Comments
Hanson et al 2003[8] RCT – double-blind	30 day point prevalence at 10 weeks (end of treatment) NRT patch: 10/50, 20% Placebo patch: 9/50, 18% P for difference: 1.0	One statistically significant difference out of 15 groups. 34/45, 76% experienced headaches in placebo group and 27/48, 56% in NRT group (p=0.05)		
Stotts et al 2003[9] RCT	All tobacco, 30 day point prevalence at 1 year NRT patch + BI: 6/98, 6% Placebo patch + BI: 13/100, 13% Usual care: 8/105, 8% Spit tobacco, 30 day point prevalence at 1 year NRT patch + BI: 17/98, 17% Placebo patch + BI: 25/100, 25% Usual care: 12/105, 11%	Brief comments about absence of severe adverse events, but not quantified		
Roddy et al 2006[10] RCT – double-blind	Carbon monoxide validated quit rates (point prevalence) at 13 weeks (7 weeks post treatment) NRT patch + BC 0 Placebo patch + BC 0 Carbon monoxide validated quit rates (point prevalence) at 4 weeks NRT patch + BC 5/49, 10% Placebo patch + BC 4/49, 8%	Adverse events (no in active trial arm vs no in placebo): ■ Itching 16 vs 7 ■ Rash 6 vs 3 ■ Pain or tingling at patch site 6 vs 4 ■ Dizziness/nausea/headache 2 vs 3 No tests of statistical significance provided		

3.1.3 Pregnant Women

Smoking in pregnancy can cause many adverse outcomes including miscarriage, premature birth, still birth and low-weight babies. There is also the possibility of post-natal outcomes such as elevated risk of sudden infant death and neonatal mortality.

Whilst being pregnant acts as motivation for one third of smokers to quit, it is estimated that over a quarter of pregnant women in the UK still smoke.[11] Many who do quit smoking during pregnancy return to smoking after giving birth.

In pregnancy nicotine is metabolised more rapidly with clearance rates of nicotine and cotinine from plasma being greatly increased.[12] This could lead to those who continue to smoke elevating consumption to compensate and thus potentially increasing any harm to the foetus.[13]

Reducing cigarette consumption during pregnancy is a key public health aim as indicated in the Government White Paper on Tobacco.[14]

3.1.3.1 MHRA Clinical Effectiveness Evidence

The MHRA considered evidence from several studies.

Two were randomised controlled trials; Wisborg et al (2000)[15] and Kapur et al(2001).[16] A third trial, Hegaard et al (2003),[17] cannot provide evidence on the clinical effectiveness of NRT in pregnancy as the design of the study was a comparison of a multimodal intervention for smoking cessation with usual care and not an NRT regimen compared to usual care/other care. Furthermore, several elements of the methodology of the study do not address confounding/bias by motivation to quit.

Other studies referred to by the MHRA were on the metabolism of nicotine and cotinine during pregnancy and not about the clinical effectiveness of NRT in pregnancy[12] or were narrative reviews and editorials.[13,18]

The characteristics, methodological quality and results of the two randomised controlled trials can be found in Table 7, Table 8 and Table 9 respectively. Both studies randomised pregnant women to receive either NRT patch or placebo patch.

One of the trials, Kapur et al,[16] had a small sample size and was of short duration of follow-up and the women who took part in this study tended to be heavy smokers. Compliance was poor and enrolment was terminated early due to the apparent case of foetal distress in a woman randomised to receive placebo (the distress subsided on recommencement of smoking). Whilst a well conducted study, due to the factors above it cannot contribute much to our knowledge of NRT in pregnancy.

The other RCT, Wisborg et al,[15] enrolled 250 women less than 22 weeks pregnant, who smoked at least 10 cigarettes per day to NRT patch (15mg [16hr/day] for 8 weeks then 10mg for 3 weeks) or placebo patch. Both groups received counselling on 4 occasions (baseline, 8 weeks, 11 weeks and 4 weeks prior to delivery). Non-attendees at follow-up visits increased with study duration but were contacted by telephone for outcome data (Table 7). Methodological quality of the study appears to be relatively good and analysis for the most part was intention to treat with women who were lost to follow-up categorised as being smokers rather than abstainers (Table 8). The findings of the study were that there were no significant differences in point prevalence abstinence between NRT and placebo at any time points in the study (Table 9). Four weeks before the due date 28% of the NRT women and 25% of the placebo receiving women were abstinent (non-smoking for the 7 days before assessment) (p=0.52). 21% of the NRT group and 19% of the placebo group had been continuously abstinent from the start of the study to this time point. One year after delivery continuous abstinence had reduced to 15% in the NRT group and 14% in the placebo group. Compliance was poor with less than 1 in 5 women using all patches (less than 1 in 10 for most types of patch), with compliance being lower in the placebo group. Outcomes relating to the foetus were limited to assessment of birth weight (women who had spontaneous abortions and twins were excluded from this analysis; there were no differences in the rates of these between treatment and placebo). There were statistically significant trends to lower mean birth weight and greater number of pre-term deliveries in the placebo group compared to the NRT group. There were no statistically significant differences in proportion of babies born weighing under 2500g and rate of pre-term deliveries between NRT and placebo treatment. Whilst adverse events are given for the study (skin irritation, headache, palpitations), these are not reported by treatment group.

Therefore the findings of the RCT indicate no statistically significant benefit of NRT plus counselling over placebo plus counselling.

Table 7 Pregnancy: MHRA Identified Trials: Trial Characteristics

Trial ID	Intervention and control	N *(location; centres)*	Patients	Outcomes	Comments
Wisborg et al 2000[15] RCT – double blind	Nicotine Patches*: 15mg (16hr/d) for 8 wks; 10mg (16hr/d) for 3 weeks N= 124 Placebo patches*: no details N=126 All women appeared to get smoking cessation counselling by a midwife on four independent occasions during pregnancy, and were supplied written material on smoking in pregnancy. First session was a baseline, one at 8 weeks, one at 11 weeks and the final session 4 weeks prior to delivery. * Pharmacia & UpJohn	611 invited on to the study. 250 actually enrolled/randomised 1 centre (Denmark)	Pregnant woman due to deliver at a single centre ≥10 cigarettes/day Less than 22 weeks pregnant Other factors are given by treatment group.	Smoking status (self-reported abstinence of at least 7 days at each clinic session plus 3 months and 1 year post partum. Compliance Side effects Cotinine in saliva Birth weight Continuous abstinence defined as abstinent at 8 weeks, 11 weeks in to the study and 4 weeks before expected delivery date and had a salivary cotinine level less than 26ng/ml at the last visit.	Non-attendees at follow-up visits were telephoned to determine outcome data. The proportion of non-attendees increased with length of study so that 31%, 44% and 53% of participants needed to be interviewed by telephone at the 2, 3, and 4th follow up respectively. 7 women had spontaneous abortions and one who had twins was excluded from analysis of birth weight.
Kapur et al 2001[16] RCT – double blind	Nicotine patches** 15mg (18hr/d) for 8 weeks, 10 mg for 2 weeks. N=17 Placebo patches**: “identical placebo patch” N=13 All women received counselling at baseline including information on how to use patches. Additional counselling was provided at each clinic visit (1, 4 ,8 weeks). Weekly telephone support including encouragement and monitoring for adverse events was provided. **Pharmacia Inc	N=30	Pregnant women 12-24 weeks gestation ≥15 cigarettes/day Wanted to quit smoking but could not do so in the first trimester.	Daily diary for smoking status and withdrawal symptoms. Cotinine: serum and salivary at baseline, 1 4 and 8 weeks.	Enrolment terminated on safety grounds as foetus of 1 woman exhibited rapid, forceful movements 3 hrs after last cigarette. Movements subsided after commencement of smoking. Investigators decided it was unethical to continue to randomise women to placebo. Women had already tried but failed to quit.

Table 8 Pregnancy: MHRA Identified Trials: Trial Quality

Trial ID	Randomisation and concealment	Blinding	Duration, missing data and loss to follow-up	ITT analysis	Comments
Wisborg et al 2000[15] RCT – double blind	Pre-generated randomisation list, blocks of size 6. Treatment appears to be centrally assigned and the randomisation list concealed until end of data collection. Groups appear reasonably well balanced at baseline (no statistically significant difference)	Placebo patches: no details given Stated that throughout the study the treatment status was not known by the women or the midwife who had contact with the women 44% of the treatment group correctly guessed they were receiving nicotine patches, whereas only 11% of the placebo group did. Suggesting that 81% of placebo group knew they were receiving the placebo. The effect of this is unknown.	11 weeks of treatment with follow-up to 1 year post partum Women who missed visits were automatically given a second appointment within 2 weeks and if failing to attend this they were followed up by telephone. 9% (n=23), 13% (n=33) and 13% (n=33) of women had missing data about smoking at second, third and fourth follow-up visit. All were categorised as smokers.	Stated as ITT for smoking cessation 7 women had spontaneous abortions and one who had twins was excluded from analysis of birth weight.	SAMPLE SIZE DETERMINED BASED ON SMOKING CESSATION RATE FROM STUDY IN NON-PREGNANT POPULATION (80% POWER (ALPHA LEVEL 0.05) TO DETECT A DIFFERENCE IN SMOKING CESSATION OF 20% IN THOSE GIVEN NICOTINE PATCHES AND 5% IN THOSE GIVEN PLACEBO.
Kapur et al 2001[16] RCT – double blind	Unclear Reference made to “opening the code” on patient experiencing a fetal adverse event (forceful movements) suggesting that there was some attempt at concealment. Baseline characteristics supplied appear similar between groups.	“identical placebo patch” No other details stated.	8 weeks Unclear if those discontinuing the program were followed up. Number discontinuing was high in each group 10/17 in the nicotine group, 13/13 in the placebo arm.	No	No power calculation Small numbers Short follow up

Table 9 Pregnancy: MHRA Identified Trials: Trial Results

Trial ID	Smoking cessation	Safety	Other	Comments
Wisborg et al 2000[15] RCT – double blind	26% of all participants were non-smoking at fourth visit (4 weeks before due date). No significant difference between groups: 28% of the nicotine patch group and 25% of the placebo were non-smoking at this time (p=0.52). 21% of the nicotine group and 19% of the placebo group were continuously abstinent after the start of intervention to the fourth visit. One year after delivery the continuous abstinence rates had dropped to 15% in the nicotine and 14% in the placebo group. Salivary cotinine levels were measured at all time points however there were considerable missing data at all but the first time point (up to 43%). which render findings unreliable.	Adverse events: 11 (5%) of the women did not use all their patches due to adverse events (skin irritation, headache). Other adverse events reported were palpitation (n=5, 2% of the study population) and nausea (n=2, 0.8%). The distribution of these events across intervention and placebo groups is unclear.	*Compliance:* low in both groups. Nicotine patch group: 17% used all 15mg patches, 11% all 10mg patches. Mean of 14 patches (0-77) were used Placebo patch group: 8% used all 15mg patches, 7% all 10mg patches. Mean of 7 patches (0-77) were used. *Birth weight* (mean): Nicotine group = 3457g Placebo: 3271g, mean difference 186g 95CI 35-336g). In children born after 37 weeks the figures are 3539g vs 3381g (mean difference 157g 95CI 25, 291g) *Low birth weight* (under 2500g): No-significant difference - nicotine group: 3% Placebo group 9% (RR: 0.4 CI 0.1, 1.1) Pre-term delivery: nicotine group: no significant difference: 8%, placebo group 10% (RR 0.8 95%CI 0.4-1.7)	Adverse event data not fully reported. 7 women had spontaneous abortions and one who had twins was excluded from analysis of birth weight – these appear evenly distributed across treatment and placebo.
Kapur et al 2001[16] RCT – double blind	Nicotine patch: 4/17 had quit smoking by 8th week, 10/17 had discontinued the program in the first week. 3/17 continued with the patches for 3 weeks Placebo patch: none completed the programme. 3/13 discontinued after 4-5 weeks, 10 discontinued in the first week.	Enrolment terminated on safety grounds as the foetus of the last woman enrolled exhibited rapid and forceful movements three hours after the mothers' last cigarette, necessitating a series of tests which proved normal. The movements subsided after the woman commenced smoking again. The code for this woman was broken to reveal that the she was receiving placebo. The investigators decided it was unethical to continue to randomise women to placebo	None	None

3.1.3.2 Other Evidence

No relevant systematic reviews were identified.

A good recent narrative review accurately summarises the information from the RCTs assessed by the MHRA (see Section 3.1.3.1).[19]

We identified only one other randomised study of NRT in pregnant women where smoking cessation or other woman/baby clinically relevant outcomes of long-term NRT use were measured.[20] This was a pilot study conducted in Australia in 40 women randomised to nicotine patch plus counselling or just counselling. 15% of women using NRT had confirmed cessation in late pregnancy compared to zero in the non-NRT group. However, the study was not blinded and therefore this difference could be influenced by knowledge of receipt (or not) of NRT. Further details of this study are detailed in Table 10, Table 11 and Table 12, however the study does not add to the information identified by the MHRA. It was unclear whether this pilot study was being followed by a full trial.

Several other studies were identified which assessed short-term utilisation (hours, days) of nicotine patch or gum on biomarkers in mother and foetus[21,22,23,24] or were of longer duration and measured clinically relevant outcomes but were uncontrolled and therefore likely not to be as strong evidence as that from the RCTs.[25]

Although the RCTs (Section 3.1.3.1) provide some evidence on the utilisation of NRT in pregnancy, the findings of these studies do not clearly show that NRT improves cessation rates, nor have harms to the foetus from NRT been adequately studied. There are a number of issues still to be addressed:

- The RCTs only used patch, and not other forms of NRT and therefore apart for very limited evidence from two of the short-term non-RCTs[21,22] we can only hypothesise about the effectiveness and safety of gum and inhaler NRT.
- There is still limited evidence on the safety of NRT plus smoking as may occur during the early stages of quitting in some women.
- There is no evidence on what constitutes a ‘safe’ level of nicotine/cotinine for the foetus,
- The inertness of other components of the NRT to the foetus is unclear.

- With the availability of gum and inhaled NRT for cut down to quit, there will be concerns about the long-term use of these interventions. With regard to pregnancy this will be strongest in those women who struggle to reduce and quit and therefore might for a long period be subjecting their baby to greater nicotine and cotinine than just smoking alone, whilst the baby is also subjected to the other toxins associated with smoking.

Given all the above it is clear that many questions regarding the efficacy and safety of NRT in pregnancy still exist and this is confirmed by the fact that a double blind placebo controlled RCT of NRT in pregnancy is currently being undertaken in the UK. The aims of the study are:

- To compare at delivery: the effectiveness and cost-effectiveness for achieving biochemically-validated smoking cessation of nicotine replacement therapy and placebo patches in pregnancy.
- To compare at two years after delivery: the effects of maternal nicotine replacement therapy and placebo patch use in pregnancy on behaviour and cognitive development in children.

Women 12-24 weeks gestation who smoke 10 or more cigarettes per day (confirmed by CO greater than 8ppm) are being randomised to either an eight week course of 15 mg/16 hour NRT transdermal patches or an identical placebo. This study is being coordinated by the Queen's University Medical Centre in Nottingham and is funded by NHS Research and Development Health Technology Assessment Programme - HTA (UK). The trial is due to complete in early 2012.

Table 10 Pregnancy: Additional Identified Trials: Trial Characteristics

Trial ID	Intervention and control	N *(location; centres)*	Patients	Outcomes	Comments
Hotham et al 2006[20] Pilot RCT – feasibility study.	Nicotine Patches: 15mg (16hr/d) for up to 12 weeks + standard counselling (approx 5 min at start of study and approx 2 min at subsequent antenatal visits) N= 20 Placebo*: standard counselling (as above) N=20 * investigators could not source any placebo patches	N=40 1 centre (Australia)	Pregnant woman due to deliver at a single centre ≥15 cigarettes/day (confirmed by CO >8ppm) 12-28 weeks pregnant Interested in quitting	Smoking status (self-reported, breath CO. Cotinine in saliva Recorded monthly with the primary outcome at the last prenatal visit. Secondary end points were 48hrs post delivery (breath CO) and 6 and 12 weeks post delivery (self reported smoking status only) No foetal/baby outcomes were measured.	1426 pregnant women screened. 367 were smokers of whom 133 met the smoking frequency criteria. Of these 40 were excluded as planned care did not allow sufficient contact, 21 were too far into pregnancy (more than 28 weeks) , 33 were not interested in the study and/or stopping smoking. One woman appears unaccounted for.

Table 11 Pregnancy: Additional Identified Trials: Trial Quality

Trial ID	Randomisation and concealment	Blinding	Duration, missing data and loss to follow-up	ITT analysis	Comments
Hotham et al 2006[20] Pilot RCT – feasibility study.	Sealed envelope system using computer generated numbers No other details given Some baseline data on groups given but no statistical analysis presented. From this limited data the groups appear reasonably well balanced for the characteristics presented	None	Up to 12 weeks of patch with follow-up to 3 months post partum 14 women withdrew from the study. 7 in each arm. Reasons for withdrawal included, decided they did not want to quit, or too hard to partake in study (9/14).	Stated as ITT	PILOT STUDY WITH NO SAMPLE SIZE CALCULATION, NO BLINDING AND A HIGH WITHDRAWAL RATE.

Table 12 Pregnancy: Additional Identified Trials: Trial Results

Trial ID	Smoking cessation	Safety	Other	Comments
Hotham et al 2006[20] Pilot RCT – feasibility study.	Cessation: Patch: 15% (self-reported and confirmed by cotinine analysis) Control: 0% Reduction (50% reduction in cotinine level): Patch: 35% (7/20) Control:25% (5/20)	5 women stopped patch due to adverse events. These included rashes, dead arm, felt ill/nauseous, increased morning sickness symptoms, exacerbation of existing depression. 2 of the 5 women withdrew due to these adverse events.	*Compliance: 2*5% of women (N=5) complied with patch protocol (12 week continuous use), most women used patches intermittently and 20% (4) used few or no patches. No woman appeared to use patch and smoke simultaneously.	No statistical analysis undertaken

3.1.4 Breastfeeding Women

Women who smoke after giving birth not only expose their baby to passive smoke but if they are breast feeding as well may expose their baby to water and fat soluble tobacco toxins and their metabolites. Only limited research has been undertaken on the nature and quantity of any toxins transmitted to the infant via breast milk. It is known that nicotine and cotinine are able to be transferred from mother to baby via breast milk and there might be some relationship between concentration of nicotine in breast milk and maternal smoking frequency. The half-life of nicotine in breast milk is similar to that of maternal serum. Smoking may also decrease maternal milk production.[18,26]
Thus to reduce passive smoke inhalation by the baby and toxin transmission via breast milk, mothers are advised not to smoke.

3.1.4.1 MHRA Clinical Effectiveness Evidence

The MHRA did not identify any studies on the effectiveness and safety of NRT in breast feeding. The MHRA document does contain a consensus that:

> *… there was limited clinical data available on the use of NRT in…breast-feeding women but also that concerns about the potential adverse effects of nicotine on…the new-born were often theoretical whereas the danger of continuing to smoke were well established and considerably more damaging to mother and baby.*
>
> *The Working Group advised that…lactation should not be a contraindication to the use of NRT…*
>
> *…product information should advise that slow-release 24-hour patches should not be used in …lactation to avoid administration of nicotine overnight.*
>
> *For breast-feeding mothers intermittent NRT products will allow the time between NRT use and feeding to be as long as possible.*

3.1.4.2 Other Evidence

No systematic reviews were found.

Only one relevant primary study was identified. This was a before and after study assessing the effect of NRT patches on nicotine and cotinine concentration in breast milk of mothers who smoked.[27]

The characteristics of this study are detailed in Table 13. Twenty-five women were initially enrolled in the study and they smoked an average of 17 cigarettes per day and had been smoking for a mean of 15.5 years. Nicotine and cotinine levels in breast milk were measured at baseline whilst still smoking and whilst stabilised on 21mg/day patch for weeks 1-6, 14mg/day patch in weeks 7and 8, and 7mg/d patch in weeks 9 and 10. Other outcomes were infant dose of nicotine and cotinine determined by estimation of baby milk intake, and carbon monoxide confirmed smoking status of the mother.

Details of the methodological quality of the study are detailed in Table 14. There are uncertainties around how the sample of mothers was chosen and what criteria if any needed to be met before they were enrolled as these are not detailed in the study report. Of the 25 mothers enrolled initially, only 15 completed the study and were analysed (for some outcomes even less were analysed i.e. plasma nicotine concentration). Four mothers withdrew prior to patch wearing as they had begun to artificially feed their babies. The reasons for non-completion in the other mothers were related to personal issues or baby health concerns and needs. However, one woman was excluded from the analysis as she continued to smoke. Therefore it appears that the 15 mothers analysed were all abstainers (or very occasionally had a single cigarette; n=4, CO less than 10ppm, except for a single reading in one mother). Thus the findings of the study predominantly relate to the use of patch wearing and not patch wearing whilst smoking or reducing smoking. This study therefore does not give reliable information about the quit rate in breastfeeding women.

Assessment of the main outcomes of the study – nicotine/cotinine levels in breast milk, smoking – whilst not completely free from subjective influences were probably objective enough.

The findings of the study are detailed in Table 15. Nicotine and cotinine in breast milk whilst using a 21mg/day patch are of a similar order of magnitude to when smoking approximately 17 cigarettes per day. Exact data are not explicitly stated although from the graphs presented nicotine concentration is approximately 200µg/L (95%CI 160-245) and cotinine 55 µg/L (95%CI45-60) of breast milk when smoking an average of 17 cigarettes per day. The use of 14mg/day and 7mg/day patches significantly reduced nicotine levels to approximately 2/3 and 1/3 of the level found when smoking an average of 17 cigarettes per day, and to 3/4 and 1/2 in the case of cotinine. When infant dose of nicotine

equivalents was calculated a similar statistically significant reduction was found with the 14mg/day and 7 mg/day patch compared to smoking.

The study does report on the volume of breast milk consumed during each smoking/patch regimen however as the infants will be developing and growing it is difficult to assess whether there are any regime-related changes to this volume due to the nature of the study design.

No other clinically relevant outcomes were reported.

Although this study provides some evidence on the utilisation of NRT in breastfeeding there are a number of issues still to be addressed:

- The study only used patch, and not other forms of NRT and thus we can only hypothesise about what the effects of gum and inhaler and their more variable delivery of nicotine to the mother has on the concentrations in breast milk.
- The study only assesses effects of NRT patch use compared to smoking. There is still no evidence on NRT plus smoking as may occur during the early stages of quitting.
- There is no evidence on what constitutes a ‘safe’ level of nicotine/cotinine in breast milk or infant plasma.
- The inertness of other components of the NRT to the infant and their concentration in breast milk are unclear.
- With the availability of gum and inhaled NRT for cut down to quit, there will be concerns about the long-term use of these interventions. With regard to breastfeeding this will be strongest in those women who struggle to reduce and quit and therefore might for a long period be subjecting their baby to greater nicotine and cotinine via breast milk than just smoking alone, whilst the baby is also subjected to the other toxins associated with smoking.

In the absence of more evidence to address these issues and given the benefits to mother and baby of not smoking, the recommendation of the MHRA (Section 3.1.4.1) particularly the emphasis on minimising nicotine dose to the infant via careful scheduling of NRT usage does seem a sensible approach.

Table 13 Breastfeeding: Study characteristics

Study ID	Intervention and control	N *(location; number of centres)*	Patients	Outcomes	Comments
Ilett et al 2003[27] Before and After Study	Smoking at baseline - 21mg/day patch* weeks 1-6 - 14mg/day patch* weeks 7 & 8 - 7mg/day patch* weeks 9 & 10 - wean off patches around week 11 * Nicabate CQ	N=25 (? 1 centre, Western Australia)	Breastfeeding mothers who smoked Mean Age: 32 (range: 21-36) Cigarettes: 17/day (95%CI- 13.7-20.3) Time Smoked: 15.5years (95% CI- 13.2-17.7) Fagerström Score: 6.3 (95% CI- 5.7-6.9) Infants** Age: median 4.8 months (range: 2.5-21) Birth weight: mean 3.4 kg (range: 2.6-4.1) Denver Development ratio: mean 1.0 (range: 0.8-1.2) Sex (M:F): 8:7 ** data only for mothers analysed	Nicotine and Cotinine levels in breast milk samples collected from both breasts at each feed on the day before a clinic visit. Clinic visits were at the start of the study, after stabilisation on a patch regimen for at least one week and at the end of the study. Infant milk intake (baby weight pre/post feeding) Infant dose of nicotine and cotinine Smoking status of mother Carbon monoxide testing of mother (abstinence not clearly defined – assumed to be >10ppm)) Nicotine and cotinine in plasma of mother and baby whilst on the highest dose patch.	*One low smoking mother (6/d) had a different NRT regimen: w1-6 14mg/d, w7&8-7mg/d then no NRT.* *Only 15 mothers included in analysis. Stated characteristics of these women appear similar to the whole population.*

Table 14 Breastfeeding: Study Quality

Study ID	Is the study based on a representative sample selected from a relevant population?	Are the criteria for inclusion explicit?	Were the characteristic of the mothers and babies similar at time of enrolment?	What were the follow up rates and was follow-up long enough for important events to occur?	Were outcomes assessed using objective criteria or was blinding used?	Comments
Ilett et al 2003[27] Before and After Study	It is unclear how the mothers were identified and recruited.	No It is assumed that they were mothers who smoked and were breastfeeding their baby	Unclear However, from the information supplied it appears that the mothers had all smoked for a similar length of time and were all smoking at a similar frequency. There was a fairly wide range of ages of the babies of the mothers whose data was analysed.	15 mothers completed the study. 4 dropped out before the study commenced (3 had begun artificial feeding, 1 for personal reasons) 5 withdrew after the start of the study (2 for personal reasons, 1 due to poor milk expression, 1 for reasons regarding baby health and use of NRT, 1 woman continued to smoke) One woman was enrolled twice but dropped out twice (data from the second enrolment was used for 21mg/d and 14 mg/d analysis). Follow–up was only long enough to determine the nicotine/cotinine load on the baby on one day at each patch dose.	Mothers were aware of the nature of the study Mothers were not blinded and knew which patch strength they were receiving. Some outcomes were objective or objectively verified. Some were less objective and potentially open to influence by the unblinded mother. Where blinding of outcome assessors could have been used it is not clear if it was.	Although some patients dropped out of the study, one was not included in the analysis because she did not quit smoking. Data in the study is on short-term outcomes and only relevant to abstinent mothers who use NRT patch and breastfeed their babies.

Table 15 Breastfeeding: Results

Study ID	Smoking cessation	Safety	Other	Comments
Ilett et al 2003[27] Before and After Study	All mothers included in the analysis (N=15) appeared for the most part to be abstinent from smoking whilst using the patch. 4/15 mothers had an 'occasional' cigarette whilst using patches. Only one CO reading in one mother exceeded 10ppm.	Nicotine and cotinine levels in breast milk using a 21mg/d patch are of a similar order of magnitude to when smoking about 17 cigarettes/day. Using 14 and 7 mg/d patch significantly reduces the nicotine (approx.1/3 and 2/3) and cotinine (approx. 1/4 and 1/2) content of breast milk compared to smoking an average of 17 cigarettes/day. Infant dose of nicotine and cotinine are similar with 21mg/d patch and smoking an average of 17 cigarettes per day, but infant dose is much lower on 14mg/d and 7 mg/d patch. Nicotine equivalents are statistically lower with 14 and 7 mg/d patch compared to smoking. Plasma results are only available for 9 mother/infants and therefore are not reported in this table.	No significant difference in milk intake by the baby between smoking and any of the patch regimens.	Some outcomes are not reported for all 15 mother/babies analysed. Mothers were predominantly abstinent whilst outcomes were being measures in the patch using phases of the study.

3.1.5 Cardiovascular disease

Smoking is a major risk factor for cardiovascular disease. A reduction in the risk of coronary artery disease (CAD) following quitting smoking has been shown for patients with existing heart disease, especially following myocardial infarction (MI). Studies have shown reductions in 5 year mortality rates of 8-15% in quitters compared to smokers.[28]

Smoking is thought to increase cardiovascular risk via at least 4 mechanisms: promotion of thrombosis; inflammatory effects and progression of atherosclerosis; reduction of oxygen delivery through inhalation of carbon monoxide, and haemodynamic effects of nicotine.

Since the introduction of nicotine replacement, some concerns have been raised about potential cardiovascular side effects from nicotine and the suitability of NRT for cardiovascular patients. However, it has been pointed out that NRT replicates only one of the mechanisms of cardiovascular damage associated with smoking, that this is considered the least important mechanism of harm and that the concentration of nicotine in the blood produced by NRT is typically lower than that produced by smoking. Therefore, whilst NRT may not be entirely risk free for people with stable cardiovascular disease it is likely to be preferable to continuing smoking for those individuals who find it difficult to stop.

Recently, the MHRA reviewed the evidence and supported revisions of the product information as follows:

- in stable cardiovascular disease, NRT presents a lesser hazard than continuing to smoke;

- dependent smokers hospitalised with a recent myocardial infarct, severe dysrythmia or recent cerebrovascular accident and/or who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions. If this fails, NRT may be considered but as data on safety in this group are limited, initiation should be under medical supervision.

3.1.5.1 MHRA Clinical Effectiveness Evidence

The main concern for the MHRA in considering this amendment to the license was the safety of NRT in this population. An important element of the evidence considered was a large population-based study considering the risk of acute MI, stroke and death associated with the use of NRT published by Hubbard et al in 2005.[29] Information was collected on 33,247 individuals who had been prescribed NRT, of whom 861 had had a myocardial infarction and 506 a stroke. The study found that there had been a progressive increase in the incidence of first myocardial infarction in the 56 days leading up to the first NRT prescription, which is probably related to the reasons for NRT being instituted. Incidence fell following prescription of NRT and in particular was not increased in the first 8 weeks after NRT was started. The results were similar for second myocardial infarction and stroke, and for subgroups of people with pre-existing angina and hypertension. There were 960 deaths in the cohort over a mean follow-up period of 2.6 years after starting NRT, with no evidence of an increased mortality in the first 8 weeks after the NRT prescription (incidence ratio 0.86, 95% CI 0.60 to 1.23).

The figures below, reproduced from Hubbard et al, shows the pattern of MI and stroke respectively in the weeks before and after NRT prescription for this large cohort.[29]

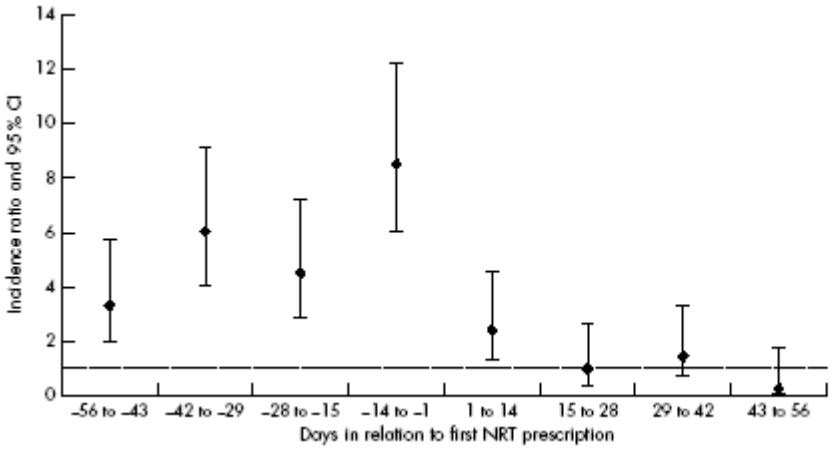

Figure 2 Temporal relationship between the relative incidence of acute myocardial infarction and first prescription for NRT.

Tobacco Control 2005;14:416-421 Reproduced with permission from the BMJ Publishing Group

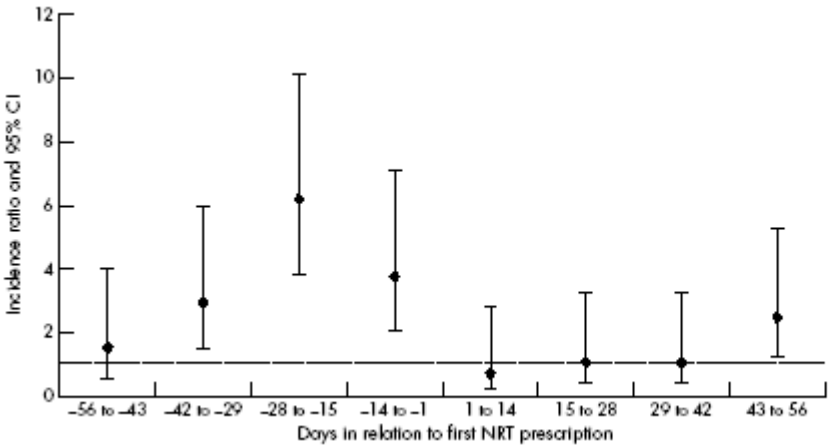

Figure 3 Temporal relationship between the relative incidence of acute stroke and first prescription for NRT.

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The MHRA utilised the results of several clinical studies and reviews, including three randomised controlled trials and a large population-based study. The RCTs are summarised in Table 16, Table 17 and Table 18 below.

Only one of these trials[30] is really of adequate size to detect important differences in safety and this trial recruited an almost exclusively male population (8 women of 548 participants). The other two trials[31,28] recruited 156 and 106 patients respectively. All trials were of fairly short duration, with the largest study also having the longest duration (10 weeks). The trials were all of moderately good quality; the poorest quality trial was Tzivona et al.[28] Of greatest concern in this trial is the failure to report the method of randomisation and concealment of allocation. There were some substantial imbalances at baseline in this trial, particularly with respect to cardiovascular fitness, with the placebo group being considerably less healthy on average. While these sorts of imbalances will happen purely by chance from time to time, the fairly extreme differences add to concerns about the quality of randomisation in this trial. The analyses presented in the paper do not account for baseline imbalances in the characteristics being measured and so the results should be interpreted with caution.

Overall the results of these trials confirm the results of larger population based studies and clinical expectation; that although there may be some cardiovascular risk associated with NRT this is substantially lower than the risk of continuing to smoke. Cardiovascular event rates in the NRT arms were not higher, and were in some cases lower, than those in the placebo arms of these trials.

Table 16 Cardiovascular Disease: Trial Characteristics

Trial ID	Intervention and control	N *(location; centres)*	Patients	Outcomes	Comments
Joseph, 1996[30]	Patches* (21mg/day for 6 wks, 14mg/day for 2 wks, 7mg/day for 2 wks)** Placebo patches *Nicoderm **treatment discontinued at 6 weeks if subjects reported smoking >5 cigarettes in previous week or CO>8ppm	548* (USA; 10) *target 580 NB: only 8 women recruited	Age ≥45 ≥15 cigarettes/day with ≥2 previous attempts to quit and CO≥8ppm History of MI, CABS, angioplasty, stenosis ≥50% in at least one major artery or a clinical history of angina, CHF, cor pulmonale, arrhythmia, peripheral vascular disease or cerebrovascular disease No unstable angina, MI, CABS, angioplasty, hospitalisation for arrhythmia within 2 weeks of randomisation No prior continuous use of transdermal nicotine for >48 hours, unwillingness to stop current use of tobacco products or nicotine gum, unstable psychiatric illness or disorder involving use of alcohol or controlled substances, history of severe dermatitis, pregnancy	Patient diaries (smoking and symptoms) Expired CO Mortality MI Cardiac arrest Hospital admissions and outpatient visits Side effects	Only 8 female subjects (most were veterans)
STNPCAD, 1994[31]	Patches* (14mg/day)** + *weekly group counselling* Placebo patches (<1mg/day) + *weekly group counselling* *Nicoderm **Increased to 21mg/day for patients smoking >7 cigarettes in first week	Patches: 77 Placebo: 79 (78**) Total: 156* (155**) (USA; 4) *target 160 **couples randomised as a pair and one spouse excluded from results – one patient excluded from efficacy results after randomisation for this reason	CAD, defined as coronary angiography showing ≥ 60% obstruction of ≥1 major artery or primary branches, or documented MI, or clinical history typical of angina pectoris with exercise treadmill test or nuclear scan consistent with myocardial ischaemia, or prior CABS or angioplasty Age 21-70 ≥20 cigarettes/day and Fagerström score ≥7 Expired CO ≥10ppm above ambient levels at screening No acute MI within 3 months of study entry, unstable angina, vasospastic conditions, symptomatic valvular heart disease, uncontrolled CHF, serious ventricular arrhythmias, ≥2nd degree atrioventricular block, IDDM, active peptic ulcer or any contra-indication to use of transdermal systems	Smoking diary Weekly expired CO Cardiac symptom diary Withdrawal symptom diary 12-lead ECG 24 hour ambulatory ECG monitoring (AEM) in one centre only Blood pressure Heart rate Body weight Plasma nicotine and cotinine	

Trial ID	Intervention and control	N *(location; centres)*	Patients	Outcomes	Comments
Tzivoni, 1998[28]	*>20/day smokers:* Nicotine patches* 20cm^2 (14mg/24hr) +*SCP*** "Placebo" low dose nicotine patches 20cm^2 (2g/24hr) +SCP** *<20/day smokers:* Nicotine patches* 30cm^2 (21mg/24hr) +*SCP*** "Placebo" low dose nicotine patches 30cm^2 (3g/24hr) +SCP** * Nicotinell ** weekly group smoking cessation programme	Patches: 52 Placebo: 54 Total: 106 81 in higher dose group (Israel; 2 centres)	CAD (angiographic evidence, stable angina pectoris with positive exercise test or previous MI) Age 30-75 Nicotine dependent (≥15 cigarettes/day for ≥ 5 years and Fagerström score ≥5) Wishing to stop smoking No MI, coronary artery bypass surgery, coronary angioplasty or stroke within 3 months prior to screening ≤12 ischaemic episodes during 48 hour ambulatory ECG monitoring Blood pressure ≤110mmHg (diastolic) and ≤200mmHG (systolic) No reduced LVF or clinical signs of heart failure, complex ventricular arrhythmias or episodes of supraventricular tachycardia of >60 seconds duration	48 hour ambulatory ECG monitoring (AEM) Smoking diary Carbon monoxide testing (abstinence defined as <12ppm) Symptoms Skin tolerability	

Table 17 Cardiovascular Disease: Trial Quality

Trial ID	Randomisation and concealment	Blinding	Duration, missing data and loss to follow-up	ITT analysis	Comments
Joseph, 1996[30]	Pre-generated randomisation list, blocks of size 10. Treatment appears to be centrally assigned, but no clear statement given Groups appear reasonably well balanced at baseline	Placebo patches identical in smell and appearance – no further details given	10 weeks 27% of patches group and 44% of placebo group had discontinued treatment at 6 weeks	Yes	Sample size determined based on safety endpoints (90% power to detect an increase of 10% from a baseline of 15% in rate of adverse) events
STNPCAD, 1994[31]	Central randomisation, list in blocks of 4, separate list for each centre but not otherwise stratified Couples randomised "separately" (?as a pair) so that they received the same treatment with one member of the couple excluded from analysis Patient characteristics well-balanced across groups	Placebo patches contained very low dose nicotine to give identical colour and odour	5 weeks 32 (20.5%) withdrew (13 on patches, 19 on placebo). 11 for AEs, 9 for lack of efficacy, 5 for non-study- related reasons, 4 for non-compliance/loss to follow-up and 3 for unrelated illness 155/156 evaluable for efficacy – 1 patient excluded as randomised as a pair with spouse	Withdrawals treated as "failures" for smoking cessation ECG performed immediately after withdrawal for safety endpoints One participant excluded from efficacy due to randomisation as a couple, with one set of data "selected" for exclusion during randomisation	Sample size calculation based on cessation rates in previous studies of nicotine gum; no consideration of power for safety outcomes
Tzivoni, 1998[28]	No description Placebo group appears to have much higher rate of ischaemic episodes during pre-treatment screening (42 *vs* 87, mean 2.5 *vs* 3.5). Consistent with chance but may affect interpretation of results.	Placebo patches contained very low dose nicotine to give identical colour and odour	2 weeks 12 withdrawals during treatment (reasons not reported)	Not clear ("The data on all patients who were randomised to treatment and received at least one dose of study medication were analysed. A total of 106 patients were included in the analysis.") Numbers randomised match numbers analysed, but definition is not ITT.	Small study; no sample size calculation. Analysis does not use baseline values. Of some concern as there were some baseline differences which may affect interpretation of the results

Table 18 Cardiovascular Disease: Trial Results

Trial ID	Smoking cessation	Safety	Other	Comments
Joseph, 1996[30]	*CO confirmed cessation at 14 weeks:* 21% on patches vs 9% on placebo (p=0.001) *CO confirmed cessation at 24 weeks:* 14% on patches vs 11% on placebo (p=0.67)	*Deaths:* 1 on patches vs 6 on placebo (p=0.07) *Death or MI, cardiac arrest, admission for angina, arrhythmia or CHF:* 5.4% vs 7.9% (p=0.23 inc deaths) *Other admissions:* 11.9% vs 9.7% (p=0.37) *All:* 16.3% vs 16.2% (p=0.97) Results similar when considered only for patients continuing on treatment	*Weight:* +1.4kg on patches, +0.3kg on placebo (p=0.001) *Blood pressure/pulse:* negligible changes in both groups *Sleep disturbance, skin reactions and GI distress:* similar in both groups	Fewest events in non-smokers on placebo, but no evidence that patches cause more events than smoking
STNPCAD, 1994[31]	*Required increased dose patches:* 19 (25%) on patches vs 40 (51%) on placebo *Smoking cessation (from diaries confirmed by CO)*: 36% on patches vs 22% on placebo (p<0.05). Much higher cessation rates in one centre but no centre-treatment interaction found; this centre had more patients with advanced NYHA class and performed 24 hour ECG monitoring *Mean withdrawal symptom scores*: 1.8 on patches vs 2.2 on placebo (p<0.05)	*Angina*: frequency declined in both groups *Cardiac symptoms:* 90% on both arms reported symptoms unchanged from baseline; no consistent changes in ECG for either group except a minor prolongation of PR and QRS intervals for placebo group *24 hour AEM:* available for 48 patients; no statistically significant changes from baseline except a fall in heart rate at week 1 in placebo group; other small changes comparable across groups *Blood pressure:* no changes *Heart rate:* fell in placebo group only, especially those who quit smoking, by 3-10 bpm *Body weight:* increased 2.2kg for patches and 1.3kg for placebo (p<0.05); increases greater in those who quit smoking (3.3 vs 2.4kg, p<0.05) *Adverse effects:* 50% reported AEs in each group. Those on patches reported more transient itching at the patch site (36% vs 9%). Those on placebo reported more dizziness, insomnia, diarrhoea, body aches, nervousness and angina. Local erythema occurred in 20% of patients on patches but required no treatment 11 withdrawals for adverse events, 3 on patches (nausea, palpitations and malaise; severe chest pain; severe nausea) and 8 on placebo (increased angina intensity; hospitalisation for chest pain and bypass surgery; new ischaemic electrocardiographic changes; increased angina; hospitalised for severe nicotine withdrawal symptoms; parasthesia, dizziness, dyspnoea, palpitations; rash; 2 minute syncopal episode)	Compliance >90% for both groups (determined by number of patches returned at follow-up)	
Tzivoni, 1998[28]	*Patient reported smoking cessation:* 14/52 (27%) on patches vs 7/54 (13%) on placebo *Mean cigarettes smoked:* 7.7/day vs 9.1/day *CO <12ppm:* 38/52 (73%) vs 28/54 (52%)	*AEM:* no significant differences reported but analysis does not account for baseline values. Ischaemic episodes at baseline 33% (42 episodes in 17 patients) on patches vs 46% (87 episodes in 25 patients) on placebo, CI for difference (-29%, -2%); at 2 weeks, 31% (46 episodes in 16 patients) vs 22% (65 episodes in 12 patients), CI for difference (-6%, 23%). *Exercise testing:* no significant differences reported. Positive exercise test 40% on patches vs 31% on placebo, CI for difference (-6%, 24%). Mean exercise duration 11 vs 10.3 minutes (-0.1, 1.5). Time to 1mm ST depression 7.5 vs 9.3 minutes (-0.3, -0.6). Mean maximal ST depression 1.2 vs 1.3 (-0.3, 0.1) *Blood pressure:* unchanged (before/after data reported but no direct comparison between groups) *Pulse rate:* unchanged (before/after data reported but no direct group comparisons) *SAEs:* 2 on patches (angina at rest; unstable angina with documented ischaemia), 1 on placebo (worsening angina, catheterisation and CABS)	*Mean weight:* "virtually unchanged", +0.1kg vs –0.9kg (groups not clear)	CO testing only done at end of 2 week study period - the much higher percentages of non-smokers according to CO than patient reported suggested that participants "gave up" shortly prior to the final follow-up tests

3.1.5.2 Other Evidence

We did not identify any RCTs which had not been considered by the MHRA.

We identified one systematic review by Wiggers et al[32] based on a series of reviews by the Cochrane Tobacco Addiction Review Group. This review identified only two studies considering the effectiveness of NRT in cardiovascular patients, one of which (Joseph et al, 1996)[30] is reported above. The second study included in this review was a small trial of 85 hospital inpatients by Campbell et al,[33] this trial was not considered for inclusion in this report due to the inpatient population.

3.1.6 Combination Therapy NRT + NRT

Until recently, NRT product information warned against the concurrent use of more than one product. However, whilst nicotine patches appear to be effective at maintaining a background level of nicotine and maybe more effective overall than other “on demand” delivery systems, such as gum, inhalers and nasal spray, there may be advantages to combined use of patches with an “on demand” product to satisfy intermittent cravings.

The MHRA Working Group recently reviewed the evidence on the combination of different NRT products and recommended that these warnings against combined use be removed to allow smokers to identify and use the combination most appropriate for them.

3.1.6.1 MHRA Clinical Effectiveness Evidence

The MHRA considered the results of 5 RCTs in their report. Two of these investigated the use of patches and gum,[34,35] two the use of patches and inhalers[36,37] and one the use of patches combined with nasal spray.[38]

Details of the studies can be found in Table 19, Table 20 and Table 21.

Four of the five trials had treatment periods of 3-9 months and all had follow-up at one year. Overall trial quality was good with reasonably large sample sizes (range 237-446), adequate methods of randomisation and allocation concealment (where reported) and use of intention-to-treat analysis.

All five trials reported a trend towards improved efficacy for the combined NRT strategies. Early differences in success rates were statistically significant in all trials, although success rates in all groups declined over time and few statistically significant differences were reported at one year although differences in quit rates persisted in all trials.

One systematic (Cochrane) review by Silagy et al[39] was considered by the MHRA. This review was well conducted and included 7 comparisons of combination NRT+NRT of various types. The included trials are discussed in more detail elsewhere in this report. The combined OR for smoking cessation was 1.42 (1.14, 1.76), suggesting a benefit for combination compared to single treatment approaches, but as the authors note there is substantial clinical heterogeneity in terms of the forms of NRT combined and which single treatments were used as the comparator.

Table 19 Combination NRT+NRT: MHRA Identified Trials - Trial Characteristics

Trial ID	Intervention and control	N *(location; centres)*	Patients	Outcomes	Comments
Blondal, 1997[38]	Patch (15mg) + nasal spray Patch + placebo spray	237 total (Iceland; 1)		Sustained abstinence at 1 year	Abstract only
Bohadana, 2000[36]	Patch (15mg/day) + inhaler (10mg** capsules, 6-12 capsules/day)*** Placebo patch + inhaler **4mg available from 10mg capsule ***For 6 weeks, placebo patch thereafter	400 (France;)	Age 18-70 ≥10 cigarettes/day and expired CO≥10ppm One or more previous attempts to quit and willing to stop smoking No MI within 3 months, unstable angina, severe cardiac arrhythmia, serious renal, pulmonary, endocrine or neurological disorders, pregnancy or breastfeeding or use of any form of tobacco or nicotine substitution Subjects using any smoking cessation program within 6 months, alcoholics or illegal drug users and those with dermatological diseases also excluded	Smoking status at 3 months Continuous abstinence (self-reported non-smoking weeks 2-52 and expired CO<10ppm at each follow-up) Expired CO Weight Craving and withdrawal symptoms Pulmonary symptoms and lung function AEs	
Kornitzer, 1995[34]	Patch** + gum Patch + placebo gum Placebo patch + placebo gum **15mg/day for 12 wks, 10mg/day for 6 wks, 5mg/day for 6 weeks	374 (149+150+75 on placebo) (Belgium; 3 workplaces)	*Workplace recruitment (white collar)* Age ≥20 ≥10 cigarettes/day and having smoked for at least 3 years No severe and/or symptomatic cardiac disease, pregnancy, breastfeeding, regular psychotropic medication, abuse of alcohol or other drugs, generalised chronic dermatological disorders or active peptic ulcer, use of any form of smokeless tobacco or current involvement in smoking cessation program	Smoking cessation, patient reported and CO measurement Abstinence defined as no smoking after week 1 and CO<10ppm at all follow-up after week 1 Cotinine testing at weeks 1, 18 and 24 Compliance Adverse events	
Puska, 1995[35]	Patch* + gum** Placebo patch + gum** *Nicorette,15mg/day for 12 weeks, 10mg/day for 3 weeks, 5mg/day for 3 weeks **2mg/piece, encouraged to use at least 4 pieces a day for up to 12 months, with withdrawal encouraged after 6 months	300 (Finland;10)	Age 20-65 ≥10 cigarettes/day, smoker for 3 years or more and wishing to stop smoking No recent MI, pregnancy, breastfeeding, regular psychotropic medication, use of smokeless tobacco, generalised dermatological disorder, active peptic ulcer, active temporomandibular joint disease, or currently on a smoking cessation programme	Smoking status Expired CO Abstinence defined as no smoking after week 1 with CO<10ppm Diary on gum use AEs	

Trial ID	Intervention and control	N *(location; centres)*	Patients	Outcomes	Comments
Tonnesen, 2000[37]	Patch (15mg/day)* Inhaler (10/mg per container**, 4-12 container/day used hourly)* Patch (15mg/day) + inhaler Low dose (placebo) patch (5mg/day) * Nicorette **5mg available from 10mg/container	446 (Denmark;1)	*Recruited from attendees at a lung clinic* ≥10 cigarettes/day Age 20-70 Willing to quit smoking and use NRT No suspicion of lung cancer, tuberculosis. senility, pregnancy or lactation	Smoking cessation (confirmed by CO and cotinine if possible) assessed at follow-up and 1 year Sustained abstinence (no smoking after week 2 and CO<10ppm at all visits) Abstinence with slips (abstinence with smoking on two occasions with up to 10 cigarettes consumed, CO<10ppm at all visits) Nicotine dependency (Fagerström score)	

Table 20 Combination NRT+NRT: MHRA Identified Trials - Trial Quality

Trial ID	Randomisation and concealment	Blinding	Duration, missing data and loss to follow-up	ITT analysis	Comments
Blondal, 1997[38]	Computer generated code, dispensed by pharmacy (from Silagy et al[39])	Double blind (no details) (from Silagy et al[39])	Treatment recommended for 3 months; follow-up at one year and up to 6 years		Abstract only
Bohadana, 2000[36]	Sealed envelopes held by hospital pharmacy Patients characteristics well-balanced at baseline	Double blind up to 6 weeks, single blind from week 6-12 and open thereafter	6 weeks (+6 weeks with both groups on placebo) and one year follow-up	Yes; non-attendees defined as relapsers	Sample size seems optimistic; 80% power to detect at least 15% difference at 1 year based on observed success rates of 40% vs 55%
Kornitzer, 1995[34]	Computer-generated list, sealed code envelopes helped by PI for emergency unblinding (not required) – no other details given Groups well balanced at baseline (3.1yr difference in mean age consistent with chance)	Identical placebos used – placebo gum designed to taste similar	24 weeks with follow-up at one year No information on loss to follow-up; compliance reported	Yes; withdrawals and loss to follow-up counted as treatment failures	
Puska, 1995[35]	No information given Groups appear well-balanced at baseline	"strictly double blind"; no further information	24 weeks and one year follow-up No loss to follow-up, but compliance reported	Yes; loss to follow-up regarded as treatment failure, withdrawals from treatment continued on follow-up	
Tonnesen, 2000[37]	No description Patient characteristics well balanced	None (open label)	3-9 months treatment and follow-up at one year 68% attendance at 2 weeks, 43% at 6 weeks, 28% at 12 weeks and 11% at 1 year "Most" non-attendees contacted and confirmed as smoking again	Yes (non-attenders counted as treatment failures)	

Table 21 Combination NRT+NRT: MHRA Identified Trials - Trial Results

Trial ID	Smoking cessation	Safety	Other	Comments
Blondal, 1997[38]	*"significant increase in sustained abstinence at one year" (reported by Silagy et al[39])*			Abstract only
Bohadana, 2000[36]	*Smoking cessation at 12 months:* 19.5% (patch+inhaler) vs 14% (placebo+inhaler), p=0.14 *Smoking cessation at 6 weeks:* 60.5% (patch+inhaler) vs 47.5% (placebo+inhaler), p=0.009 *Smoking cessation at 12 weeks:* 42% (patch+inhaler) vs 31% (placebo+inhaler), p=0.02 *Time to relapse over 1 year:* logrank test, p=0.04	*Withdrawal symptoms:* significantly greater in placebo group at 1 week (p<0.001) *Craving symptoms:* significantly greater in placebo group at 6 weeks (p=0.04) *Respiratory symptoms:* decreased in both groups, slight improvements in pulmonary function *Adverse events:* rare and tolerable	*Inhaler cartridges used in abstainers:* 4.41 (patch+inhaler) vs 4.6 (placebo+inhaler) per day up to week 6; 3.75 vs 4.32 per day weeks 6-12 *Weight:* +0.49kg (patch+inhaler) vs +0.99kg (placebo+inhaler) (p=0.01) at week 2; +4.22kg vs 3.96kg at 1 year (p=0.14)	
Kornitzer, 1995[34]	*Abstinence:* 34.2% (patch+gum) vs 22.7% (patch) vs 17.3% (placebo) at week 12; 27.5% vs 15.3% vs 14.7% at 24 weeks; 18.1% vs 12.7% vs 13.3% *OR (patch vs patch+gum):* 1.72 (1.03, 2.94), p=0.039 at 12 weeks; 2.04 (1.14, 3.57), p=0.018 at 24 weeks; 1.47 (0.76, 2.78), p=.0125 at 52 weeks	No severe dermatological reactions; no statistically significant differences for itching, erythema or edema	*Gum consumption:* no significant differences between groups *Patch compliance:* 52% daily use at 12 weeks, 41% at 24 weeks (no difference between groups)	
Puska, 1995[35]	*Time to relapse:* logrank p=0.04 *Abstinence at 12 weeks:* 39.3 (patch+gum) vs 28.0 (gum only), p=0.038 *Abstinence at 26 weeks*: 27.3 (patch+gum) vs 20.7 (gum only), p=0.175 *Abstinence at 52 weeks:* 24.0 (patch+gum) vs 17.3 (gum only), p=0.154 *Cotinine:* mean 147 vs 198 (p=0.035)	Relatively few adverse events reported Itching more common with active patch (29% vs 11%, p<0.001) No other significant differences	*Compliance:* 70% (active patch) vs 58% (placebo patch) using patch ar 12 weeks *Gum use:* average 4 pieces/day in both groups over first 3 months. slightly higher in gum only group; gum use reduced over 6-12 months	
Tonnesen, 2000[37]	*12 month cessation:* 6% (placebo) vs 16% (patch) vs 9% (inhaler) vs 11% (patch + inhaler) *12 month sustained abstinence:* 1.8% vs 8.7% vs 5.1% vs 3.5% *HR for relapse (adjusted Cox regression):* 0.56 (patch), 0.75 (inhaler), 0.51 (inhaler + patch) Patch vs placebo, p<0.05	No serious AEs reported	No significant differences in body weight, cotinine and lung function Motivation, sex, age, baseline cigarette consumption, baseline CO, Fagerström score significant predictors of outcome (and included in adjusted Cox model)	

3.1.6.2 Other Evidence

We identified 3 further RCTs which were not explicitly mentioned in the MHRA report.[40-42] These trials are summarised in Table 22, Table 23 and Table 24. One further RCT was identified but this was a crossover design with 4 treatment groups (using placebo or active patches, and placebo or active patches). The treatment period was only 3 days for each treatment assignment, with a 4 days washout period with smoking. A crossover design is of questionable value for answering pragmatic questions in this area and the results of this study are not interpretable in a useful way for this report.

All three of the other RCTs identified examined the use of nicotine nasal spray in combination with patches. Two of these were reported as abstracts only and we have very little information about the study designs or results. The large trial which has been fully reported Croghan et al,[42] is of good quality and reports similar results to those trials investigating patches combined with gum or inhalers. The treatment period in this trial was only 6 weeks, with follow-up to 6 months. The results are comparable to the other trials combining patch and gum or inhaler reported above. The trial by Croghan et al was included in the systematic review by Silagy et al.[39]

Table 22 Combination NRT+NRT: Additional Identified Trials - Trial Characteristics

Trial ID	Intervention and control	N (location; centres)	Patients	Outcomes	Comments
CROGHAN, 2003[42]	Patch (15mg/day) Nasal spray (0.5mg/spray*) Patch + spray all for 6 weeks *Recommended dose of one puff/nostril as required, maximum 5 doses/hour or 40/day	1384 (USA; several)	Age ≥18 ≥15 cigarettes/day for last year No general poor health or planning pregnancy, MI within 3 months, angina pectoris, serious cardiac arrhythmia, presence of psychiatric disorder, use of psychiatric drugs, chronic nasal disorders, allergies or sinusitis, pregnancy or breastfeeding, current use of tobacco products other than cigarettes, current use of NRT or other pharmacological smoking cessation treatment, use of IND within 30 days, history of skin allergies, or participation in smoking cessation programme within last 12 months	Smoking cessation at end of study Abstinence defined as self-report of non-smoking for previous 7 days, biochemically confirmed with CO<8ppm AEs	
Landfeldt, 1998[41]	Patch + nasal spray Placebo patch + nasal spray	101	≥20 cigarettes/day and Fagerström score ≥7		Abstract only
Sutherland, 1999[40]	Nasal spray Patch Patch + nasal spray Placebo	380			ABSTRACT ONLY

Table 23 Combination NRT+NRT: Additional Identified Trials - Trial Quality

Trial ID	Randomisation and concealment	Blinding	Duration, missing data and loss to follow-up	ITT analysis	Comments
Croghan, 2003[42]	Minimisation (factors: gender, cigarettes/day at baseline, total years smoking) Presumably central allocation (given that minimisation used)	None	6 weeks with 6 month follow-up 34% completed study; 45% non-compliance;4% loss to follow-up; 10% withdrawal of consent; <3% unknown reason	Yes; non-attendees or loss to follow-up classified as treatment failure	
Landfeldt, 1998[41]			12 weeks + withdrawal period of 6 weeks		
Sutherland, 1999[40]			4 weeks with follow-up at 8 weeks		

Table 24 Combination NRT+NRT: Additional Identified Trials - Trial Results

Trial ID	Smoking cessation	Safety	Other	Comments
Croghan, 2003[42]	*CO confirmed abstinence at 3 weeks:* 25.5% (patch) vs 21.2% (spray) vs 34.4% (patch+spray), p=0.003 (patch vs patch+spray) *CO confirmed abstinence at 6 weeks:* 20.7% (patch) vs13.6% (spray) vs 27.1% (patch+spray), p=0.025 (patch vs patch+spray) *CO confirmed abstinence at 6 months:* 7.8% (patch) vs 6.9% (spray) vs 9.1% (patch+spray), p=0.554 (patch vs patch+spray)	Nasal spray associated with more burning in nose and throat (63% vs 12%), watery eyes (48% vs 14%), nose and throat irritation (53% vs 17%) and sneezing (49% vs 21%) No other adverse events reported with high frequency More withdrawals due to AEs on nasal spray (3% vs 1%)	No interactions found by race, gender, history of alcoholism or subclinical depressive symptoms	Sample size based data from previous studies and well reported
Landfeldt, 1998[41]	Abstinence: overall 18% at 12 weeks No differences between groups (no data reported)			
Sutherland, 1999[40]	*Spray+patch vs patch alone:* OR=1.66 (0.96, 2.88) at 4 weeks *Spray+patch vs spray alone:* OR=1.29 (0.78, 2.21) at 4 weeks Little evidence of a difference at 8 weeks			

3.1.7 Combination therapy NRT + Bupropion (Zyban)

Bupropion (Zyban® GSK) is a slow release prescription only drug, licensed for use in smoking cessation with motivational support. NICE guidance was issued in 2002 and recommends the use of Bupropion in smokers over the age of 18.[43] A dosage of 150mg for the first six days followed by two tablets per day for the following 6 to 8 weeks is recommended. The NICE guidance states there is currently insufficient evidence to recommend a combination therapy of NRT with Bupropion. This was based on the evidence of one trial available at the time by Jorenby *et al* 1999.[44] The trial found that quit rates at 12 months were significantly different between placebo and Bupropion treatment alone groups (16% vs. 30%) but this rate was unaltered by a combination of NRT and Bupropion (30%). However, this study showed a lack of response to NRT treatment alone in this group of smokers as the rate of quitting in the placebo group was the same as the NRT group at 12 months (16%).[44]

The NICE guidance was due for review in March 2005.

3.1.7.1 MHRA Clinical Effectiveness Evidence

Combination therapy of NRT with Bupropion is not covered in the MHRA document.

3.1.7.2 Other Evidence

We identified three RCTs[7,45,46,47,] that have been published since the NICE guidance in 2002 on NRT and bupropion.[43] Details of the RCTs are given in Table 25, Table 26 and Table 27. Two of the trials have shown no difference in abstinence with the use of NRT in the form of a patch and Bupropion.[7,45] These trials were reasonable in size (n=200) and use ITT analysis. Randomisation was well described in one of the trials and both described blinding of patients. The third and most recent trial (currently in press) has shown an improved 12 week abstinence rate with the use of combination NRT (nicotine inhaler) and Bupropion.[46,47] This trial is of high quality and is a large multicentre trial (n=1700). It used a higher dose of Bupropion (300mg) than the other trials (150mg). Continuation of this combination did not alter relapse rates after the initial 12 week period, but the trial data suggests there may be an advantage to using combination therapy in the initial phase of attempting to quit.

The trial by Simon *et al* randomised patients to either Bupropion (n=121) or placebo (n=123) with both groups also receiving nicotine patches and a counselling program.[45] This study was heavily weighted towards a male population with 210 males and 34 females enrolled in the study. The participants were followed up at 1 week, 3 weeks, at the end of treatment at 7 weeks and then at 12 weeks, 6 months and 1 year. The results showed no difference between the two arms at any of the follow-up time points with a slightly greater quit rate with NRT therapy alone at 12 months (24%) compared to NRT with Bupropion (19%), relative risk 0.80 (0.49-1.30). This trial has potentially unusual population as it identified participants from previous smoking cessation studies that were carried out at the investigating centre. These participants have probably tried NRT or other methods in the past and failed. Readiness to quit smoking was also assessed in this group by a counsellor using a previously published 'stages to change model'. Participants were only included in the study if they were deemed to be at the 'contemplation' or 'preparation' stages of attempting to quit smoking.

The trial by Killen *et al* looked at adolescent smokers and randomised smokers aged 15-18 to either nicotine patch with placebo (n=108) or nicotine patch with Bupropion (n=103) and found that nicotine patches in combination with Bupropion had no effect on abstinence at 10 and 26 weeks (23% and 8%) compared to nicotine patches plus placebo (28% and 8%).[7] Smokers were offered a $100 incentive payment for completing the full program. Despite this, the trial had only 29% in the NRT alone group and 22% in the NRT with Bupropion groups reporting using the treatment for 6 weeks. The treatment program was designed to last 8 weeks in the NRT alone group and 9 weeks in the Bupropion combination group. The analysis in this study has used regression modelling to show increased attendance to classes and increased use of NRT was associated with abstinence. When investigating the impact of treatment on craving, the study only included participants who were abstinent at the end of study. This unsurprisingly showed that craving was reduced over time in this group.

The study by Croghan *et al* assessed the use of a combination of NRT in the form of a nicotine inhaler with Bupropion and assessed by initial quit rate (abstinence at 12 weeks) and relapse in smokers over the age of 18.[46,47] The study design had three phases. In phase I the participants were randomised to receive the inhaler (n=566), Bupropion (n=567) or combination (n=567) for the initial 12 weeks. Participants in this trial also

received counselling. Following this phase, participants who were successfully abstinent, were re-randomised to either continue treatment or receive placebo in order to determine whether relapse prevention was achieved with the study drugs. This resulted in a fairly high attrition rate into phase II which the author's suggest is due to participants not wanting to receive placebo. The results showed an improvement in abstinence at 12 weeks in the combination group compared to the NRT or Bupropion groups alone. 14% in the inhaler group, 26% in the Bupropion and 34% in the combination groups achieved abstinence at 12 weeks. The dosage of Bupropion used was 300mg from the onset, which is higher than the 150mg used in the previous trials. Successful quits rates were higher in men than women in the combination therapy arm of this trial 42% vs 30% ($p>0.01$) suggesting a possible treatment preference. However, continuation on the treatment program in phase II did not alter relapse rates at follow-up. Relapse rates in the groups were similar in phase II. The author's mention a potential confounding factor in that the amount of additional medication or counselling the participants used outside of the study was not investigated.

Table 25 Combination NRT+Bupropion: Trial Characteristics

Trial ID	Intervention and control	N *(location; number of centres)*	Patients	Outcomes	Comments
Simon JA *et al* 2004 [45]	Bupropion 150mg/day for first three days. 150mg twice daily after placebo - identical treatment course Nicotine patches: doses altered to number of cigarettes smoked. Maximum dose permitted 21mg/day. Counselling program: 30-60 minutes individual counselling program by trained public health educator. Self-help literature also made available	Bupropion: 121 Placebo: 123 1 Centre: San Francisco, California.	≥20 cigarettes/day Aged over 20. 210 Male only 34 Female Had to be at certain stage of quitting (see comments) Excluded if history of alcohol abuse or if they drink >3 alcoholic drinks/day. Serious psychiatric illness including depression excluded.	Self-reported tobacco abstinence (no smoking for 7 days) confirmed by saliva cotinine measurement (should be <15ng/ml) adjusted for nicotine patch use. Hospital admissions and 1 year mortality Followed up at 1 week, 3 weeks, at the end of treatment at 7 weeks. Then at 12 weeks, 6 months and 1 year.	Potential participants identified from previous smoking cessation studies at the centre. Readiness to quit smoking assessed by counsellor using 'stages to change model' participants only included if at 'contemplation' or 'preparation' stages of quitting
Killen JD *et al* 2004[7]	Bupropion: 150mg/day 9 weeks Nicotine patch: dependent on cigarette use, maximum dose 21mg for 8 weeks Group skills training. Participants met weekly (group size 8) with trained counsellor for 45 mins session.	Bupropion: 103 Placebo: 108 Recruited from 9 High Schools in San Francisco, California.	aged 15-18 145 male, 66 girls Currently smoke >10 cigarettes/day Smoked for at least 6 months >1 failed smoking attempt Had to score >10 points on nicotine dependence test Excluded on co-morbidity, drug-use, risk of seizure, depression.	Change in amount smoked/day (random regression model) Response to treatment (survival analysis time to relapse) Impact on craving (random regression model) Effect on depression Adverse events	Smokers were offered $100 for completing the full program.

Trial ID	Intervention and control	N *(location; number of centres)*	Patients	Outcomes	Comments
Croghan et al 2006[46,47]	Nicotine inhaler (up to 16 cartridges/day) Bupropion (300mg) Combination Counselling (12-18 sessions of 10 minutes) and supportive material (booklets etc) also given. Phase I. 12 weeks: randomisation to treatment Phase II. 40 weeks: re-randomisation. Those abstinent re-randomised to continue treatment or placebo. Those unsuccessful were re-randomised to a new treatment. Phase III. 15 months follow up of relapse rates.	Multi-centre RCT 1700 smokers 566 inhaler 567 Bupropion 567 Combination 19 centres, USA (North Central Cancer Treatment Group).	Eligibility. 18 years or older Minimum 10 cigarettes/day for 12 months. Excluded. Co-morbidity, pregnancy, depression, sensitivity to study drugs.	Primary outcome was biochemically confirmed 7 day smoking abstinence rate at week 12. Air CO of < 8 parts per million or less. Secondary outcomes were relapse rate in phase II, and toxicity severity.	

Table 26 Combination NRT+Bupropion: Trial Quality

Trial ID	Randomisation and concealment	Blinding	Duration, missing data and loss to follow-up	ITT analysis	Comments
Simon JA *et al* 2004[45]	Computer algorithm generated random list of treatment assignments.	Study personnel blinded to treatment assignment Placebo described as identical (further details not given)	7 week treatment program. 5 subjects (2%) died during study period, and 3 (1%) were lost to follow-up.	5 dead subjects excluded and lost to follow-up included in ITT analysis as smokers requiring biochemical or spousal confirmation of quitting.	
Killen JD *et al* 2004[7]	No details of method in paper	Described as double blind Participants were asked to guess their treatment. 30% in placebo and 31% in Bupropion group were correct.	9 weeks treatment 26 weeks follow-up 20% lost to follow-up. Participants not providing biochemical measures were classified as smokers.	Losses counted as smokers. Groups remained as allocation.	Possible compliance issue. 41% of participants reported using the patch on 2 weeks or less. 29% reported using 5 weeks treatment. 44% of participants reported using pill on 2 weeks or less. Only 22% reported using 6 weeks treatment.
Croghan et al 2006[46,47]	Randomisation well described. Stratification used for site, gender, number of cigarettes smoked/day, years smoked.	No mention of blinding. Difficult with inhaler, but assume placebo was matched to study drug in phase II.	Phase I. 1700 smokers Phase II. 941 eligible to continue (837 did). Full details given of all drop-outs. Drop-outs possible high due to chance of receiving placebo in phase II after receiving study drugs in phase I.	ITT analysis using worst case scenario (smoking) for missing subjects.	Study was powered (90%) to detect a clinically significant 10-point difference in abstinence rates. Assuming baseline success of 25%. Fairly large drop-out at the end of phase I.

Table 27 Combination NRT+Bupropion: Trial Results

Trial ID	Smoking cessation	Safety	Other	Comments
Simon JA *et al* 2004[45]	No difference in self-reported quit rates or actual quit rates at 6 and 12 months between the two arms NRT therapy alone at 12 months (24%) compared to NRT with Bupropion (19%), relative risk 0.80 (0.49-1.30 p =0.36) No difference in median quit attempts after 12 months 3.6 Bupropion vs 3.1 placebo (p=0.74)	Rates of hospitalisation similar in two groups 13% Bupropion vs 19% placebo (p=0.22). No details given on reasons for hospitalisation. 60% in Bupropion group and 49% in placebo reported at least 1 adverse event (p=0.07). Insomnia (18%), dry mouth (15%), abnormal dreams (8%). More dry mouth in Bupropion group 22% vs 8% p<0.01 and GI upset 9% vs 1% p<0.01 More headache in placebo group 7% vs 2% p=0.06	No difference in weight gain between study groups 2.92kg Bupropion vs 2.43kg Placebo (p=0.78) Overall successful quitters gained more weight than non-quitters 2.65kg vs 0.41kg (p=0.1)	Per protocol analysis also included with patients who took 80% of their medication (62% in each group) 12 months validated quit rates were 33% in Bupropion group and 27% in placebo (p=0.48)
Killen JD *et al* 2004[7]	Abstinence defined as not smoking in the past 7 days and saliva cotinine level below 20ng/ml. Percentage abstinent at 10 weeks was not different between groups Bupropion 23% vs placebo 28% (p=ns) Regression analysis showed attending more sessions and reported use of patch were associated with abstinence. In contrast amount of cigarettes smoked was not associated with attendance to sessions.	A total of 47 adverse events were reported (25 placebo and 22 in Bupropion group) the most common was nausea. No adverse events were judged to be severe.	The survival analysis showed no difference in time to relapse between the groups Impact of treatment on craving (only participants who were abstinent at end of study used), Unsurprisingly craving was reduced over time in this group. Depression symptom scores also decreased over time	

Trial ID	Smoking cessation	Safety	Other	Comments
Croghan et al 2006[46,47]	Combination therapy achieved higher abstinence rates compared to the single interventions at 12 weeks (34% Vs. 14% inhaler, 26% Bupropion), but relapse rates were unaffected by the type of intervention after the 12 week abstinence period.	No details on adverse event measurement given.	The study also used logistic regression with variables including treatment arm, gender, cigarettes smoked, years smoked, ethnicity, marriage status, BMI, depression score, prior quit attempts, education level. The logistic modelling showed abstinence rates at 12 weeks were more likely in white, older subjects with lower nicotine dependence scores. The least likely to quit were subjects on the inhaler who had not previously tried to stop smoking and had high nicotine dependence.	Men achieved higher abstinence than women on combination therapy 41% vs 30% p=<0.01 but not in other arms. Ethnic minorities showed lower overall abstinence rates in all arms.

3.2 Cost-Effectiveness

It is not possible to undertake any *de novo* modelling within the resources available for this report. We have searched for existing cost-effectiveness models for these population subgroups. Where these are not available, we will consider the implications of population-specific issues and how these might affect the results of a cost-effectiveness analysis, using the existing model previously developed by WMHTAC for NRT in the general population of smokers as a reference point.[48]

3.2.1 Existing Economic Evidence/Models

The tables below give the results of the cost-effectiveness analysis previously published by WMHTAC for NRT and bupropion SR, alone or in combination, compared to brief advice or counselling for smoking cessation. Table 28 gives estimated 12 month quit rates for each intervention and the incremental cost-effectiveness per lifetime quitter. Table 29 and Table 30 consider three different scenarios for cost per life year gained and cost per QALY respectively; a gain of 1, 2 or 3 life years saved per quitter, and a QALY gain of 2.7, 1,35 and 4.05 per quitter (based on an assumed QALY gain of 1.35 per life year saved). Full details of this analysis and the inputs to the model are given in Woolacott et al, 2002.[48]

Table 28 Baseline estimates of the cost (£) per lifetime quitter of smoking-cessation interventions

STRATEGY	Cost per attempt	12 month quit rate	Lifetime quit rate	Cost per lifetime quitter	ICER1	ICER2	ICER3
Standard intervention: brief advice							
Brief advice only	3.53	0.0300	0.018	196	–	–	–
Brief advice + NRT	75.5	0.0550	0.033	2288	4798	–	–
Brief advice + bupropion SR	76.08	0.0705	0.0423	1799	2986	62	–
Brief advice + NRT + bupropion SR	143.91	0.0894	0.0536	2683	3939	3314	5981
Standard intervention: counselling							
Counselling	35.25	0.0900	0.0540	653	–	–	–
Counselling + NRT	103.08	0.1465	0.0879	1173	2001	–	–
Counselling + bupropion SR	103.66	0.1792	0.1075	964	1278	30	–
Counselling + NRT + bupropion SR	171.49	0.2175	0.1305	1314	1781	1606	2952

ICER, cost (£) per lifetime quitter; ICER1, using the brief advice only or counselling only as the reference; ICER2, using the brief advice plus NRT or counselling plus NRT as the reference; ICER3, using the brief advice plus bupropion SR or counselling plus bupropion SR as the reference

Table 29 Costs (£) per life-year saved: baseline estimates and according to different values of life-years saved per quitter

	2.0 LYS/quitter		1.0 LYS/quitter		3.0 LYS/quitter	
	Average	***Incremental***	***Average***	***Incremental***	***Average***	***Incremental***
Standard reference: brief advice						
Advice only	98	–	196	–	65	–
Advice + NRT	1144	2399	2288	4798	763	1599
Advice + bupropion SR	899	1493	1799	2986	600	995
Advice + NRT + bupropion SR	1341	1969	2683	3939	894	1313
Standard reference: counselling						
Counselling alone	326	–	653	–	218	–
Counselling + NRT	586	1000	1173	2001	391	667
Counselling + bupropion SR	482	639	964	1278	321	426
Counselling + NRT + bupropion SR	657	890	1314	1780	438	594

LYS, life-year(s) saved

Table 30 Costs (£) per QALY saved: baseline estimates and according to different values of life-years saved per quitter

	2.7 QALYS/quitter		1.35 QALYS/quitter		4.05 QALYS/ quitter	
	Average	***Incremental***	***Average***	***Incremental***	***Average***	***Incremental***
Standard reference: brief advice						
Advice only	73	–	145	–	48	–
Advice + NRT	847	1777	1695	3554	565	1185
Advice + bupropion SR	666	1106	1332	2212	444	737
Advice + NRT + bupropion SR	994	1459	1987	2918	662	973
Standard reference: counselling						
Counselling alone	242	–	484	–	161	–
Counselling + NRT	434	741	869	1482	290	494
Counselling + bupropion SR	357	473	714	947	238	316
Counselling + NRT + bupropion SR	487	660	973	1319	324	440

3.2.2 Adolescents

No economic analyses were identified specifically addressing the cost-effectiveness of NRT in this population sub-group. There would appear to be no special considerations required in assessing the cost-effectiveness of NRT in adolescents relative to the models which have been applied in adults i.e. the drivers of cost-effectiveness would be similar. However the analysis of the small number of available RCTs does cast genuine doubt on whether the levels of effectiveness of NRT in adolescents are indeed similar to adults. If so the cost-effectiveness of NRT in adolescents does need to be formally assessed. Even with the paucity of the RCT evidence in adolescents, exploratory modelling may be helpful to identify a minimum effect on smoking cessation which would be compatible with NRT being cost-effective. This in turn could help with power calculations in the design of new RCTs.

3.2.3 Pregnant Women

Assisting pregnant women to quit smoking not only leads to health gains for mother and baby but could lead to savings for the NHS due to the effects of smoking on the foetus and the resulting low birth weight which could lead to potentially costly treatment post-birth. Effective programmes to aid smoking cessation in pregnant women could therefore be very cost-effective.

We identified no economic evaluations on the use of NRT in pregnancy.

Whilst the potential for NRT to be a cost-effective intervention for smoking cessation in pregnancy is clear, there is limited evidence on clinical effectiveness and safety to the foetus, as detailed in Section 3.1.3, with which to accurately undertake such analysis.

The ongoing UK based RCT of NRT use in pregnancy seems to be collecting relevant data on effectiveness, safety and costs which should allow an appropriate analysis to be undertaken.

3.2.4 Breastfeeding Women

As with pregnancy, there are benefits to both the mother and baby of giving up smoking and also to the NHS. Thus effective programmes for smoking cessation in breastfeeding women could be very cost-effective.

We identified no economic evaluations of the use of NRT in breast feeding.

Whilst the potential for NRT to be a cost-effective intervention for smoking cessation in breastfeeding mothers is clear there is limited evidence on the clinical effectiveness and safety of NRT to the infant, as detailed in Section 3.1.4, with which to accurately undertake such analysis.

3.2.5 Cardiovascular disease

No economic evaluations of NRT specifically in cardiovascular patients were identified. A cost-effectiveness analysis of treatments to reduce cholesterol levels, blood pressure and smoking for the prevention of coronary heart disease in the Spanish population,[49] concluded that NRT to reduce smoking was by far the most cost-effective of the interventions considered. However, the populations for each analysis were not comparable and the cost-effectiveness of NRT was not considered in a cardiovascular population.

There is no evidence to suggest that NRT is less effective in this population compared to other smokers. In smokers with cardiovascular disease, quitting is associated with substantial benefits in terms of both reduced risk of subsequent cardiovascular events and decreased overall mortality. Reductions in 5 year mortality for quitters from 20% to 12%, 30% to 20% and 31% to 16% have been reported.[28] In a study of patients undergoing coronary artery bypass surgery smoking cessation after surgery reduced the risk of death over 20 year follow-up, with the survival benefit increasing from an estimated 3% at 5 years to 14% at 15 years.[32] This suggests that the benefits in terms of life years gained are at least comparable to, if not greater than, those considered by Woolacott et al,[48] for the general population of smokers. Potential cost savings due to reduction in future cardiovascular events are greater in this high risk population.

Although there is some risk of cardiovascular events due to NRT, these risks are substantially smaller than in those who continue to smoke. NRT can be considered a cost-effective and relatively safer treatment option for cardiovascular patients who cannot quit without assistance.

3.2.6 Combination therapy NRT + NRT

No economic evaluations of combination NRT+NRT were found. However, the total costs of combination NRT+NRT is likely to be similar to the cost of NRT+bupropion and the effectiveness of NRT+NRT appears to be at least as high if not higher than combination treatment with NRT+bupropion. The cost-effectiveness of NRT+NRT may be close to that of a single NRT product, if the higher estimates of relative effectiveness are plausible, and is unlikely to be less cost-effective than NRT+bupropion.

3.2.7 Combination therapy NRT + bupropion (Zyban)

The cost-effectiveness of combination NRT + bupropion was considered by Woolacott et al and these results are summarised above.[48]

4. APPENDICES

Search Strategies

Appendix 1 - Adolescents

Clinical Effectiveness

Source – Cochrane Library 2006 Issue 3

#1 nrt
#2 nicotine next replacement
#3 (nicotine next (gum* or inhaled or inhaler or inhalers or inhalator* or patch* or spray* or tablet* or lozenge* or transdermal*))
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Adolescent explode all trees
#6 (adolescent* or adolescence* or youth* or child or children)
#7 young next person*
#8 young next people
#9 (#5 OR #6 OR #7 OR #8)
#10(#4 AND #9)

Source - Ovid MEDLINE(R) 1966 to August Week 2 2006

1 (nrt or nicotine replacement).mp. (1167)
2 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers$ or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1288)
3 or/1-2 (2186)
4 adolescent/ (1159045)
5 exp child/ (1140229)
6 (adolescent$ or adolescence$ or young people or young person$ or youth$).mp. (1176505)
7 (child or children).mp. (1279386)
8 or/4-7 (1873546)
9 3 and 8 (309)
10 limit 9 to "reviews (optimized)" (52)
11 from 10 keep 1-52 (52)
12 randomized controlled trial.pt. (232368)
13 controlled clinical trial.pt. (74663)
14 randomized controlled trials.sh. (47576)
15 random allocation.sh. (58498)
16 double blind method.sh. (90309)
17 single blind method.sh. (10513)
18 or/12-17 (394278)
19 (animals not human).sh. (4070828)
20 18 not 19 (362564)
21 clinical trial.pt. (455477)
22 exp clinical trials/ (193249)
23 (clin$ adj25 trial$).ti,ab. (128418)
24 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (88778)
25 placebo$.ti,ab. (100005)
26 random$.ti,ab. (365132)
27 placebos.sh. (25578)
28 research design.sh. (45680)
29 or/21-28 (844319)
30 29 not 19 (743540)
31 30 not 20 (394686)

32 20 or 31 (757250)
33 9 and 32 (143)

Source - Ovid EMBASE 1980 to 2006 Week 32

1 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (1294)
2 (nicotine gum or nicotine replacement therapy).sh. (1783)
3 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (2497)
4 or/1-3 (3078)
5 exp adolescent/ (365141)
6 exp adolescence/ (22056)
7 exp child/ (542788)
8 (adolescent$ or adolescence$ or young people or young person$ or youth$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (392599)
9 (child or children).mp. (623047)
10 or/5-9 (866360)
11 4 and 10 (185)
12 limit 11 to "reviews (2 or more terms min difference)" (46)
13 randomized controlled trial/ (108287)
14 exp clinical trial/ (399236)
15 exp controlled study/ (2231444)
16 double blind procedure/ (60747)
17 randomization/ (19895)
18 placebo/ (89020)
19 single blind procedure/ (6029)
20 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp. (2272396)
21 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp. (101937)
22 (placebo$ or matched communities or matched schools or matched populations).mp. (136286)
23 (comparison group$ or control group$).mp. (136874)
24 (clinical trial$ or random$).mp. (640361)
25 (quasiexperimental or quasi experimental or pseudo experimental).mp. (1380)
26 matched pairs.mp. (1877)
27 or/13-26 (2665878)
28 11 and 27 (105)
29 from 28 keep 1-105 (105)

Economic Evaluations

(see also general economic evaluations below)

Source - Ovid MEDLINE(R) 1966 to August Week 2 2006

1 (nrt or nicotine replacement).mp. (1167)
2 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers$ or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1288)
3 or/1-2 (2186)
4 adolescent/ (1159045)
5 exp child/ (1140229)
6 (adolescent$ or adolescence$ or young people or young person$ or youth$).mp. (1176505)
7 (child or children).mp. (1279386)
8 or/4-7 (1873546)
9 3 and 8 (309)
10 economics/ (24393)
11 exp "costs and cost analysis"/ (126542)
12 cost of illness/ (8502)
13 exp health care costs/ (27327)
14 economic value of life/ (4800)
15 exp economics medical/ (10041)
16 exp economics hospital/ (14211)

17 economics pharmaceutical/ (1670)
18 exp "fees and charges"/ (22567)
19 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (234138)
20 (expenditure$ not energy).tw. (9949)
21 (value adj1 money).tw. (11)
22 budget$.tw. (10197)
23 or/10-22 (343820)
24 9 and 23 (25)

Ongoing research

Source – National Research Register 2006 Issue 3

Search terms as for Cochrane Library

Appendix 2 - Pregnancy

Clinical effectiveness

Source – Cochrane Library 2006 Issue 3

#1 nrt
#2 nicotine next replacement
#3 (nicotine next (gum* or inhaled or inhaler or inhalers or inhalator* or patch* or spray* or tablet* or lozenge* or transdermal*))
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Pregnancy explode all trees
#6 pregnant* or pregnancy
#7 (#5 OR #6)
#8 (#4 AND #7)

Source - Ovid MEDLINE(R) 1966 to August Week 2 2006

1 (nrt or nicotine replacement).mp. (1167)
2 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers$ or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1288)
3 or/1-2 (2186)
4 exp pregnancy/ (551560)
5 pregnant$.mp. (81011)
6 or/4-5 (559928)
7 3 and 6 (88)
8 limit 7 to "reviews (optimized)" (37)
9 randomized controlled trial.pt. (232368)
10 controlled clinical trial.pt. (74663)
11 randomized controlled trials.sh. (47576)
12 random allocation.sh. (58498)
13 double blind method.sh. (90309)
14 single blind method.sh. (10513)
15 or/9-14 (394278)
16 (animals not human).sh. (4070828)
17 15 not 16 (362564)
18 clinical trial.pt. (455477)
19 exp clinical trials/ (193249)
20 (clin$ adj25 trial$).ti,ab. (128418)
21 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (88778)
22 placebo$.ti,ab. (100005)
23 random$.ti,ab. (365132)
24 placebos.sh. (25578)
25 research design.sh. (45680)
26 or/18-25 (844319)
27 26 not 16 (743540)
28 27 not 17 (394686)
29 comparative study.sh. (1339476)
30 exp evaluation studies/ (592681)
31 follow up studies.sh. (337060)
32 prospective studies.sh. (217352)
33 (control$ or prospectiv$ or volunteer$).ti,ab. (1741598)
34 or/29-33 (3449098)
35 34 not 16 (2428789)
36 34 not (17 or 28) (2925137)
37 17 or 28 or 36 (3682387)
38 7 and 37 (37)

Source – Ovid EMBASE 1980 to 2006 Week 32

1 (smoking or smokers or smoker or tobacco or nicotine or cigarette$).mp. (126320)
2 (smoking or cigarette smoking or tobacco or nicotine).sh. (85127)
3 smoking cessation.mp. (14003)
4 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (1294)
5 (nicotine gum or nicotine replacement therapy).sh. (1783)
6 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (2497)
7 or/4-6 (3078)
8 exp pregnancy/ (157449)
9 pregnant$.mp. (58430)
10 or/8-9 (178633)
11 7 and 10 (122)
12 limit 11 to "reviews (2 or more terms min difference)" (46)
13 from 12 keep 1-46 (46)
14 randomized controlled trial/ (108287)
15 exp clinical trial/ (399236)
16 exp controlled study/ (2231444)
17 double blind procedure/ (60747)
18 randomization/ (19895)
19 placebo/ (89020)
20 single blind procedure/ (6029)
21 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp. (2272396)
22 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp. (101937)
23 (placebo$ or matched communities or matched schools or matched populations).mp. (136286)
24 (comparison group$ or control group$).mp. (136874)
25 (clinical trial$ or random$).mp. (640361)
26 (quasiexperimental or quasi experimental or pseudo experimental).mp. (1380)
27 matched pairs.mp. (1877)
28 or/14-27 (2665878)
29 11 and 28 (65)

Economic evaluations

(see also general economic evaluations below)

Source - Ovid MEDLINE(R) <1966 to August Week 2 2006>

1 (nrt or nicotine replacement).mp. (1167)
2 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers$ or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1288)
3 or/1-2 (2186)
4 exp pregnancy/ (551560)
5 pregnant$.mp. (81011)
6 or/4-5 (559928)
7 3 and 6 (88)
8 economics/ (24393)
9 exp "costs and cost analysis"/ (126542)
10 cost of illness/ (8502)
11 exp health care costs/ (27327)
12 economic value of life/ (4800)
13 exp economics medical/ (10041)
14 exp economics hospital/ (14211)
15 economics pharmaceutical/ (1670)
16 exp "fees and charges"/ (22567)
17 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (234138)
18 (expenditure$ not energy).tw. (9949)
19 (value adj1 money).tw. (11)

20 budget$.tw. (10197)
21 or/41-53 (343820)
22 7 and 21 (7)

Ongoing research

Source – National Research Register 2006 Issue 3

Search terms as for Cochrane Library

Appendix 3 - Breastfeeding

All studies (clinical effectiveness and economic evaluations)

Source – Cochrane Library 2006 Issue 3

#1 nrt
#2 nicotine next replacement
#3 (nicotine next (gum* or inhaled or inhaler or inhalers or inhalator* or patch* or spray* or tablet* or lozenge* or transdermal*))
#4 (#1 OR #2 OR #3)
#5 breast next feeding
#6 breast next feed
#7 breast next fed
#8 breastfeed* or breastfed
#9 lactat*
#10 lactate or lactating or lactation or lactates
#11 MeSH descriptor Breast Feeding, this term only
#12 MeSH descriptor Lactation, this term only
#13 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
#14 (#4 AND #13)

Source - Ovid MEDLINE(R) 1966 to September Week 1 2006

1 (nrt or nicotine replacement).mp. (1177)
2 (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (1294)
3 or/1-2 (2200)
4 breast feeding.mp. (20357)
5 (breastfed or breast fed or breast feed$ or breastfeed$ or lactate or lactating or lactation or lactates).mp. (142736)
6 or/4-5 (142736)
7 3 and 6 (12)

Source – Ovid EMBASE 1980 to 2006 Week 33

1 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (1296)
2 (nicotine gum or nicotine replacement therapy).sh. (1789)
3 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (2502)
4 or/1-3 (3086)
5 breast feeding.mp. (12895)
6 (breast fed or breastfed or breast feed$ or breastfeed$ or lactate or lactating or lactation or lactates).mp. (82009)
7 or/5-6 (82009)
8 4 and 7 (17)

Ongoing research

Source – National Research Register 2006 Issue 3

Search terms as for Cochrane Library

Appendix 4 - Cardiovascular disease

Clinical Effectiveness

Source – Cochrane Library 2006 Issue 3

#1 nrt
#2 nicotine next replacement
#3 (nicotine next (gum* or inhaled or inhaler or inhalers or inhalator* or patch* or spray* or tablet* or lozenge8 or transdermal*))
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Cardiovascular Diseases explode all trees
#6 cardiovascular next disease*
#7 coronary next heart next disease*
#8 fibrillation
#9 infarction
#10 ischaemia or ischemia or ischaemic or ishemic
#11 stroke*
#12 cardiac disease*
#13 coronary artery disease*
#14 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
#15 (#4 AND #14)

Source - Ovid MEDLINE(R) 1966 to August Week 2 2006

1 (nrt or nicotine replacement).mp. (1167)
2 (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (1288)
3 or/1-2 (2186)
4 exp cardiovascular diseases/ (1296186)
5 cardiovascular disease$.mp. (73695)
6 coronary heart disease$.mp. (26580)
7 fibrillation.mp. (41432)
8 infarction.mp. (166067)
9 (ischaemia or ischemia or ischemic or ischaemic).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (199266)
10 stroke$.mp. (91189)
11 cardiac disease$.mp. (7897)
12 coronary artery disease$.mp. (36748)
13 or/4-12 (1372531)
14 3 and 13 (159)
15 limit 14 to "reviews (optimized)" (59)
16 from 15 keep 1-59 (59)
17 randomized controlled trial.pt. (232368)
18 controlled clinical trial.pt. (74663)
19 randomized controlled trials.sh. (47576)
20 random allocation.sh. (58498)
21 double blind method.sh. (90309)
22 single blind method.sh. (10513)
23 or/17-22 (394278)
24 (animals not human).sh. (4070828)
25 23 not 24 (362564)
26 clinical trial.pt. (455477)
27 exp clinical trials/ (193249)
28 (clin$ adj25 trial$).ti,ab. (128418)
29 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (88778)
30 placebo$.ti,ab. (100005)
31 random$.ti,ab. (365132)
32 placebos.sh. (25578)
33 research design.sh. (45680)

34 or/26-33 (844319)
35 34 not 24 (743540)
36 35 not 25 (394686)
37 25 or 36 (757250)
38 14 and 37 (64)

Ovid EMBASE 1980 to 2006 Week 33

1 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (1296)
2 (nicotine gum or nicotine replacement therapy).sh. (1789)
3 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (2502)
4 or/1-3 (3086)
5 exp Cardiovascular Disease/ (1096297)
6 cardiovascular disease$.mp. (68317)
7 coronary heart disease$.mp. (22029)
8 fibrillation.mp. (35697)
9 infarction.mp. (136770)
10 (ischaemia or ischemia or ischemic or ischaemic).mp. (206990)
11 stroke$.mp. (85681)
12 cardiac disease$.mp. (6661)
13 coronary artery disease$.mp. (55877)
14 or/5-13 (1146907)
15 4 and 14 (497)
16 limit 15 to "reviews (1 term min difference)" (160)
17 randomized controlled trial/ (108481)
18 exp clinical trial/ (400143)
19 exp controlled study/ (2236619)
20 double blind procedure/ (60815)
21 randomization/ (19963)
22 placebo/ (89222)
23 single blind procedure/ (6038)
24 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp. (2277643)
25 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp. (102042)
26 (placebo$ or matched communities or matched schools or matched populations).mp. (136522)
27 (comparison group$ or control group$).mp. (137119)
28 (clinical trial$ or random$).mp. (641620)
29 (quasiexperimental or quasi experimental or pseudo experimental).mp. (1381)
30 matched pairs.mp. (1879)
31 or/17-30 (2671832)
32 15 and 31 (287)

Economic Evaluations

(see also general economic evaluations below)

Ovid MEDLINE(R) 1966 to August Week 2 2006

1 (nrt or nicotine replacement).mp. (1167)
2 (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (1288)
3 or/1-2 (2186)
4 exp cardiovascular diseases/ (1296186)
5 cardiovascular disease$.mp. (73695)
6 coronary heart disease$.mp. (26580)
7 fibrillation.mp. (41432)
8 infarction.mp. (166067)
9 (ischaemia or ischemia or ischemic or ischaemic).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (199266)
10 stroke$.mp. (91189)

11 cardiac disease$.mp. (7897)
12 coronary artery disease$.mp. (36748)
13 or/4-12 (1372531)
14 3 and 13 (159)
15 economics/ (24393)
16 exp "costs and cost analysis"/ (126542)
17 cost of illness/ (8502)
18 exp health care costs/ (27327)
19 economic value of life/ (4800)
20 exp economics medical/ (10041)
21 exp economics hospital/ (14211)
22 economics pharmaceutical/ (1670)
23 exp "fees and charges"/ (22567)
24 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (234138)
25 (expenditure$ not energy).tw. (9949)
26 (value adj1 money).tw. (11)
27 budget$.tw. (10197)
28 or/15-27 (343820)
29 14 and 28 (12)

Ongoing research

Source – National Research Register 2006 Issue 3

Search terms as for Cochrane Library

Appendix 5 - Combination Therapy NRT + NRT

Clinical effectiveness

Source – Cochrane Library 2006 Issue 3

#1 nrt
#2 nicotine next replacement
#3 (nicotine next (gum* or inhaled or inhaler or inhalers or inhalator* or patch* or spray* or tablet* or lozenge* or transdermal*))
#4 (#1 OR #2 OR #3)
#5 concurrently or concurrent or combined or combination:ti,ab
#6 MeSH descriptor Combined Modality Therapy, this term only
#7 (#5 OR #6)
#8 (#4 AND #7)

Source - Ovid MEDLINE(R) 1966 to August Week 2 2006

1 (nrt or nicotine replacement).mp. (1167)
2 (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (1288)
3 or/1-2 (2186)
4 (combined or concurrent or concurrently or combination).mp. (819935)
5 combined modality therapy/ (117119)
6 or/4-5 (819935)
7 3 and 6 (346)
8 limit 7 to "reviews (optimized)" (112)
9 randomized controlled trial.pt. (232368)
10 controlled clinical trial.pt. (74663)
11 randomized controlled trials.sh. (47576)
12 random allocation.sh. (58498)
13 double blind method.sh. (90309)
14 single blind method.sh. (10513)
15 or/9-14 (394278)
16 (animals not human).sh. (4070828)
17 15 not 16 (362564)
18 clinical trial.pt. (455477)
19 exp clinical trials/ (193249)
20 (clin$ adj25 trial$).ti,ab. (128418)
21 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (88778)
22 placebo$.ti,ab. (100005)
23 random$.ti,ab. (365132)
24 placebos.sh. (25578)
25 research design.sh. (45680)
26 or/18-25 (844319)
27 26 not 16 (743540)
28 27 not 17 (394686)
29 17 or 28 (757250)
30 7 and 29 (208)

Source – Ovid EMBASE 1980 to 2006 Week 33

1 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (1296)
2 (nicotine gum or nicotine replacement therapy).sh. (1789)
3 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (2502)
4 or/1-3 (3086)
5 (combined or concurrent or concurrently or combination).mp. (523468)

6 4 and 5 (282)
7 limit 6 to "reviews (2 or more terms min difference)" (98)
8 from 7 keep 1-98 (98)
9 limit 6 to "treatment (1 term min difference)" (138)

Economic evaluations

(see also general economic evaluations below)

Source - Ovid MEDLINE(R) 1966 to August Week 2 2006

1 (nrt or nicotine replacement).mp. (1167)
2 (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (1288)
3 or/1-2 (2186)
4 (combined or concurrent or concurrently or combination).mp. (819935)
5 combined modality therapy/ (117119)
6 or/4-5 (819935)
7 3 and 6 (346)
8 economics/ (24393)
9 exp "costs and cost analysis"/ (126542)
10 cost of illness/ (8502)
11 exp health care costs/ (27327)
12 economic value of life/ (4800)
13 exp economics medical/ (10041)
14 exp economics hospital/ (14211)
15 economics pharmaceutical/ (1670)
16 exp "fees and charges"/ (22567)
17 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (234138)
18 (expenditure$ not energy).tw. (9949)
19 (value adj1 money).tw. (11)
20 budget$.tw. (10197)
21 or/8-20 (343820)
22 7 and 21 (23)

Ongoing research

Source – National Research Register 2006 Issue 3

Search terms as for Cochrane Library

Appendix 6 - Combination Therapy NRT + Bupropion

Clinical Effectiveness

Source – Cochrane Library 2006 Issue 3

#1 nrt
#2 nicotine next replacement
#3 (nicotine next (gum* or inhaled or inhaler or inhalers* or inhalator* or patch* or spray* or tablet* or lozenge* or transdermal*))
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Bupropion, this term only
#6 zyban or bupropion or buproprion or amfebutamone or wellbutrin
#7 (#5 OR #6)
#8 (#4 AND #7)

Source - Ovid MEDLINE(R) 1966 to August Week 2 2006

1 (nrt or nicotine replacement).mp. (1167)
2 (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (1288)
3 or/1-2 (2186)
4 bupropion/ (1285)
5 (zyban or amfebutamone or bupropion or buproprion or wellbutrin).mp. (1760)
6 or/4-5 (1760)
7 3 and 6 (260)
8 limit 7 to "reviews (specificity)" (28)
9 from 8 keep 1-28 (28)
10 randomized controlled trial.pt. (232368)
11 controlled clinical trial.pt. (74663)
12 randomized controlled trials.sh. (47576)
13 random allocation.sh. (58498)
14 double blind method.sh. (90309)
15 single blind method.sh. (10513)
16 or/10-15 (394278)
17 (animals not human).sh. (4070828)
18 16 not 17 (362564)
19 clinical trial.pt. (455477)
20 exp clinical trials/ (193249)
21 (clin$ adj25 trial$).ti,ab. (128418)
22 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (88778)
23 placebo$.ti,ab. (100005)
24 random$.ti,ab. (365132)
25 placebos.sh. (25578)
26 research design.sh. (45680)
27 or/19-26 (844319)
28 27 not 17 (743540)
29 28 not 18 (394686)
30 18 or 29 (757250)
31 7 and 30 (109)

Source – Ovid EMBASE 1980 to 2006 Week 32

1 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (1294)
2 (nicotine gum or nicotine replacement therapy).sh. (1783)
3 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (2497)
4 or/1-3 (3078)
5 (zyban or amfebutamone or bupropion or buproprion or wellbutrin).mp. (5877)

6 4 and 5 (623)
7 limit 6 to "reviews (2 or more terms high specificity)" (21)
8 from 7 keep 1-21 (21)
9 randomized controlled trial/ (108287)
10 exp clinical trial/ (399236)
11 exp controlled study/ (2231444)
12 double blind procedure/ (60747)
13 randomization/ (19895)
14 placebo/ (89020)
15 single blind procedure/ (6029)
16 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp. (2272396)
17 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp. (101937)
18 (placebo$ or matched communities or matched schools or matched populations).mp. (136286)
19 (comparison group$ or control group$).mp. (136874)
20 (clinical trial$ or random$).mp. (640361)
21 (quasiexperimental or quasi experimental or pseudo experimental).mp. (1380)
22 matched pairs.mp. (1877)
23 or/9-22 (2665878)
24 limit 6 to "treatment (2 or more terms min difference)" (180)

Economic evaluations

(see also general economic evaluations below)

Source - Ovid MEDLINE(R) 1966 to August Week 2 2006

1 (nrt or nicotine replacement).mp. (1167)
2 (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (1288)
3 or/1-2 (2186)
4 bupropion/ (1285)
5 (zyban or amfebutamone or bupropion or buproprion or wellbutrin).mp. (1760)
6 or/4-5 (1760)
7 3 and 6 (260)
8 economics/ (24393)
9 exp "costs and cost analysis"/ (126542)
10 cost of illness/ (8502)
11 exp health care costs/ (27327)
12 economic value of life/ (4800)
13 exp economics medical/ (10041)
14 exp economics hospital/ (14211)
15 economics pharmaceutical/ (1670)
16 exp "fees and charges"/ (22567)
17 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (234138)
18 (expenditure$ not energy).tw. (9949)
19 (value adj1 money).tw. (11)
20 budget$.tw. (10197)
21 or/8-20 (343820)
22 7 and 21 (45)

Ongoing research

Source – National Research Register 2006 Issue 3

Search terms as for Cochrane Library

Appendix 7 - General Economic and Decision Analytic Model Searches

Source – HEED August 2006

A series of searches were done which incorporated the following terms: NRT OR nicotine replacement OR nicotine gum OR nicotine inhaler(s) OR inhaled nicotine OR nicotine inhalator(s) OR nicotine patch (es) OR nicotine spray (s) OR noctine lozenge(s) OR nicotine tablet(s) OR transdermal nicotine

Source - Ovid MEDLINE(R) 1966 to September Week 1 2006

1 (nrt or nicotine replacement).mp. (1177)
2 (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalers or inhalator$ or patch$ or spray$ or tablet$ or lozenge$ or transdermal$)).mp. (1294)
3 or/1-2 (2200)
4 decision support techniques/ (5939)
5 markov.mp. (5169)
6 exp models economic/ (4939)
7 decision analysis.mp. (2268)
8 cost benefit analysis/ (39581)
9 economic model$.mp. (696)
10 monte carlo method$.mp. (9449)
11 monte carlo.mp. (11965)
12 exp decision theory/ (6453)
13 (decision$ adj2 (tree$ or analy$ or model$)).mp. (10756)
14 or/4-13 (70344)
15 economics/ (24405)
16 exp "costs and cost analysis"/ (127296)
17 cost of illness/ (8586)
18 exp health care costs/ (27572)
19 economic value of life/ (4903)
20 exp economics medical/ (10048)
21 exp economics hospital/ (14283)
22 economics pharmaceutical/ (1679)
23 exp "fees and charges"/ (22637)
24 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (236102)
25 (expenditure$ not energy).tw. (10005)
26 (value adj1 money).tw. (11)
27 budget$.tw. (10257)
28 or/15-27 (346257)
29 14 or 28 (371750)
30 3 and 29 (163)

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Archived ARIF Request

Photodynamic Therapy
Age-Related Macular Degeneration (AMD/ARMD)
Sub-foveal Predominantly Classic Choroidal Neovascularisation (CNV)

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in April 1999 and Update in 2004.

The Problem Submitted for ARIF to Advise Upon:

Is photodynamic therapy an effective treatment for wet age-related macular degeneration with predominantly classic CNV?

Photodynamic therapy (PDT) is a newly developed type of treatment combining:

- injection of a light-sensitive dye which concentrates in areas of “abnormality”
- low power laser

The rationale is that abnormal cells can be destroyed without damage to nearby normal cells.

PDT has applications in a number of areas, particularly cancer. However, requests to ARIF have focused on the use of this technology in treatment of eye disease. In this application the only currently commercially available light sensitive dye is verteporfin.

Age-related macular degeneration is the most common cause of blindness in older people in the UK. It has several features but the one which is most responsible for loss of sight is choroidal neovascularisation (new fragile blood vessels which leak blood and fluid, which in turn cause scarring). There are two types of CNV – classic and occult. Classic lesions tend to lead to more rapid deterioration in sight.

Reviews Identified

- Wormald R et al. Photodynamic therapy for neovascular age-related macular degeneration (Cochrane Review): In: The Cochrane Library, Issue 4, 2002. Oxford: Update Software
- Meads C et al. Clinical effectiveness and cost utility of photodynamic therapy for wet age-related macular degeneration. Birmingham: West Midlands Health Technology Assessment Group, University of Birmingham, January 2002.

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Comments

This topic is the subject of NICE guidance. Definitive population level decisions should await the publication of this.

The reviews of research, which are both systematic in approach, indicate that PDT is effective in predominantly classic wet AMD, particularly in reducing loss of sight (visual activity and contrast sensitivity). Uncertainty appears to centre around the size of benefits (particularly do sub-group analyses used inflate these) and whether these are worth the additional costs of treatment estimated to be £6,000 to £7,000 per person treated over a two-year period (2000 prices).

Request Carried Out: April 1999

Updated: January 2004 - NICE has issued Guidance on this topic.

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Archived ARIF Request

Photodynamic Therapy
Age-Related Macular Degeneration (AMD/ARMD)
Sub-foveal Occult Choroidal Neovascularisation (CNV)

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The Problem Submitted for ARIF to Advise Upon:

Is photodynamic therapy an effective treatment for wet age-related macular degeneration with occult CNV?

Photodynamic therapy (PDT) is a newly developed type of treatment combining

- injection of a light-sensitive dye which concentrates in areas of “abnormality”
- low power laser

The rationale is that abnormal cells can be destroyed without damage to nearby normal cells.

PDT has applications in a number of areas, particularly cancer. However, requests to ARIF have focused on the use of this technology in treatment of eye disease. In this application the only currently commercially available light sensitive dye is verteporfin.

Age-related macular degeneration is the most common cause of blindness in older people in the UK. It has several features but the one which is most responsible for loss of sight is choroidal neovascularisation (new fragile blood vessels which leak blood and fluid, which in turn cause scarring). There are two types of CNV – classic and occult. Classic lesions tend to lead to more rapid deterioration in sight.

Reviews Identified

None.

Trials Identified

- Verteporfin in Photodynamic Therapy (VIP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularisation in pathological myopia with verteporfin. Ophthalmology 2001;108:841-852.

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Comments

We have confirmed that although AMD with occult CNV is a recently licensed indication, this use of PDT will not be covered by NICE guidance.

There are no systematic reviews. There appears to be only one published RCT which was generally well conducted. This shows that verteporfin PDT reduces the loss of sight and contrast sensitivity, relative to placebo PDT in a statistically significant manner.

However, like PDT for predominantly classic AMD the key issue would seem to be whether benefits are worth the costs. As benefit in relative terms seems to be similar in occult and predominantly classic, as are the costs, some indication of whether benefits are worth costs will be obtained from the final NICE guidance on predominantly classic AMD. (See related request - Age-Related Macular Degeneration (AMD/ARMD)/Sub-foveal Predominantly Classic Choroidal Neovascularisation (CNV)/Photodynamic Therapy)

Request Carried Out: January 2003

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Archived ARIF Request

Antiretroviral Agents (Combination Therapy) AIDS/HIV

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the evidence base of clinical guidelines on the use of antiretroviral agents e.g. zidovudine and protease inhibitors, particularly their use in combination? ARIF was asked to contribute to a West Midlands working group on HIV/AIDS care whose aim in December 1996, was to decide the priorities for expenditure in the forthcoming financial year.

Reviews Identified

- Carpenter CC, Fischi MA , Hammer SM et al. Antiretroviral therapy for HIV infection in 1996. Recommendations of an international panel. Journal of the American Medical Association 1996;276:146-154

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Comments

The review above was not systematic in approach, but was the best review/set of guidelines available at the time the group met.

Regional guidelines were developed on the basis of this review and other research material eg Saag MS et al. HIV viral load markers in clinical practice. Nature Medicine 1996;2(6):625-629.

However, it was impossible to make the local guidelines truly evidence based because:

- The review in question did not set out in detail the method by which the literature was ascertained or summarised.
- The review relied, particularly for the effects of combination therapy involving protease inhibitors, on material which had been presented in conferences alone and was not therefore published and available for detailed scrutiny.

The available material does make clear that the new antiretroviral therapies, although expensive, alone or in combination with more established drugs do have enormous potential to improve health of those suffering form HIV/AIDS. However, decisions on the rational commissioning of these therapies in future

years will be even more hampered by the lack of reliable summaries of the available research than was the case for our working group because:

- The volume of research literature is expanding exponentially
- New drugs are being developed
- Consequently the number of potential combination therapies is greatly increasing
- The interpretation of benefit is becoming more difficult with the greater use of HIV viral load, alone, as the primary outcome in new randomised trials

This point was fed back to the National NHS HTA Programme Co-ordinating Centre; we were assured that systematic reviews of antiretroviral therapies are in progress.

This is an area particularly prone to need for regular updating as new information is continually becoming available.

Request Carried Out: December 1996

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Archived ARIF Request

Health Promotion
Brief Interventions
Primary Care
Alcohol Consumption

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in July 2005.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to reducing alcohol consumption?

The evidence supporting brief advice on giving up smoking provides the benchmark for an effective brief health promotion intervention par excellence - Lancaster T, Stead LF. Physician advice for smoking cessation. The Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No: CD000165.pub2. DOI: 10.1002/14651858.CD000165.pub2.

Reviews Identified

- Bertholet N, Daeppen J-B, Wietlisbach V, Fleming M, Burnand B. Reduction of Alcohol Consumption by Brief Alcohol Intervention in Primary Care. Arch Intern Med. 2005;165:986-995

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Comments

Bertholet et al (2005) evaluated the efficacy of brief alcohol interventions aimed at reducing long-term alcohol use and related harm in individuals attending primary care facilities but not seeking help for alcohol related problems. A formal appraisal of the review indicated it was clearly focused and well-executed.

The systematic review and meta-analysis identified 19 trials conducted between 1987 and 2002 involving 5,639 participants. A meta-analysis of 10 of these trials with sufficient data to allow meta-analysis indicated brief alcohol interventions are effective in reducing alcohol consumption at 6 and 12 months with a mean difference of –38g ethanol/week (95% CI: -51 to –24g/week) in favour of the intervention group (1 unit alcohol = 8g).

In conclusion the provision of brief advice in a primary care setting has been shown to reduce alcohol consumption.

Request Carried Out: July 2005

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Archived ARIF Request

Alcohol Counselling Domestic Violence

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of brief interventions including alcohol counselling services in reducing the frequency and severity of domestic violence?

In particular this request was on the effectiveness of such services on male perpetrators of domestic violence who seek help.

Reviews Identified

- Dinh-Zarr T, DiGiuseppi C, Heitman E, and Roberts I. Interventions for preventing injuries in problem drinkers (Cochrane review). In: the Cochrane Library, Issue 2, 2002. Oxford: Update Software
- Moyer A. Finney JW. Swearingen CE. Vergun P. Brief interventions for alcohol problems: a meta-analytic review of controlled investigations in treatment-seeking and non-treatment-seeking populations. Addiction. 97(3):279-92, 2002
- Moyer A. Finney JW. Swearingen CE. Vergun P. Brief interventions for alcohol problems: a meta-analytic review of controlled investigations in treatment-seeking and non-treatment-seeking populations. Addiction. 97(3):279-92, 2002

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Comments

There is a paucity of information evaluating brief interventions and/or alcohol counselling to reduce the incidence of domestic violence. We identified one review (Dinh-Zarr et al) that assessed interventions to reduce injuries in problem drinkers. Included in this review one small trial that examined reductions in domestic violence, which suggested that interventions aimed at partners of male perpetrators of domestic violence may reduce the incidence of domestic violence. However this trial was too small for the review to draw any meaningful conclusions.

We also identified one systematic review evaluating brief interventions to reduce alcohol consumption. In the systematic review by Moyer et al (2002) for the evaluation of treatment-seeking patients, there were few differences in alcohol consumption and other alcohol-related outcomes between the patients

who received brief intervention and patients who received extended treatments. Drawing conclusions from these reviews is difficult due to the lack of detail around composition of both the brief and extended intervention.

ARIF has undertaken two related requests on Domestic Violence
How effective is routine screening for domestic violence by healthcare professionals?
What is the effectiveness of counselling for the victims of domestic violence?

Request Carried Out: September 2002

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Archived ARIF Request

Allergies

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The Problem Submitted for ARIF to Advise Upon:

What is the strength of the research evidence for the diagnosis and treatment of multiple allergies by provocation-neutralisation techniques (The Miller technique) and controlled environments?

Reviews Identified

None identified. There are a number of reviews (listed below) claiming to show that diagnosis and treatment of multiple allergies is effective or ineffective. In either case the reviews have been conducted in ways which are prone to bias. In particular, review authors predisposed to such treatments would not have guarded against a tendency to preferentially select those studies which prove their point and vice versa.

- Kay AB, Lessof MH. Allergy: Conventional and Alternative Concepts.London: Royal College of Physicians, 1992. Ppvii; 44.
- Position Paper on Allergen Immunotherapy: Report of a BSACI Working Party January - October 1992. Clinical and Experimental Allergy, 1993. 23(Supplement 3, August): 1-44
- American College of Physicians. Position Paper: Clinical Ecology. Annals of Internal Medicine 1989; 111: 168-178
- Good Allergy Practice: Standards of Care for Providers and Purchasers of Allergy Services within the National Health Service. London: Royal College of Physicians and Royal College of Pathologist, 1994. pp20
- Effective Allergy Practice: A Document on Standards of Care and Management for the Allergy Patient. Southampton: British Society for Allergy and Environmental Medicine with The British Society for Nutritional Medicine, 1994.

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Comments

Decisions in relation to providing "alternative" allergy services should take into account that there is neither compelling evidence for their effectiveness nor against them. A decision to err on the side of caution and not make available these treatments, which are in theory not without risk, is compatible with the available summaries of research evidence.

Request Carried Out: April 1996

Updated: December 1999 - Original searches were re-run but no additional reviews or other material was identified that would change our original conclusions.

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Archived ARIF Request

Alpha Agonists
Common Cold

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The Problem Submitted for ARIF to Advise Upon:

What treatments have been shown to be effective in the treatment of the common cold?

Question Reformulated

Due to the breadth of this question, we focused our attention on those interventions for which there was a substantial body of evidence on their effectiveness, and on those that appeared to have a positive effect. Interventions excluded because of a lack of research evidence included mast cell stabilisers, iodine, guaifenesin, glucocorticoids, interferon and other antiviral drugs. Antibiotics were also excluded as a Cochrane review provided reliable evidence of no effect.

Reviews Identified

None.

Trials Identified

- Akerlund A et al. Nasal decongestant effect of oxymetazoline in the common cold: and objective dose-response study in 106 patients. The Journal of Laryngology and Otology 1989;103:743-746
- Ferguson EA and Eccles R. Changes in nasal nitric oxide concentration associated with symptoms of common cold and treatment with a topical nasal decongestant. Acta Otolaryngol 1997; 117: 614-617

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Comments

The two trials cited are good sized, reasonably well-conducted randomised controlled trials of oxymetazoline versus placebo in participants with natural colds. Both demonstrated objective differences in nasal patency favouring the decongestant, with minimal side effects, but significant effects in other symptoms did not occur. Neither trial was of sufficiently long duration to gauge the duration of benefits, and the occurrence of tolerance and rebound congestion, which is generally regarded as an important adverse effect of topical alpha agonists.

Additional information relevant to this request is available in the other requests on the Common Cold

entitled Zinc; Vitamin C; Antihistamines; Anticholinergics; "Over-the-Counter" Remedies; Echinacea; NSAIDs; Steam Inhalation.

Request Carried Out: July 1999

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Archived ARIF Request

Donepezil (Aricept)
Dementia - Alzheimer's Disease

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the evidence on the effects/effectiveness of donepezil (Aricept)?

ARIF contributed to the work of a West Midlands based Anti Dementia Drugs Working Party. (For report produced by this group contact Prof R Griffiths / Dr Bruce Court, West Midlands Office of NHSE, Bartholomew House, 142 Hagley Road, BIRMINGHAM B16 9PA)

Reviews Identified

- Stein K. Donepezil in the treatment of mild to moderate senile dementia of the Alzheimer disease type (SDAT). Winchester: Wessex Institute for Health Research and Development, 1997. (DEC Report No. 69)

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Comments

The West Midlands group concluded:

"The evidence for its [donepezil's] effectiveness is as yet very limited and as such suggests a relatively minor effect on the illness. The drug appears to prevent some deterioration in cognitive function in the small number of early Alzheimers cases on which it has been tried, but no effect was shown on other indications such as activities of daily living, nursing and care requirements or impact on relatives and informal carers."

ARIF would concur with this summary of the available evidence and would add that a further problem is that the effects of donepezil where Alzheimers coexists with other conditions is important and undetermined.

The report of the West Midlands group suggests a strategy for the introduction of donepezil. The main thrust of this is that the introduction should only occur in the context of further rigorous evaluation.

We noted in passing that a significant number of Cochrane Reviews on other aspects of the drug treatment of dementia have been completed (tacrine) or are in progress.

This is an area prone to need for regular updating as new information is continually becoming available, particularly because research is in progress on donepezil and other drugs eg exelon, mirameline, xanomeline are becoming available.

Request Carried Out: May 1997

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Archived ARIF Request

Donepezil
Alzheimer's Disease

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Is there any new evidence of benefits for people with Alzheimer's Disease, from treatment with Donepezil, since the West Midlands Regional Anti-Dementia Drugs Working Party Recommendations and the establishment of the AD2000 trial? What are the current indications for treatment with Donepezil?

Question Reformulated:

Based on our overall reading of the request we set out to address three key questions:

- What was the nature of the evidence base for Donepezil pre-1997 and what did it say?
- Is there any new evidence on the benefits of /indications for the treatment of Alzheimer's Disease with Donepezil, that has been published since 1997?
- What are the current indications for treatment with Donepezil?

Reviews Identified

- Wolfson C, Moride Y, Perrault A et al. Drug treatments for Alzheimer's Disease. I. A comparative analysis of clinical trials. Ottawa: Canadian Co-ordinating Office for Health Technology Assessment (CCOHTA); 2000

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Comments

The pre-1997 evidence base consisted of three randomised controlled trials and several reviews of those. Most concluded that Donepezil had a beneficial effect on the symptoms of Alzheimer's, but not on the underlying disease process. Modest benefits in cognitive function were observed, but there was little or no evidence of benefit in terms of clinical functioning and patient or carer quality of life. Treatment resulted in a small initial improvement followed by a subsequent decline at the usual rate, effectively resulting in a delayed disease progression of around 3-6 months. All the reviews were unanimous in their assertion that more research was urgently required.

Our searches identified a number of new reviews, the most up-to-date and comprehensive of which is that by the CCOHTA. This review incorporates all of the pre-existing research and most of the recent

trials. It is a well-conducted and reliable review. It is, however, a broad overview of all drug treatments for Alzheimer's Disease and it does not cover any specific treatments in depth (sections 3.2 and 4.1 cover Donepezil). It concludes that Donepezil is well tolerated and has moderate effects on cognition and global clinical status, but that the clinical significance of these benefits is unclear.

It does appear as though certain subgroups of patients will experience greater benefits than others, and that some might not benefit at all. However, we were unable to identify any clear evidence at this point in time on exactly who those subgroups of patients are.

This is an area prone to need for regular updating as new information is continually becoming available.

Request Carried Out: June 2000

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Archived ARIF Request

Galantamine
Alzheimer's Disease

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of galantamine in the treatment of Alzheimer's disease (AD)?

Reviews Identified

No systematic reviews identified.

A NICE report on treatments for dementia which will include a section on galantamine is due for publication in 2001.

Trials Identified

- Raskind MA, Peskind ER, Wessel T. Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension. Neurology 2000;54(12):2261-2268
- Tariot PN, Solomon PR, Morris JC. A 5-month, randomized, placebo-controlled trial of galantamine in AD. Neurology 2000; 54(12): 2269-2276

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Comments

The two RCTs (Raskind et al 2000, Tariot et al 2000) address the efficacy and safety of galantamine for mild to moderate Alzheimer's disease. Both were multicentred studies undertaken in the USA. The trials possess similarities in design and conduct and are generally well conducted and reported. The duration of the randomised phase of each trial was 5 and 6 months respectively and both contained multiple treatment arms that employed different doses of galantamine. Both trials reported small but significant beneficial effects with higher doses of galantamine (> 16mg/day) on cognitive function and the clinical impression of patient status when compared to placebo. In both studies adverse events were more common in the treatment arms than placebo. The events were described by the authors as mild to moderate in severity and were predominantly gastrointestinal.

From the limited evidence of the relatively short duration studies above, it appears that galantamine could potentially be a promising intervention for AD. However, further studies are required to confirm the impact on patient function and to explore long-term benefits and safety.

NICE guidance on the use of cholinesterase inhibitors (which includes galantamine) for Alzheimer's disease is due to be published in the near future. No final commissioning decision on use of galantamine or cholinesterase inhibitors for AD should be made until this guidance is available.

This is an area prone to need for regular updating as new information is continually becoming available.

Request Carried Out: October 2000

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Archived ARIF Request

Exercise ECG Angina

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in August 1996.

The Problem Submitted for ARIF to Advise Upon:

What are the implications of implementing the recommendation from the North of England Guideline Development Group (BMJ 1996; 312: 827-832) that all patients with angina should have an exercise ECG test?

Question Reformulated:
In patients with clinically certain angina, which patients would most benefit from exercise ECGs to predict benefit from further intervention such as Coronary Artery Bypass grafting or angioplasty?

Reviews Identified

- Open access to exercise electrocardiograms for patients with angina pectoris. Winchester: Development and Evaluation Committee, Wessex Institute of Public Health Medicine, 1994. pp13

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Comments

Although the review identified is not systematic, it does bring together and consider some of the important evidence on the diagnostic accuracy of exercise ECGs and is thus at the least a useful background document.

Particularly useful is the introduction of the idea that rather than being rigid about assigning populations who might benefit, eg new cases, a better approach might be to make referral decisions on the basis of the likelihood that a positive exercise test will change the estimate of odds of significant disease before and after the test. In general the DEC Report suggests that where the symptoms are severe and the odds of surgically remediable disease high, exercise ECG has little to add.

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Coronary artery bypass grafting (CABG) and other interventional cardiological procedures (PTCA)
Angina/Myocardial Infarction (MI) - Ischaemic heart disease (IHD)

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What are the effects/effectiveness of CABG and other interventional cardiological procedures ie PTCA, specifically in relationship to prioritisation of those procedures?

Question Reformulated

The specific targets for this request were:

- to identify systematic reviews of the effects of CABG and other interventional cardiological procedures
- to assess the evidence base of the New Zealand priority criteria project, which included CABG among the interventions it considered

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Reviews Identified

General

- Gunnell D et al. The invasive management of angina: issues for consumers and commissioners. Journal of Epidemiology and Community Health 1995;49:335-343

Effects of CABG vs Standard Medical Therapy

- Yusuf S et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Triallists Collaboration. Lancet 1994;344:563-70

Effects of PCTA vs Standard Medical Therapy

None identified.

Effects of CABG vs PCTA

- Sim I et al. A meta-analysis of randomized trials comparing coronary artery bypass grafting with percutaneous transluminal coronary angioplasty in multivessel coronary artery disease. American

Journal of Cardiology 1995;76:1025-1029

Other LIterature Identified

- Hadorn DC, Holmes AC. The New Zealand priority criteria project. Part I: Overview. British Medical Journal 1997;314:131-4
- Hadorn DC, Holmes AC. The New Zealand priority criteria project. Part II: Coronary artery bypass graft surgery. British Medical Journal 1997;314:135-8

Additional information provided in relation to the two articles above, available on BMJ web-site

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Comments

The reviews identified, all of which are systematic in approach, provide a good evidence-base for purchasing decisions. However, the relative roles of PTCA and CABG are not completely clarified, particularly for acute manifestations of IHD and particularly in the light of new antiplatelet agents such as abciximab (intra-venous glycoprotein IIb/IIIa receptor (GPIIb/IIIa) inhibitor).

Other important issues needing to be considered are:

- Use of intracoronary stents
- Diagnosis of surgically remediable IHD - see related ARIF request on exercise ECG in angina

The evidence base of the priority list for CABG given is deceptively secure, being founded on a systematic review, quoted above, by Yusuf S et al and other research. However there are problems in how the evidence has been translated into the priorities, which becomes much clearer on reading the additional information provided by the authors.

Thus, in ARIF's view:

- The draft priority criteria were generally based on research evidence
- The link between the research evidence and the final priority criteria has been distorted by the way in which the criteria were developed
- The priority criteria contain some anomalies which may create problems if they were operationalised eg a patient's priority will be reduced if they do not have an exercise ECG, which may not actually be necessary

This is an area particularly prone to need for regular updating as new information is continually becoming available.

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Archived ARIF Request

Angiotensin II Receptor Antagonists Blood Pressure Lowering

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in July 2005.

The Problem Submitted for ARIF to Advise Upon:

What is the relative effectiveness of the different angiotensin II receptor antagonists (AIIRAs) in lowering blood pressure?

Reviews Identified

- Conlin PR, Spence JD, Williams B, Ribeiro AB, Saito I, Benedict C, Bunt AMG. Angiotensin II Antagonists for Hypertension: Are There Differences in Efficacy? American Journal of Hypertension. 2000; 13: 418-26

Additional Papers

- Burnier M. Angiotensin II Type 1 Receptor Blockers. Circulation. 2001; 103: 904-12
- UKMi Therapeutic Class Summaries. Angiotensin 2 Receptor Antagonists: Evaluated information for the NHS UK Medicines Information Pharmacists Group. March 2003 http://www.ukmi.nhs.uk/NewMaterial/html/docs/TCSA2RA1111.pdf
- Hobbs FDR, Irwin P, Rubner J. Evidence-Based Treatment of Hypertension: What's the Role of Angiotensin II Receptor Blockers? Br J Cardiol. 2005; 12 (1): 65-70

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Comments

One systematic review (Conlin et al, 2000) assessing the effectiveness of the angiotensin II receptor antagonists (AIIRAs), losartan, valsartan, irbesartan and candesartan, in reducing blood pressure was identified. The review contains a meta-analysis of 43 randomised controlled trials (RCT's) involving 11,281 patients with mild to moderate hypertension. In summary, the results of the meta-analysis indicate that reductions in diastolic and systolic blood pressure are comparable for the four AIIRAs assessed.

Conlin et al's generally well conducted review continues to be cited as the main piece of evidence for the relative effectiveness of the different AIIRAs. However, as it only includes RCTs published up to 1998, it is now somewhat out of date. Since 1998 three further AIIRAs have come on the market (telmisartan, eprosartan & olmesartan) and several papers (Burnier, 2001; UK Medicines Information

Pharmacists Group, 2003; Hobbs et al, 2005) have highlighted more recently conducted head-to-head comparisons of AIIRA's which indicate the newer drugs may be more effective.

In conclusion, the available evidence seems insufficient to either confirm or refute differences in blood pressure lowering efficacy amongst the available AIIRA's within the class. A new systematic review of all available evidence for the seven AIIRA's on the market (losartan, valsartan, irbesartan, candesartan, telmisartan, eprosartan & olmesartan) would therefore be beneficial.

Request Carried Out: July 2005

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In-patient versus intensive out-patient (community) intervention for anorexia nervosa

Synopsis

Question:	1. How does the effectiveness of in-patient treatment compare to intensive out-patient (community based) treatment for patients with severe or moderate anorexia nervosa? 2. What type of out-patient treatment is most effective?
Evidence Identified:	Question 1: Gowers S, Clark A, Roberts C, Griffiths A, Edwards V, Bryan C, et al. Clinical effectiveness of treatments for anorexia nervosa in adolescents. British Journal of Psychiatry 2007; 191:427-435. Crisp AH, Norton K, Gowers S, Halek C, Bowyer C, Yeldham D, et al. A controlled study of the effect of therapies aimed at adolescent and family psychopathology in anorexia nervosa. British Journal of Psychiatry 1991;159:325-333. Question 2: Fisher CA, Hetrick SE, Rushford N. Family therapy for anorexia nervosa. Family therapy for anorexia nervosa Cochrane Database of Systematic Reviews 2010 (4): CD004780 Hay P, Bacaltchuk J, Claudino A, Ben-Tovim D, Yong PY et al. Individual psychotherapy in the outpatient treatment of adults with anorexia nervosa. Cochrane Database of Systematic Reviews 2003;(4):CD003909.
Comments:	1. There is limited evidence to suggest that out-patient treatment is similarly effective to in-patient treatment in the short-term. 2. There is limited evidence to suggest that family therapy may be more effective compared to standard out-patient treatment in the short term; there is no evidence to suggest an advantage of family therapy over other psychological interventions. There is limited evidence to suggest that a specific psychotherapy may be more effective than no treatment or treatment as usual. There is insufficient evidence to determine the relative effectiveness of different psychological therapies. There is a need for a large, well-conducted RCT in this area.
Date Completed:	June 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

In-patient versus intensive out-patient (community) intervention for anorexia nervosa

Request completed: June 2010

Question

1. How does the effectiveness of in-patient treatment compare to intensive out-patient (community based) treatment for patients with severe or moderate anorexia nervosa (AN)?

2. What type of out-patient treatment is most effective?

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol www.arif.bham.ac.uk/strategy.shtml. Text and index terms were used to represent the population and the intervention. Sources were searched from their inception to May 2010. No language restriction was applied to the searches. The MEDLINE search can be found in Appendix A. The following inclusion criteria were used for study search and selection:

Population	Patients with severe or moderate anorexia nervosa (severe defined as BMI of 15 or less; or as defined by the authors)
Intervention	Any type of out-patient intervention, including more or less intensive interventions (as defined by the authors)
Comparator	Any type of in-patient intervention or different out-patient intervention
Study design	Systematic reviews, health technology assessments and randomised controlled trials (RCTs)

Results

Full search results can be found in Appendix B

3. Comparison of in-patient versus out-patient treatment

One systematic review[1] was identified, which directly addressed the question of in-patient versus out-patient care for eating disorders. A further five systematic reviews[2-6] and two guidelines[7,8] were identified; these had as their main focus a comparison of different types of out-patient treatment, though some also briefly addressed the issue of in-patient versus out-patient care. On scrutiny of all reviews and guidelines, it was found that all evidence relating to in- versus out-patient treatment was based on only four RCTs[9-14], two[9-12] of which are fully published and one is an ongoing trial[14]. It was therefore decided to focus directly on the RCT evidence. Main characteristics of the studies are presented in Table 1.

Crisp 1991[11] trial (also reported in Gowers 1994[12])

This was a trial in 90 young women meeting the DSM-III-R definition of AN, with a mean age of 22 and a BMI of around 15 (calculated from weight and height numbers given in the paper). Intensive in-patient treatment (1) was compared to out-patient individual and family psychotherapy (2), out-patient group psychotherapy (3) and assessment interview only (4). Seventy-three patients (81%) accepted and commenced the allocated treatments and there were further (unspecified) drop-outs. Patients in all treatment groups were significantly improved at one and two years. Results as measured by the mean matched-population weight (MMPW) and Russell-Morgan global scores were slightly better at one, two and five years for the out-patient groups compared to the in-patient and assessment groups only. However, there were no statistically significant differences between any groups at any time. The lack of statistical significance may be due to the small sample size, and there is likely to be some uncertainty around results. There was one death in the out-patient group treatment arm (before treatment could commence), and one death in the in-patient group at 5 years. It is not known how comparable the in- and out-patient treatments in this trial are to those currently offered (see Table 1 for details of treatments – more detailed results are presented in Table 2).

Gowers 2007[10] TOuCAN trial (economic evaluation reported in Byford 2007[9])

This was a trial in 170 adolescents (92% female), aged between 11 and 17. Mean BMI was between 15.3 and 15.5 and all met a DSM-VI diagnosis of AN. In-patient treatment (1) was compared to out-patient treatment 'as usual' (2) and specialised out-patient treatment (3). Patients in all three groups improved significantly over time, but there were no significant differences between the three groups at year one or two for any of the outcome measures (Morgan-Russell score and further interviewer and participant based outcome measures, see Table 1). Results were better for patients who adhered fully to treatment; patients who did not adhere to out-patient treatment and were subsequently admitted to in-patient treatment did not do well. It is of note that those declining in-patient treatment did better than those accepting in-patient treatment, however, this finding should be interpreted cautiously as it may be due to differences in characteristics of these sub-groups. There was no report of any deaths occurring. For further details on the nature of the treatments, see Table 1.

The economic evaluation of this trial[9] suggests that specialist out-patient services are most likely to be cost-effective, however, there was no statistically significant difference between the three treatment options, possibly due to inadequate sample sizes for the economic evaluation.

Freeman 1992[13] trial

One further small trial (n=32) was identified (Freeman 1992, reported in Meads 1999[1]). This trial does not appear to have been fully published and it was not possible to assess this trial in detail, so results must be treated very cautiously. The trial found no differences in terms of weight gain or general psychopathology at two years follow-up in patients randomised to in-patient or day-patient treatment.

MCTAAN[14] trial

One 'ongoing trial' was identified, the results of which could potentially be relevant (see Appendix C for details). The trial objectives are to compare in-patient treatment to out-patient family therapy and multi-family day treatment in adolescents aged 13-20 with a DSM-IV diagnosis of AN (or an eating disorder not otherwise specified). No published results were identified and no response from the listed contact was received upon enquiry. The anticipated end date of the study was June 2008.

2. Different types of out-patient treatment

Seven systematic reviews[2-6] or guidelines[7] were identified, which addressed the question of the most effective type of out-patient treatment. One review[6] considered mental health problems rather than AN specifically and was not further considered. One Cochrane review[4] looked at the effectiveness of (guided) self-help versus other interventions for eating disorders, but none of the included studies were in patients with anorexia. Of the remaining reviews, we focussed on those two[2,3] with the most recent searches (up to February and August 2008) and most appropriate methodology. Detailed critical appraisals of the reviews can be found in Appendix D and Appendix E.

Fisher 2010[2] Cochrane review

This review compared the effectiveness of family therapy for AN to standard treatment and other treatments (e.g. psychological treatments) and also aimed to investigate the relative efficacy of different forms of family therapy. This was a well conducted review with a comprehensive search strategy, which is likely to have included the majority of relevant studies. Thirteen small RCTs (between 18 and 90 patients) were included. The populations were mainly female and aged between 13 and mid-20's, with a BMI between 13 and 17 (most were in the middle of this range). There was large variation between RCTs in types of therapy compared and outcome measures used; therefore only few trials contributed to a particular set of results. In addition, there was substantial risk of bias for all trials. The main findings were that family therapy may be more effective compared to standard or routine out-patient treatment in the short term. This is based on a statistically significant result from two trials (n=81), which have different types of 'standard'

treatment. There appears to be little advantage of family therapy over other forms of psychological interventions. Different types of family therapy also appear to be of similar efficacy. It is possible that the trials were not sufficiently powered to show differences between the interventions. Only 3/13 trials explicitly reported deaths, so no conclusions can be drawn regarding the effect of the different therapies on mortality.

Hay 2010[3] Cochrane review

This review compared the effectiveness of any outpatient-based psychological therapy (such as cognitive behavioural therapy (CBT), cognitive analytic therapy (CAT), interpersonal psychotherapy (IPT) etc.) with either a different psychological therapy, 'treatment as usual' or dietary advice. Again, this was a well conducted review with a comprehensive search strategy and it is unlikely to have missed any relevant studies. Only seven small RCTs (between 13 and 84 participants, median 27) were identified. These were of older adolescents and adults (aged > 16 years, mainly female) with anorexia nervosa, though two trials also included children. Studies varied in the therapies compared and the outcome measures used, and no studies could be pooled. It appeared that not all outcome measures were comprehensively reported (at all time-points) and all studies were at some risk of bias. Where multiple outcome measures were used, it is possible that a statistically significant difference may have occurred by chance. Given the small size of the trials, it is likely that they were underpowered and thus may not show differences between therapies. There is limited evidence to suggest that a specific psychotherapy may be more effective than no treatment or treatment as usual. There is insufficient evidence to determine the relative effectiveness of different psychological therapies. Only one study reported a death and no conclusions can be drawn regarding the risk of death with different therapies.

Conclusions

1. In-versus out-patient treatment

There was limited evidence in the form of two RCTs (n=90 and n=170). Results suggested that out-patient treatment is similarly effective to in-patient treatment in young (mainly female) patients with a BMI of around 15. Both trials are fairly small, and both suffer from lack of patient compliance and/or drop-outs, therefore results must be treated with some caution. The larger of the trials only had a follow-up of two years, so it is not known what the long-term outcomes are. The specific nature of the treatments offered in the trials should be taken into account when interpreting the results.

2. Different types of out-patient treatment

Evidence was available in the form of two recent Cochrane reviews, which investigated the efficacy of family therapies and psychological therapies. Both reviews included RCTs but these were small and at risk of bias. Family therapy may be more effective compared to standard out-patient treatment in the short term, but there appears to be little advantage of family therapy over other forms of psychological interventions. Different types of family therapy appear to be of similar efficacy. There is limited evidence to suggest that a specific psychotherapy may be more effective than no treatment or treatment as usual. There is insufficient evidence to determine the relative effectiveness of different psychological therapies. No conclusions regarding the likelihood of deaths with different treatments could be drawn from these reviews. There is a need for a large, well-conducted RCT in this area.

Table 1 Study characteristics of RCTs comparing in-and out-patient care

Study	Study Design	Population	In-patient treatment(s)	Out-patient treatment(s)	Outcomes
Crisp 1991[11] and Gowers 1994[12]	5 year RCT with four treatment arms UK based	90 women; DSM-III-R definition of AN; mean age 22 (range 20-23); duration of AN <10 years; BMI around 15	Option 1: intensive in-patient treatment (in-patient stay of several months, weight restoration, weekly individual therapy, family therapy, group therapy, dietary counselling, occupational therapy) followed by 12 sessions of out-patient psychotherapy	Option 2: Out-patient individual and family psychotherapy (12 sessions) plus separate dietary counselling (offered on four occasions) Option 3: Out-patient group psychotherapy (10 group sessions including patient and 10 group meetings for parents only) plus separate dietary counselling (offered on four occasions) Option 4: No treatment by study coordinators; one-off assessment and referral back to family doctor or local consultant with advice on further management In option 1, 2 and 3 a behavioural approach was coupled with psychotherapy directed at adolescent maturational problems.	-Morgan-Russell (1975) score, which includes nutritional status, menstrual function, mental state, sexual and socio-economic adjustment and an overall global rating score -Weight gain
Gowers 2007[10] and Byford 2007[9] (TOuCAN trial)	2 year RCT with three treatment arms UK based	170 adolescents (92% female); DSM VI diagnosis of AN; mean age 14 yrs 11 months (range 11-17); mean duration of AN 13 months; BMI between 15.3 and 15.5	Option 1: In-patient psychiatric treatment, 6 weeks in first instance, extended as clinically indicated; multi-disciplinary psychiatric approach with aim of restoring weight and cognitive change; individual supportive or cognitive therapies and family therapy	Option 2: Treatment as usual in general community: included multi-disciplinary, family-based approach, with variable dietetic, individual supportive therapy and paediatric (medical) liaison; out-patient arms not matched for intensity, but duration of therapy set at six months Option 3: 6 month specialised out-patient treatment devised for the trial comprising: initial motivational interview, individual CBT plus parental feedback (12 sessions), parental counselling with the patient (4-8 sessions), dietary therapy (4 sessions), multi-modal feedback monitoring	Interviewer based: -Clinical diagnosis (DSM-VI) -Morgan-Russell (1975) score (as above) -Health of the Nation Outcome Scale for Children and Adolescents (HoNOSCA; yields a total severity score) Participant based: -Eating Disorder Inventory (EDI) 2 -HoNOSCA self rated -Family Assessment Device (FAD) -Mood and Feelings Questionnaire (MFQ)

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Table 2 Results of RCTs comparing in- and out-patient care

Study	Compliance/ (loss to) follow-up	Main results	Adverse events	Comments
Crisp 1991[11] and Gowers 1994[12] Additional data from Meads 1999[1] (partly based on personal communications with authors)	Of 90 patients randomised, 18 (60%) accepted treatment for option 1, 18 (90%) for option 2, 17 (85%) for option 3 and 20 (100%) for option 4 In practice, only 6 patients in option 4 received no treatment, the remainder sought out in- or out-patient treatment Mean length of in-patient treatment was 20 weeks, mean number of out-patient sessions was nine and mean number of out-patient groups was five NB It is stated that there were drop-outs (especially for group-psychotherapy), but numbers are not given; results are presented for all patients and compliers, but there are no details on how missing data was dealt with	**Weight gain** expressed as change in percentage of mean matched-population weight (% MMPW (SD), some numbers approximate as read off graph): At 1 year follow-up: (1) In-patient: 72 (9.4) at start, 83.8 (12.4) ay year 1, 86.9 (11.6) at year 2 (2) Out-patient (individual/family): 74 (6.9) at start, 88.9 (11.7) at year 1, 94.5 (14.0) at year 2 (3) Out-patient (group): 73.8 (8.7) at start, 91.8 (16.3) at year 1, 93.2 (13.4) at year 2 (4) 'No treatment' group: 75 (8.5) at start, 79.5 (14.1) at year 1, 83 (15.4) at year 2 No significant differences between groups 1, 2 and 3 at year 1 or 2; all significantly better than group 4 at year 1 **Morgan-Russell global score (mean, SD)** For total group: (1) In-patient: 3.4 (1.3) at start, 5.5 (3.2) at year 1, 6.1 (3.0) at year 2 (2) Out-patient (individual/family): 3.8 (1.3) at start, 6.6 (2.6) at year 1, 7.5 (2.8) at year 2 (3) Out-patient (group): 3.8 (1.9) at start, 6.2 (2.7) at year 1, 7.7 (3.2) at year 2 (4) 'No treatment' group: 3.4 (1.1) at start, 5.7 (2.9) at year 1, 6.2 (3.2) at year 2 No significant differences between all four groups for global score or for change (though significant improvement over time within all groups) Percentage of patients who were 'well' (based on Morgan-Russell scale) was higher in out-patient groups compared to in-patients and 'no treatment' group, but there was no statistically significant difference between in- and out-patient groups	There was one death in the option 3 group (before treatment commenced) One further death from the in-patient group was reported at 5 years.	This was a small trial, with only 73 patients accepting one of four different types of treatments and an additional unknown amount of drop-outs. It is possible that there are differences between treatment options 2, 3 and 4 that could not be shown in this small trial. Follow-up after one year was not reported for all treatment arms in the published literature and therefore relies on information received from the author by Meads 1999[1]

Study	Compliance/ (loss to) follow-up	Main results	Adverse events	Comments
Gowers 2007[10] and Byford 2007[9] (TOuCAN trial)	170 patients were randomised, with 3 excluded due to mistaken diagnosis; 60/167 (36%) did not received the intervention (patient or clinician decision) and a further 7 (4%) were lost to follow-up 49% adhered to in-patient treatment, 69% to general out-patient treatment and 74.5% to specialist out-patient treatment An intention-to-treat analysis was used (including all patients who could be traced and for whom measurements could be obtained)	**Morgan-Russell scale, overall outcome:** All groups improved significantly, but scores were very similar for all three treatment groups and there were no statistically significant differences between the groups either for the overall outcome or on the various sub-scales. Scores were between 7.3 and 7.5 at year 1, and between 8.3 and 8.4 at year 2 for the three treatment groups. **Other outcome measures:** There were no statistically significant differences between the three treatment groups for BMI, weight for height, EDI, FAD, MFQ or HoNOSCA (self- or clinician rated) at one or two years. There was a slight (non-significant) trend for the general out-patient group to do better compared to the other two groups on BMI, weight for height, EDI, MFQ and self-rated HoNOSCA. Poor adherence to treatment (49%) may have influenced the relatively poor outcomes in the in-patient group; however, the authors found that those refusing admission did significantly better at one and two years on most outcome measures. It may be that there were differences between those deciding to accept treatment compared to those declining it (e.g. in terms of motivation, family resources). For the two out-patient groups, there was a much better outcome for those who fully adhered to treatment; of those allocated to the out-patient treatment and who were subsequently admitted to hospital, very few had a good outcome.	There is no report of any deaths occurring.	This appeared to be a well conducted trial, but as with all research in this area, suffers form a lack of adherence to treatment, which may influence the results.

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10 Gowers S, Clark A, Roberts C, Griffiths A, Edwards V, Bryan C, et al. Clinical effectiveness of treatments for anorexia nervosa in adolescents. British Journal of Psychiatry 2007; 191:427-435.

11 Crisp AH, Norton K, Gowers S, Halek C, Bowyer C, Yeldham D, et al. A controlled study of the effect of therapies aimed at adolescent and family psychopathology in anorexia nervosa. British Journal of Psychiatry 1991; 159:325-333.

12 Gowers S, Norton K, Halek C, Crisp AH. Outcome of out-patient psychotherapy in a random allocation treatment study of anorexia nervosa. International Journal of Eating Disorders 1994; 15(2):165-177.

13 Freeman C. Day patient treatment for anorexia nervosa. British Review of Bulimia and Anorexia 1992; 6(1):3-8.

14 Current Controlled Trials. A MultiCentre randomised Trial of the outcome, acceptability and cost-effectiveness of family therapy and multi-family day treatment compared with inpatient care and outpatient family therapy for Adolescent Anorexia Nervosa. Access date: 9 June 10 A.D., URL: http://www.controlled-trials.com/ISRCTN11275465

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 anorexia nervosa.mp.
2 exp community health services/
3 out patient$.ti,ab.
4 outpatient$.ti,ab.
5 Ambulatory Care/
6 community.ti,ab.
7 2 or 3 or 4 or 5 or 6
8 1 and 7
9 limit 8 to "reviews (optimized)"

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Appendix B – Literature search results

Systematic reviews

Source – Cochrane Library (CDR) 2010 Issue 2

Fisher Caroline A, Hetrick Sarah E, Rushford Nola. Family therapy for anorexia nervosa. Cochrane Database of Systematic Reviews: Reviews 2010 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD004780.pub2

Hay Phillipa PJ, Bacaltchuk Josué, Byrnes Roanna T, Claudino Angélica M, Ekmejian Avedis A, Yong Poh Yee. Individual psychotherapy in the outpatient treatment of adults with anorexia nervosa. Cochrane Database of Systematic Reviews: Reviews 2003 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD003909

Perkins Sarah S J, Murphy Rebecca RM, Schmidt Ulrike US, Williams Chris. Self-help and guided self-help for eating disorders. Cochrane Database of Systematic Reviews: Reviews 2006 Issue 3 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD004191.pub2

Source – Cochrane Library (DARE) 2010 Issue 2

Meads C, Gold L, Burls A, Jobanputra P.
In-patient versus out-patient care for eating disorders
University of Birmingham, Department of Public Health and Epidemiology; 1999
http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12000008253/frame.html

Bell L. What can we learn from consumer studies and qualitative research in the treatment of eating disorders?
Eating and Weight Disorders 2003; 8 (3): 181-87

Berkman ND, Bulik CM, Brownley KA, Lohr KN, Sedway JA, Rooks A et al.
Management of eating disorders. Agency for Healthcare Research and Quality; 2006.
http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12006008475/frame.html

Source – Cochrane Library (HTA Database) 2010 Issue 2

National Institute for Clinical Excellence. Eating disorders: Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders.
London: National Institute for Clinical Excellence (NICE); 2004
http://www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-32004000100/frame.html

Source – MEDLINE 1950 – May week 3 2010

Signorini A, De Filippo E, Panico S, De Caprio C, Pasanisi F, Contaldo F.
Long-term mortality in anorexia nervosa: a report after an 8-year follow-up and a review of the most recent literature.
European Journal of Clinical Nutrition. 2007; 61(1):119-22

Beumont P, Hay P, Beumont D, Birmingham L, Derham H, Jordan A et al. Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Anorexia Nervosa. Australian and New Zealand clinical practice guidelines for the treatment of anorexia nervosa.[Erratum appears in Aust N Z J Psychiatry. 2004 Nov-Dec;38(11-12):987]
Comment in: Aust N Z J Psychiatry. 2005 Jul;39(7):639-40; author reply 640-1;
Australian & New Zealand Journal of Psychiatry. 2004; 38(9):659-70.

Becker AE.
Outpatient management of eating disorders in adults.
Current Women's Health Reports. 2003; 3(3):221-9.

Herzog T, Hartmann A.
[Psychoanalytically oriented treatment of anorexia nervosa. Methodology-related critical review of the literature using meta-analysis methods]. [German]
Psychotherapie, Psychosomatik, Medizinische Psychologie. 1997; 47(9-10):299-315.

Rosenvinge JH.
Group therapy for anorexic and bulimic patients. Some aspects on the conduction of group therapy and a critical review of some recent studies.
Acta Psychiatrica Scandinavica, Supplementum. 1990; 361:38-43.

Source - EMBASE (Ovid) 1980 to 2010 Week 21

Lamb C.E.
Alternatives to admission for children and adolescents: Providing intensive mental healthcare services at home and in communities: What works?
Current Opinion in Psychiatry. 2009; 22(4): 345-350.

Wallis A, Rhodes P, Kohn M, Madden S.
Five-years of family based treatment for anorexia nervosa: The Maudsley Model at the Children's Hospital at Westmead.
International Journal of Adolescent Medicine and Health. 2007; 19(3): 277-283.

Meads C, Gold L, Burls A.
How effective is outpatient care compared to inpatient care for the treatment of anorexia nervosa? A systematic review.
European Eating Disorders Review. 2001; 9(4): 229-241.

Source – ARIF database

Beumont PJV. Treatment of anorexia nervosa. Lancet 1993; 341:1635-1640.

Freeman CP. Anorexia nervosa:what treatments are most effective? In: Practical problems in psychiatry Edited by K Hanton and P Cowen Oxford: Oxford University Press; 1992.

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Appendix C - Details of the MCTAAN trial (taken from: Current Controlled Trials. Access date: 9 June 10 A.D., URL: www.controlled-trials.com/ISRCTN11275465)

A multicentre randomised trial of the outcome, acceptability and cost-effectiveness of family therapy and multi-family day treatment compared with inpatient care and outpatient family therapy for adolescent anorexia nervosa (ISRCTN11275465).[14]

The following main research hypotheses will be tested:
1. In severely ill patients Multi-Family Day Treatment (MFDT) will be equally effective as inpatient treatment in returning patients to a normal nutritional state by the three month assessment.
2. The overall cost-effectiveness of MFDT will be significantly higher than inpatient treatment and will compare favourably with outpatient family therapy.
3. In less severely ill patients MFDT will lead to a more rapid nutritional recovery than outpatient family therapy.
4. MFDT will lead to the highest levels of client and family satisfaction of the three treatments.

A subsidiary hypothesis is that MFDT will lead to the greatest reduction of distress and difficulties experienced by other family members.

Independent research assessors will evaluate the outcome, costs and client acceptability before the start of treatment, at three months, 12 months (end of treatment) and 18 months (six month follow-up).

Inclusion criteria: Patients referred to five eating disorder services (South London and Maudsley NHS Trust, St Georges and South West London NHS Trust , Blackwater Valley Primary Health Care Trust, Central & Northwest London Trust, The Child and Adolescent Eating Disorder Service of the Royal Free Hampstead Trust), who meet Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for anorexia nervosa or eating disorders not otherwise specified and who are aged between 13 and 20 years.

Exclusion criteria: 1. Patients in care
2. Patients with learning disabilities, psychosis or alcohol/substance dependence
3. Patients with medical condition that may lead to significant weight loss (e.g. Crohn's disease)

Anticipated end date: 30/06/2008

Target number of participants: 400

Interventions:

Group one:
Inpatient treatment is based around a carefully structured nursing regimen, the main aims of which are:
1. To form a therapeutic alliance
2. To achieve weight restoration
Other members of the multidisciplinary team provide additional therapeutic input depending on the needs of individual patients. Patients allocated to inpatient treatment will be admitted to a specialist Eating Disorder Unit for approximately 12 weeks. The actual length of inpatient stay will be determined by the time needed for each individual patient to reach a healthy weight. The study design, however, will limit the length of time from reaching a healthy weight to discharge from hospital to two weeks. Following discharge from hospital they will receive regular follow-up treatment for six months for themselves and their families. We are currently developing a modification of the outpatient family therapy treatment manual so that it can be used for patients entering family therapy at a point when their weight is normal. To ensure continuity of treatment the therapist responsible for the follow-up treatment will engage the patient and her family during the last two weeks of the inpatient stay. The overall length of treatment (i.e. inpatient plus follow-up) will be 12 months.

Group two:
Outpatient family therapy for adolescent anorexia nervosa has been the focus of our previous treatment trials and a treatment manual has been developed to guide the therapists' interventions. Patients are seen for a number of sessions over a period of 12 months. These are mainly conjoint family meetings although some individual sessions are included where appropriate (particularly with older adolescents at later stages of the treatment). Therapy begins with an emphasis on the parents taking control of re-nutrition, with a gradual move towards conversations exploring more general implications of adolescence for children and parents as soon as the nutrition level is safe. The aim is to help the family to disentangle individual psychological issues (e.g. self esteem, individuation, psychosocial functioning) and family relationship issues from the eating disorder behaviour and the interactional patterns that have developed around it.

Group three:
MFDT is a new treatment programme that has been developed over the past three years at the Maudsley Hospital and at the Eating Disorder Service in Dresden. The treatment provides a more intensive form of family intervention than the usual outpatient family therapy but is conceptually very similar. In common with our outpatient family therapy, MFDT aims to help families rediscover

their own resources by emphasising ways in which parents can take control of re-nutrition. At the same time the families are encouraged to use the group setting to explore how the eating disorder and the interactional patterns in the family have become entangled, making it difficult for the family to follow the normal developmental course of the family life-cycle. The sharing of experiences and the dynamics of the multiple family group are important components of the treatment. The treatment starts with an intensive one week multiple family day programme for up to six families and is followed by a further four to five one day meetings at four to eight week intervals. Individual family meetings are scheduled in the intervals between group meetings as needed, with the overall length of treatment for each family being 12 months. A wide range of intervention techniques is used (including group, family, psycho-educational and creative techniques) with multiple family, parent or adolescent groups as well as individual family meetings. There is also practical input around managing mealtimes and food.

Primary outcome measures: 1. Symptomatic change:
a. Body Mass Index (kg/m^2)
b. Severity of Eating Disorder (SEED) symptomatology
c. Eating Disorder Examination (EDE)
d. Children's Eating Disorder Examination (C-EDE)
2. Health economic costs
a. Client service receipt inventory

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Appendix D - Critical appraisal of Fisher 2010

1. Was the review up-to-date?

Searches were completed in August 2008.

2. Was a clear review question defined?

Yes. The aim of the review was:
1. To evaluate the efficacy of family therapy compared with standard treatment and other treatments.
2. To investigate the relative efficacy of different forms of family therapy (see section below on 'Types of Interventions').
3. To investigate the efficacy of family therapy in patients with chronic AN vs non-chronic AN.
4. To investigate the efficacy of family therapy in adolescents with AN compared to adults with AN.

3. Were inclusion/exclusion criteria clearly stated?

Yes, inclusion and exclusion criteria were clearly stated:

Population: Patients of any age or gender with a primary clinical diagnosis of anorexia nervosa (AN), either or both purging or restricting subtype based on DSM or ICD criteria or clinicians' judgement, of any severity.

Intervention: Trials were included where the intervention was described as 'family therapy'. These interventions may have been delivered as a monotherapy or in conjunction with other interventions (including standard care which may or may not be in the context of an inpatient admission).

Comparators: Standard care or treatment as usual, biological interventions, educational interventions, psychological interventions, alternative or complementary interventions.

Additionally, different types of family therapy were compared to each other. The addition of family therapy to other interventions (including standard care) was also compared to other interventions.

Outcomes: Primary: Remission and all cause mortality
Secondary: Relapse, dropout, family functioning, general functioning, cognitive distortion, weight

Study design: RCTs

4. What are the implications for the validity of the review given the type and range of study designs included?

RCTs are most likely to provide unbiased evidence.

5. Was the search strategy adopted likely to have missed many potentially relevant studies?

The search strategy was comprehensive and included electronic databases, hand searching, reference checking and contacting experts. ClinicalTrials.gov was searched for ongoing studies. The strategy is unlikely to have missed many relevant studies.

6. Were the methods used to decide on study inclusion/exclusion stated?

Yes, there is a detailed description of study selection. This was performed independently by two review authors.

7. Was the process of data abstraction adequate?

Yes, data abstraction was performed independently by two review authors and there are further details on which criteria were selected for data abstraction and why.

8. Was the validity of included studies assessed?

Yes. Two review authors independently assessed the risk of bias of the included trials using a descriptive approach as advocated by the Cochrane Handbook for Systematic Reviews of Interventions.

9. What were the relevant and justifiable review conclusions?

The included 13 RCTs (between 18 and 90 participants) were found to have a considerable risk of bias. This included for example inadequate reporting of missing data, baseline imbalances, inconsistencies in result reporting, selective reporting etc. It is difficult to estimate the effect of this on the results. There was little between group analysis and a lack of description of the nature of some treatments.

The population was mainly female and aged between 13 and mid-20's, with a BMI between 13 and 17 (most were in the middle of this range); all studies were in an out-patient setting, except one which included both in-and out-patient settings (in-patient results not used as comparator) and one which included only in-patients.

Due to the differences in types of therapy and outcome measures used across trials, only few trials contributed data to the individual comparisons. Even where trials measured the same outcome, e.g. functioning, several different scales were used. Only 1/13 and 2/13 trials respectively measured general or family functioning.

Seven comparisons were undertaken:

1. Family therapy versus 'usual/standard care'
- Based on two trials there was a significant increase in the rate of remission in those being treated with family therapy.
- Based on two trials there was no significant difference in the number of drop-outs with family therapy or usual care.
- Only one trial reported relapse and found no evidence of a treatment effect. There was one death (based on one trial) in the treatment as usual arm.

2.(i) Family therapy versus psychological interventions
- There was no significant difference in remission (based on four trials) or cognitive distortion (based on three trials with considerable heterogeneity).
- Based on one small sub-group from one trial, there was evidence that younger participants may benefit more from family therapy (this should be regarded as a hypothesis only and should be tested in future trials).

2. (ii) Family therapy versus individual psychological intervention

- There was no significant difference in weight (BMI) post-intervention or at follow-up (based on two trials), though there was a trend favouring family therapy.
- Based on two papers, there were three reported deaths, however it is not clear which treatment group these were in.

3. Family therapy versus educational intervention

- Based on one small trial there was no significant difference at 9 months in remission.

4. Short-term versus long-term family therapy

- Based on one trial that compared 6 months versus 12 months of therapy, there were no statistically significant differences in remission (at mean 3.96 years), functioning, drop-outs, BMI or relapse. There was a significant difference in cognitive distortion post-intervention (using one scale), but not at follow-up (using a different scale) and favouring the 12 month intervention.

5. Conjoint family therapy versus separated family therapy

- There was no significant difference in remission, drop-outs or relapse based on one trial, and no significant difference in cognitive distortion or weight based on two trials.
- One trial reported that there were no deaths.

6. Family therapy versus family therapy plus meal

- There was no significant difference in remission, drop-outs, cognitive distortion or weight based on one trial. There was a significant improvement in family functioning with the added meal therapy post-intervention but there were no data for follow-up.

7. Individual family therapy versus group therapy (in an in-patient setting)

- There was no significant difference in functioning, drop-outs, cognitive distortion or weight based on one trial.

Overall there are only few trials investigating the same intervention and using the same outcome measures; all trials are small and associated with potentially significant risks of bias. Family therapy may be more effective compared to standard or routine out-patient treatment in the short term. This is based on a statistically significant result from two trials (n=81), which vary in their 'usual' treatment. There appears to be little advantage of family therapy over other forms of psychological interventions.

It is possible that the trials were not sufficiently powered to show differences between the interventions. Where numerous outcomes have been measured, it is also possible that a statistically significant outcome may have occurred by chance.

The authors note that where different types of family therapy were being compared, these were often very similar interventions. There is little data on chronic versus non-chronic AN; there was some evidence based on one trial that family therapy may be more effective compared to individual supportive therapy in those with a shorter duration of illness. There is also little data on older versus younger patients; one small sub-group found that family therapy may be more effective compared to other psychological intervention in younger patients.

Only 3/13 trials explicitly reported deaths, and no further conclusions can be drawn from this.

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Appendix E - Critical appraisal of Hay 2010

1. Was the review up-to-date?

Updated searches were completed in February 2008.

2. Was a clear review question defined?

Yes. The aim of the review was to evaluate the evidence from randomised controlled trials for the efficacy of outpatient psychotherapies used in the treatment of older adolescents and adults with anorexia nervosa.

3. Were inclusion/exclusion criteria clearly stated?

Yes, inclusion and exclusion criteria were clearly stated:

Population: Older adolescents and adults (aged > 16 years) with anorexia nervosa (DSM, ICD or Russell 1970 criteria)

Intervention: Any outpatient-based psychological therapy, specifically cognitive behavioural therapy (CBT), behavioural therapy (BT), cognitive analytic therapy (CAT), educational behaviour treatment (EBT), interpersonal psychotherapy (IPT), psycho-dynamic psychotherapy, motivational enhancement therapy, feminist therapy, their combinations and/or variants and any other individual psychotherapies.

Comparators: Treatment as usual, dietary advice, 'control' psychotherapy, waiting list

In addition specific individual psychotherapy comparisons will be made of:
CBT versus time-limited individual psychodynamic therapies
CBT versus IPT
CBT versus CAT
Individual psychotherapy versus a pharmacological therapy
Combinations of pharmacological therapy and individual psychotherapy versus either drug therapy or psychotherapy alone.

Outcomes: Primary: Weight restoration to within the normal weight range (e.g. body mass index, BMI)
Secondary: Recovery according to the Morgan scale (based on weight and menstruation), mean eating disorder symptom scores (as measured by any recognized and validated questionnaire or interview), proportion of study "drop-outs" or non-completers for any reason, proportion of study "drop-outs" or non-completers due to an adverse event or experience, patient satisfaction ratings, side effects or negative effects of therapy, general psychiatric symptomatology, depression, interpersonal function

Study design: RCTs

4. What are the implications for the validity of the review given the type and range of study designs included?

RCTs are most likely to provide unbiased evidence.

5. Was the search strategy adopted likely to have missed many potentially relevant studies?

The search strategy was comprehensive and included electronic databases, hand searching, reference checking and contacting experts. The strategy is unlikely to have missed many relevant studies.

6. Were the methods used to decide on study inclusion/exclusion stated?

Yes, there is a description of study selection. This was performed independently by two review authors.

7. Was the process of data abstraction adequate?

Yes, data abstraction was performed independently by two review authors and there are further details on which criteria were selected for data abstraction.

8. Was the validity of included studies assessed?

Yes. Two review authors independently assessed the risk of bias of the included trials using the Quality Rating Scale (QRS), a 23-item scale measuring differing aspects of internal and external validity of trials. For this update trials were also evaluated according to proposed guidelines for "risk of bias appraisal" in REVMAN v 5.

9. What were the relevant and justifiable review conclusions?

Seven RCTs were included, with a median participant number of 27 (range 13-84). The studies were found to be at risk of bias mainly due to lack of blinding at outcome assessment and/or unclear allocation concealment. There was some missing outcome data and lack of data reporting at follow-up. Presentation of many of the results was judged to be inadequate and not all relevant data could be extracted.

The population was mainly female and aged above 16 years of age, although two trials included children/adolescents. All studies were in an out-patient setting.

There were insufficient trials for meta-analysis and all analyses are based on single trials.

Four comparisons were undertaken:
1. Individual psychotherapies (IPT, CAT or CBT) versus treatment as usual
- FPT significantly better than treatment as usual as measured by recovery on Morgan & Russell categories (based on one trial)
- No significant difference between CAT and treatment as usual as measured by recovery on Morgan & Russell categories (based on one trial)
- No significant difference between CAT and EBT as measured by Morgan and Russell 'poor and intermediate' outcomes, BMI at 12 months and average Morgan & Russell scores at 12 months (based on one trial)
- No significant differences in drop-outs (based on two trials)

2. IPT, CAT or CBT versus a 'control' psychotherapy
- No significant difference between CAT and IFP (based on Morgan & Russell categories, one trial)
- No significant difference in number of non-completers with CBT, BT or 'eclectic therapy' (based on one trial, no other outcome data could be extracted)
- CBT significantly better than IPT in two outcome categories, no significant difference for three other outcomes; No significant differences between CBT and non-specific clinical management

(NSCM) for five outcomes; NSCM significant better than IPT for three outcomes, no significant difference for two outcomes (all based on one trial)

3. Dietary advice versus individual time-limited psychotherapies and/or IPT, CAT or CBT
- No significant difference in mean BMI at end of treatment with CBT or dietary advice

4. Waiting list versus IPT, CAT or CBT
- No studies comparing these interventions were identified.

Miscellaneous studies:
- Self-psychology treatment (SPT) significantly better than cognitive-orientation treatment (COT) in terms of participants achieving a good outcome (based on one very small trial, n=13)
- Significantly more patients went into remission after treatment (nutritional and behavioural) compared to patients in the delayed treatment group (one trial)

.

There are a number of different therapies being compared in the trials, and a variety of outcome measures are used. Where multiple outcome measures are used in a single trial, it is possible that some statistically significant findings might occur by chance. It appears that not all outcome measures have been comprehensively reported (at all time-points). It is likely that trials were underpowered and this, together with insufficient replication of findings, leads the authors to conclude that a specific approach cannot be recommended.

Only one study reported a death and no conclusions can be drawn from this review regarding the frequency of death with different therapies.

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Archived ARIF Request

Anterior Cruciate Ligament (ACL) Tears of Knee Surgery - Repair and Augmented Repair

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in May 1999.

The Problem Submitted for ARIF to Advise Upon:

What are the effects and effectiveness of surgical repair of acute tears of the anterior cruciate ligament (particular emphasis on incomplete tears where there is little instability of the knee)?

Question Reformulated:

Considering the nature of the question identifies a number of important sub issues.

Intervention: Different types of surgery need to be considered, e.g.

- Simple repair (torn ends are sutured together) vs. repair with "augmentation" (join is strengthened)
- Open vs. closed repairs (using an arthroscope)

Most surgery would be followed by a period of immobilisation in a cast and "rehabilitation" over several months to improve muscle strength under the supervision of a physiotherapist.

The main alternative would be conservative treatment consisting of rest, graded remobilisation and strength training under the supervision of a physiotherapist. Most "conservative" treatment as defined in research at least usually also consists of an arthroscopy to diagnose the exact nature of any damage to the knee and repair of any damage to the structures of the knee, e.g. the menisci.

Population: Varying characteristics of the patient will be important, e.g.

- Age and pre-existing (and desired future) level of physical activity [can be quantified on the "Tegner" scale]
- Severity of ACL tear (partial or complete; resulting in little or severe instability of the knee)
- Whether ACL tear is associated with damage to other structures in the knee (menisci, medial collateral, posterior oblique and arcuate ligaments)

Outcomes: The key outcome of interest is likely to be patient quality of life. This however would need to be measured at several points in time to capture both the potential disbenefits of surgery resulting from complications, immobilisation and rehabilitation AND potential benefits in terms of better ultimate knee function which may only appear in excess of a year after surgery. Other outcomes which could be measured, which together might give an indication of impact on quality of life include operative complications, knee stability and function e.g. Lysholm score, muscle strength, ability to perform set exercises e.g. one legged hopping and figure of eight running and eventual activity levels.

Reviews Identified

- Crandell DM, Richmond JC, Lau J, Shapiro ET. A meta-analysis of the treatment of injuries of the anterior cruciate ligament. Orthop Trans 1995; 19(1): 11-12
- Linko E, Harilainen A, Malmivaara A, Seitsalo S. Operative treatment for anterior cruciate ligament ruptures in adults (Protocol for a Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software

Trials Identified

Over 100 potentially relevant trials are listed on the Cochrane Controlled Trials register. Of these the following trials were identified, directly comparing surgical and "conservative" treatment:

- Andersson C, Gillquist J. Treatment of acute isolated and combined ruptures of the anterior cruciate ligament. A long-term follow-up study. Am J Sports Med 1992; 20(1): 7-12
- Andersson C, Odensten M, Gillquist J. Knee function after surgical or non-surgical treatment of acute rupture of the anterior cruciate ligament: a randomized study with a long-term follow-up period. Clin Orthop 1991; 264: 255-63
- Andersson C, Odensten M, Good L, Gillquist J. Surgical or non-surgical treatment of acute rupture of the anterior cruciate ligament. A randomized study with long-term follow-up. J Bone Joint Surg Am 1989; 71(7): 965-74
- Sandberg R, Balkfors B, Nilsson B, Westlin N. Operative versus non-operative treatment of recent injuries to the ligaments of the knee. A prospective randomized study. J Bone Joint Surg Am 1987; 69(8): 1120-6.
- Odensten M, Hamberg P, Nordin M, Lysholm J, Gillquist J.Surgical or conservative treatment of the acutely torn anterior cruciate ligament. A randomized study with short-term follow-up observations. Clin Orthop 1985; 198 87-93

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Comments

The review identified appears to be generally systematic in approach, although as it is presented in abstract form only a number of important details about review method are absent. The main results of this review were:

- Identification of three "randomised studies" comparing surgery (repair or repair with augmentation) with "conservative" treatment
- That these studies were open to bias despite being randomised
- That with the proviso of there being a small number of studies of imperfect quality, there was evidence that surgery resulted in greater knee stability as measured by the presence or absence of "pivot-shift". Further there was evidence of a statistically significant 3.6 point improvement in knee function using the Lysholm score. However as the minimum score is 0 and the maximum 100 the clinical importance of this difference was questioned.

Scrutiny of the trials identified from the Cochrane Controlled Trials register reveals why the reviewers were very non-committal in concluding that, "There have not been enough studies of sufficient methodologic quality, using adequately validated measures of outcome, to determine scientifically the best treatment for ACL injuries." Problems which we identified on close scruting and appraisal of the listed trials included:

- Lack of clarity about whether the work from Linköping in Sweden reported in articles by Andersson C et al and Odensten M et al, referred to the same or different groups of patients
- Uncertainty about the adequacy of processes used to randomise patients
- Use That "conservative" treatment often actually involved surgery, with injury to other knee structures e.g. menisci (but not the ACL) being repaired.
- of surgical procedures which may not be typical of those in current use

However, detailed scrutiny of the trials also suggested in a way not conveyed in the review, that the improvements in stability and function do seem to be mirrored by more frequent return to pre-existing activity levels, particularly when follow-up is extended to three or more years after the operation.

On this basis ARIF suggests that:

- In our view there is sufficient evidence on effectiveness to commission surgery for ACL as one component of any services for the treatment of acute knee injuries.
- However, there is considerable uncertainty to which commissioners should remain responsive.
- Some of this uncertainty may be resolved when a more comprehensive and up-to-date systematic review of the literature by the Cochrane Collaboration becomes available (expected August 1999) - any commissioning decisions now should be reviewed in the light of its results.
- Even with the Cochrane Review, it is highly likely that an absence of conclusive effectiveness evidence on key questions will be confirmed. We believe that a particularly important question which will fall into this category is, "What is the effect of current surgical techniques versus conservative management on patient quality of life over three or more years in ACL tears which lead to moderate instability/deterioration in knee function and/or where the level of function required by the patient does not involve competitive sport (levels 7-10 on the Tegner scale)?"
- Commissioners should encourage and facilitate rigorous evaluative research in this general area.

Request Carried Out: May 1999

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These pages are maintained by Ann Massey

Archived ARIF Request

Anthroposophical Medicine
Chronic Fatigue Syndrome

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in December 2001.

The Problem Submitted for ARIF to Advise Upon:

What is the evidence on effectiveness of anthroposophical medicine in the treatment of chronic fatigue syndrome (CFS)?

Anthroposophical medicine is a science in which both the human being and the natural world are described not only physically, but also in terms of soul and spirit. Conventional medical technology may be used during treatment, but patients are also prescribed herbal and homeopathic preparations as well as counselling and art therapy.

Reviews Identified

No systematic reviews on the treatment of CFS with anthroposophical medicine were identified.

However, the following systematic review on the effectiveness of interventions for CFS was identified :

- Bagnall AM, Whiting P, Wright K, Sowden AJ. The effectiveness of interventions used in the treatment and management of chronic fatigue syndrome and/or myalgic encephalomyelitis in adults and children. The NHS Centre for Reviews and Dissemination, University of York, York. 2001. This review can be downloaded via the Internet from: http://www.york.ac.uk/inst/crd/listcomp.htm.

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Comments

We identified no systematic reviews specifically on anthroposophical medicine for CFS.

To pursue with request we attempted to identify those treatments which appeared to be effective in the treatment on CFS and to establish which of those might in our view come under the definition of anthroposophical treatment

The systematic review suggests that CBT (cognitive behaviour therapy) appears to be effective for CFS and that this is supported by a recent Cochrane review. The review also suggests that graded exercise shows promising results. From our observations it appears that CBT and graded exercise maybe

similar to some of the interventions coming within the range of anthroposophical medicine such as encouraging participation in activities and undertaking physical activities (e.g. movement therapy - eurythmy).

Request Carried Out: December 2001

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Archived ARIF Request

Antibiotics Bronchiolitis

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Question Reformulated

We identified a list of currently employed treatments for bronchiolitis. This request focuses on the use of antibiotics.

Reviews Identified

None identified.

Trials Identified

- Field CM, Connolly JH, Murtagh et al. Antibiotic treatment of epidemic bronchiolitis: a double blind trial. BMJ 1966; (5479): 83-85
- Friis B, Anderson P, Brenoe et al. Antibiotic treatment of pneumonia and bronchiolitis. A prospective randomised study. Archives of Disease in Childhood 1984; 59: 1038-1045

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Comments

No relevant systematic reviews were identified but a number of primary studies were available. Field et al is a fairly good, but rather dated, trial undertaken in Ireland in 1966, which did not detect any statistically significant benefits for treatment. The paper by Friis et al is a report of a more recent randomised placebo controlled trial, again of reasonable quality. The participants were all children admitted to hospital with bronchiolitis, but again the study failed to detect any differences in the course of the illness and complications between the two groups.

Although scant, the evidence is not suggestive of large benefits from treatment with antibiotics. It should be noted that we have not done a systematic review to arrive at this conclusion. One should be done.

Additional information relevant to this request is available in the requests entitled Bronchiolitis/Bronchodilators, Bronchiolitis/Continuous Negative Extrathoracic Pressure (CNEP), Bronchiolitis/Ribavirin, Bronchiolitis/Immunoglobulin, Bronchiolitis/Steroids, Bronchiolitis/Assisted Ventilation.

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Antibiotics
Pelvic Inflammatory Disease

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence on effectiveness of antibiotic regimes in the treatment of pelvic inflammatory disease (PID)?

Question Reformulated

A number of important sub-questions were identified:

- which classes of antibiotic are most effective
- the length of antibiotic therapy to achieve clinical cure
- the effectiveness of different routes of administration
- whether out patient treatment is more or less effective than inpatient treatment
- the cost effectiveness of the alternative therapies

Reviews Identified

- Ross J. Pelvic inflammatory disease. Clinical Evidence. December 2001; 6 : 1256-1260
- Ross JDC. Outpatient antibiotic therapy for pelvic inflammatory disease: What is the evidence? BMJ 2001 ; 322 : 251-251. (this is a summary of the article by the same author above)
- Walker CK, Workowski KA, Washington AE, Soper DE, Sweet RL. Anaerobes in Pelvic inflammatory disease: implications for the Centers of Disease Control and Prevention's Guidelines for Treatment of Sexually Transmitted Diseases Clin Infect Dis 1999 ; 28 (Supplement 1) : S29-S36
- Walker CK, Kahn JG, Washington AE, Peterson HB, Sweet RL. Pelvic inflammatory disease: meta analysis of antimicrobial regimen efficacy Journal of Infectious Diseases 1993 ; 168(4): 969-978
- Peterson HB, Walker CK, Kahn JG, Washington AE, Eschenbach DA, Faro S. Pelvic inflammatory disease. Key treatment issues and options. [Review] [58 refs]. JAMA 1991 ; 266(18):2605-11 Comment in : JAMA 1991; 266(18): 2612

Primary Studies

Contact ARIF for a list.

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Comments

We identified a systematic overview of the topic (Ross 2001) and three potential systematic reviews (Peterson et al 1993, Walker et al 1993, 1999). We also identified a number of primary studies.

The overview by Ross is most up to date and from what we can ascertain from the methodology employed in the production of articles for Clinical Evidence it is likely to be robust and the findings trustworthy. Readers should find this article helpful. This review identifies the limitations in the available evidence base and particularly problems answering the sub-questions listed in the section on question reformulated above.

In the three potential systematic reviews by Peterson et al (1991) and Walker et al (1993, 1999) there is reporting of the methods and results sections, which hindered detailed appraisal. Methodological weakness, including the pooling of randomised and non-randomised trials, suggests the need for caution in accepting the results of these reviews uncritically.

A systematic review is currently being undertaken on this topic by the West Midlands Health Technology Assessment Collaboration.

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Archived ARIF Request

Anticholinergics Common Cold

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The Problem Submitted for ARIF to Advise Upon:

What treatments have been shown to be effective in the treatment of the common cold?

Question Reformulated

Due to the breadth of this question, we focused our attention on those interventions for which there was a substantial body of evidence on their effectiveness, and on those that appeared to have a positive effect. Interventions excluded because of a lack of research evidence included mast cell stabilisers, iodine, guaifenesin, glucocorticoids, interferon and other antiviral drugs. Antibiotics were also excluded as a Cochrane review provided reliable evidence of no effect.

Reviews Identified

None.

Trials Identified

- Gaffey MJ et al. Ipatropium bromide treatment of experimental rhinovirus infection. Antimicrobial Agents and Chemotherapy 1988;32(11):1644-1647
- Diamond L et al. A dose-response study of the efficacy and safety of ipatropium bromide nasal spray in the treatment of the common cold. J Allergy Clin Immunol 1995; 95: 1139-1146
- Hayden FG et al. Effectiveness and safety of intranasal ipatropium bromide spray in common colds. A randomised, double blind, placebo controlled trial. Annals of Internal Medicine 1996; 125(2): 89-97

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Comments

The trials cited were all well-designed and well-conducted. The studies by Hayden and Diamond were both large trials (n=411 and 955 respectively), but that by Gaffey was smaller (n=69). All three compared intranasal ipatropium bromide spray with placebo or no treatment and all demonstrated reductions in nasal secretions with the intervention. Some side effects were noted including excess dryness in the nose and throat and headache.

Additional information relevant to this request is available in the other requests on the Common Cold entitled Zinc; Vitamin C; Antihistamines; "Over-the-Counter" Remedies; Alpha Agonists; Echinacea; NSAIDs; Steam Inhalation.

Request Carried Out: July 1999

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Anti-Coagulation Clinics

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The Problem Submitted for ARIF to Advise Upon:

Siting and staffing of anti-coagulation clinics; what is the variation in effectiveness and cost-effectiveness?

The specific question posed by the requester, a GP was:
Should we continue to provide an in-practice, nurse run anticoagulation clinic?

Reviews Identified

- Fitzmaurice DA et al. Monitoring oral anticoagulation in primary care. British Medical Journal 1996; 312: 1431-32

Trial/Evaluations Identified

- Pell JP et al. Comparison of anticoagulant control among patients attending general practice and a hospital anticoagulant clinic. British Journal of General Practice 1993; 43: 152-54
- Anderson DR et al. Evaluation of a portable prothrombin time monitor for home use by patients who require long-term oral anticoagulant therapy. Archives of Internal Medicine 1993;153:1441-1447

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Comments

No systematic review was identified; the review cited is an editorial which provides useful background.

The three primary studies given, are useful starting points in considering the research evidence on the question stated. However, readers should be aware that the studies may not be representative of all research on this topic. Given this ARIF's tentative conclusions were:

In response to: "Should we continue to provide an in-practice, nurse run anticoagulation clinic", the research identified suggests that practice based anticoagulation can achieve as good, if not better control than hospital clinics, with high levels of patient satisfaction, and equivalent rates of haemorrhagic complications. The important proviso is that the quality control of the anticoagulation assay is maintained.

Unfortunately, there is little guide on whether the benefits are worth the costs. Indeed it is suggested

that as useful information may be obtained by examining the local situation as attempting to generalise from a health economic study. It will depend greatly on how "good" the local hospital based anticoagulation service is.

This is an area prone to need for regular updating as new information is continually becoming available.

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Archived ARIF Request

Antihistamines
Common cold

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The Problem Submitted for ARIF to Advise Upon:

What treatments have been shown to be effective in the treatment of the common cold?

Question Reformulated

Due to the breadth of this question, we focused our attention on those interventions for which there was a substantial body of evidence on their effectiveness, and on those that appeared to have a positive effect. Interventions excluded because of a lack of research evidence included mast cell stabilisers, iodine, guaifenesin, glucocorticoids, interferon and other antiviral drugs. Antibiotics were also excluded as a Cochrane review provided reliable evidence of no effect.

Reviews Identified

None.

Trials Identified

- Hutton N et al. Effectiveness of an antihistamine decongestant combination for young children with the common cold: a randomised controlled clinical trial. Journal of Paediatrics 1991; 118(1): 125-130
- Eccles R et al. A clinical study to evaluate the efficacy of the antihistamine doxylamine succinate in the relief of runny nose and sneezing associated with upper respiratory tract infection. J Pharm Pharmacol 1995; 47: 990-993
- Turner R et al. Effectiveness of clemastine fumarate for treatment of rhinorrhea and sneezing associated with the common cold. Clinical Infectious Diseases 1997; 25: 824-830
- Clemens CJ et al. Is an antihistamine decongestant combination effective in temporarily relieving symptoms of the common cold in pre-school children? Journal of Paediatrics 1997; 130: 440-446
- Gwaltney JM et al. Randomised controlled trial of clemastine fumarate for treatment of experimental rhinovirus colds. Clinical Infectious Diseases 1996; 22: 656-66

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Comments

All the reviews we identified on this topic had significant methodological limitations, summarised studies

of low internal validity and produced conflicting results. We therefore focused our attention on any trials that were published subsequent to the most recent review.

These were generally of good size and rigorous design, and probably more reliable than those included in the reviews. Two (Hutton et al 1991 and Clemens at al 1997) studied the effectiveness of an antihistamine/decongestant combination (Dimetapp) in young children, but were unable to demonstrate any benefits over placebo. The other three trials compared antihistamines with placebo in adults, and all demonstrated significant reductions in runny nose and sneezing only, with minimal adverse effects other than drowsiness.

Additional information relevant to this request is available in the other requests on the Common Cold entitled Zinc; Vitamin C; Anticholinergics; "Over-the-Counter" Remedies; Alpha Agonists; Echinacea; NSAIDs; Steam Inhalation.

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Archived ARIF Request

Antihistamines and Decongestants
Glue Ear

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The Problem Submitted for ARIF to Advise Upon:

What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Due to the breadth of this question, we focused our attention on groups of interventions. The groups of interventions were antimicrobial drugs, steriods, antihistamines and decongestants, mucolytic agents, and auto-inflation.

This web page details our findings on antihistamines and decongestants. Links to pages on the other groups of interventions can be found at the bottom of this page.

Reviews Identified

- Williamson I. Otitis media with effusion. In: Clinical Evidence 3. London: BMJ Publishing Group, 2000. Pp248-254

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Comments

The review by Williamson is a systematic overview of treatments for glue ear and appears a concise and accurate synthesis of the evidence presented in other systematic reviews.

The overview review by Williamson includes one systematic review, published by the Agency for Health Care Policy and Research, USA (1994), that contains a section on this topic. We have not as yet obtained a copy of this review. Williamson states that it found that combined antihistamine/decongestant had no significant effect on effusion clearance rate compared to placebo. As outlined in the section on antimicrobials above, antihistamine/decongestants have been used as a placebo in some studies due to their perceived ineffectiveness.

Additional information relevant to this topic is available in the other web pages on glue ear and these are on the following interventions: antimicrobial drugs, steroids, mucolytic agents, and autoinflation.

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Antimicrobial Drugs
Glue Ear

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The Problem Submitted for ARIF to Advise Upon:

What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Question Reformulated

Due to the breadth of this question, we focused our attention on groups of interventions. The groups of interventions were antimicrobial drugs, steriods, antihistamines and decongestants, mucolytic agents, and auto-inflation.

This web page details our findings on antimicrobial drugs. Links to pages on the other groups of interventions can be found at the bottom of this page.

Reviews Identified

- Williamson I. Otitis media with effusion. In: Clinical Evidence 3. London: BMJ Publishing Group, 2000. Pp248-254
- Williams RL, Chalmers TC, Stange KC, Chalmers FT, Bowlin SJ. Use of antibiotics in preventing recurrent acute otitis media and in treating otitis media with effusion. A meta-analytic attempt to resolve the brouhaha. JAMA 1993,270(11), pp.1344-51

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Comments

The review by Williamson is a systematic overview of treatments for glue ear and appears a concise and accurate synthesis of the evidence presented in other systematic reviews.

The review by Williamson, in part based on the review by Williams et al, suggests that although antibiotics may provide some benefit in the short term (one month), they do not affect long term outcomes. The findings of the reviews appear somewhat limited by the quality of some of the primary research.

Additional information relevant to this topic is available in the other web pages on glue ear and these

are on the following interventions: steroids, antihistamines and decongestants, mucolytic agents, and autoinflation.

Request Carried Out: January 2001

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Arthroscopic surgery for hip impingement and/or hip pain

Synopsis

Question:	What is the clinical effectiveness and cost-effectiveness of arthroscopic treatment for young people (of working age) with hip impingement (femoro-acetabular impingement) and/or hip pain and what group(s) of people may be expected to benefit from it?
Evidence Identified:	Bedi A, Chen N, Robertson W, Kelly BT. Systematic review: the management of labral tears and femoroacetabular impingement of the hip in the young, active patient. Arthroscopy 2008; 24(10):1135-1145 National Institute for Health and Clinical Excellence. Interventional procedures overview of arthroscopic femoro-acetabular surgery for hip impingement syndrome. London: NICE; 2006. Interventional Procedures Programme, IP365. National Institute for Health and Clinical Excellence. Arthroscopic femoro-acetabular surgery for hip impingement syndrome. London: National Institute for Health and Clinical Excellence (NICE); 2007.
Comments:	The main limitation with the data identified in both reviews was that it had been derived from retrospective case series; therefore the effectiveness of arthroscopic surgery for hip impingement and/or hip pain compared with any conventional approach cannot be determined overall and within any particular subgroups. Neither review evaluated cost-effectiveness of this procedure.
Date Completed:	February 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Arthroscopic surgery for hip impingement and/or hip pain

Request completed: February 2010

Question

What is the clinical effectiveness and cost-effectiveness of arthroscopic treatment for young people (of working age) with hip impingement (femoro-acetabular impingement) and/or hip pain and what group(s) of patients may be expected to be benefit from it?

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol http://www.arif.bham.ac.uk/strategy.shtml. Text and index terms were employed to denote the population and the intervention. Sources were searched from their inception to January 2010. No language restriction was applied to the searches. The MEDLINE search can be found in Appendix A. The following inclusion criteria were used for search and study selection:

Population	People with hip impingement (femoro-acetabular impingement) and/or hip pain
Intervention	Arthroscopic surgery
Comparator	Conservative treatment
Outcomes	Pain (pain scores, use of painkiller drugs etc), range of movement, resumption of activities, the need for further surgical procedures in the longer term, and cost-effectiveness
Study design	Systematic reviews and health technology assessments

Results

This report is based on evidence from one systematic review[1] and one NICE guidance with its associated documents[2-3] that are most recent and relevant to the question. Full search results can be found in Appendix B.

Bedi A, Chen N, Robertson W, Kelly BT. Systematic review: the management of labral tears and femoroacetabular impingement of the hip in the young, active patient. Arthroscopy 2008; 24(10):1135-1145

This review aimed to determine the quality of literature assessing outcomes and patient satisfaction after surgical treatment of labral tears and femoroacetabular impingement (FAI) and differences in outcome with open or arthroscopic approaches.

The methodology of the review is of reasonable quality, with good search strategies, the latest database search being up to May 2008. The analysis in the review was descriptive. Unfortunately the results were presented in a format that makes it difficult to get to grips with the results, particularly those pertinent to the question in the request regarding patient characteristics.

Twelve studies on arthroscopic surgery and seven on open surgery met the review's inclusion criteria.

The 12 studies on arthroscopic surgery were published from 1999 to 2008. They were all retrospective case series, which limits their usefulness, as without a comparator the effectiveness of one treatment over another cannot be determined. Sample sizes were small ranging from six to 58 patients giving a total of 271 patients. Mean age of the patients was 33 years (range 24 to 42 years). The primary diagnosis in eight of the studies was symptomatic labral tears and/or FAI, and in the rest both the labral tears and FAI needed to be present. However, the population in the studies was heterogeneous, i.e. four of the studies included professional athletes/sportsmen, while one included active-duty soldiers, and in the rest of the studies characteristics of the patient groups were not specified. In addition, some studies included patients who had been refractory to non-surgical treatment, which makes it difficult to know if outcomes are due to treatment effects or whether patient characteristics had been of influence.

To measure outcomes, three studies used the modified Harris Hip Score (MHHS), three used the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), four solely used return-to-play outcomes and the remaining used subjective questionnaires i.e. pain relief, improvement of mechanical symptoms and patient satisfaction after surgery. Outcomes reported were the '*number of patients return to play*', '*good to excellent outcomes*' and '*data failures*' which was defined by a dissatisfied patient and/or conversion to total hip arthroplasty. The outcomes are generally positive (for details see Table 2 in the review paper). However, it is unclear how the subjective outcome of '*good to excellent results*' was defined, particularly with different instruments used and how '*patient satisfaction after surgery*' was measured in each of the studies that reported these outcomes. Mean follow-up duration in the studies varied largely from ten months to 42 months and the mean follow-up duration of the studies was 26 months, therefore information regarding long term outcomes is limited.

National Institute for Health and Clinical Excellence. Interventional procedures overview of arthroscopic femoro-acetabular surgery for hip impingement syndrome. September 2006.

This is an overview consisting of a rapid review of the medical literature and specialist opinion. It aimed to assess the safety and efficacy of arthroscopic femoro-acetabular surgery for hip impingement syndrome. The rapid review is of reasonable methodological quality, with a good search strategy and predefined inclusion and exclusion criteria. The latest database search was up to September 2006, which is somewhat out of date.

Two studies were included in the review. They were published in 2005 and 2006 respectively, however, were not included in Bedi 2008.[1] Both studies are USA based small case series, with sample sizes being ten and 158 respectively. Patients in the smaller study were aged 34 years and in the other were 14 -73 years. Characteristics of the patients in the studies are unclear as insufficient demographic data were available. Follow-up lengths were 16 months and a maximum of 22 months respectively. Outcomes reported were operative success and safety. In the study with 158 patients, nearly all patients reported resolution of impingement signs on clinical evaluation. Most of the patients had pain reduced by 50% at three months, 75% at five months and 95% at one year. Two percent (3/158) required a total hip replacement at a mean follow-up of 22 months. A pathological non-displaced or un-displaced fracture requiring pinning occurred in one of the 158 patients. In the study with ten patients, the mean non-arthritic hip score on the McCarthy scale improved from 75% points to 95% points at 14 months follow-up. However, it is unclear how the outcomes e.g. resolution of impingement signs and pain reduction, were measured, or whether validated measurement instruments were used.

The review authors identified the following limitations: there was a difference in the surgical technique between the two included studies; very limited efficacy outcomes and outcome measurement details were reported; and the degree of severity of patients' conditions was not well defined.

The NICE guidance on arthroscopic femoro-acetabular surgery for hip impingement syndrome[1], which was based on the above review, stated that "*current evidence on the safety and efficacy of arthroscopic femoro-acetabular surgery for hip impingement syndrome does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research*", and "*the natural history of hip impingement syndrome and the selection of patients for this procedure are uncertain*".

Conclusions

The main limitation with the data identified in both reviews was that it had been derived from retrospective case series; therefore the effectiveness of arthroscopic surgery for hip impingement and/or hip pain compared with any conventional approach cannot be determined overall and within any particular subgroups. Neither review evaluated cost-effectiveness of this procedure.

References

1. Bedi A, Chen N, Robertson W, Kelly BT. Systematic review: the management of labral tears and femoroacetabular impingement of the hip in the young, active patient. Arthroscopy 2008; 24(10):1135-1145

2. National Institute for Health and Clinical Excellence. Arthroscopic femoro-acetabular surgery for hip impingement syndrome. London: National Institute for Health and Clinical Excellence (NICE); 2007.
   Available from http://www.nice.org.uk/IPG213 [Accessed on 22-02-2010]

3. National Institute for Health and Clinical Excellence. Interventional procedures overview of arthroscopic femoro-acetabular surgery for hip impingement syndrome. London: NICE; 2006. Interventional Procedures Programme, IP365. Available from http://www.nice.org.uk/IPG213 [Accessed on 22-02-2010]

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 Surgical Procedures, Minimally Invasive/
2 Arthroscopy/
3 arthroscop$.tw.
4 percutan$.tw.
5 key hol$.tw.
6 keyhole$.tw.
7 or/1-6
8 ((hip$ or femor$ or femur$ or acetab$) adj3 impin$).tw.
9 ((hip$ or femor$ or femur$ or acetab$) adj3 (catch$ or trap$ or obstruct$)).tw.
10 fai.tw.
11 (cartilag$ adj3 impin$).tw.
12 (cartilag$ adj3 (catch$ or trap$ or obstruct$)).tw.
13 or/8-12
14 7 and 13
15 (femoro acetabular or femoroacetabular).tw.
16 7 and 15
17 14 or 16
18 limit 17 to "reviews (optimized)"

Appendix B – Literature search results

Systematic reviews

Source – Cochrane Library (DARE) 2010 Issue 1

Bedi A, Chen N, Robertson W, Kelly B T.
The management of labral tears and femoroacetabular impingement of the hip in the young, active patient. Arthroscopy 2008; 24 (10): 1135-1145

Source – Cochrane Library (HTA) 2010 Issue 1

National Institute for Health and Clinical Excellence
Arthroscopic femoro-acetabular surgery for hip impingement syndrome
London: National Institute for Health and Clinical Excellence (NICE);
2007.
http://www.nice.org.uk/guidance/index.jsp?action=download&o=31726

Arthroscopic hip surgery for femoroacetabular impingement (FAI). HAYES, Inc; 2008

Source – ARIF database

Robertson WJ, Kadrmas WR, Kelly BT. Arthroscopic management of labral tears in the hip: a systematic review of the literature. Clinical Orthopaedics and Related Research 2007; 455:88-92.

Source – MEDLINE (Ovid) 1950 – Jan 2010

Dienst, M. Kohn, D.
[Arthroscopic treatment of femoroacetabular impingement. Technique and results]. [Review] [25 refs] [German]
Orthopade. 38(5):429-43, 2009 May.

Friend, L. Kelly, Bryan T.
Femoroacetabular impingement and labral tears in the adolescent hip: diagnosis and surgical advances. [Review] [32 refs]
Current Opinion in Pediatrics. 21(1):71-6, 2009 Feb.

Ilizaliturri VM Jr.
National Rehabilitation Institute of Mexico, Amores 942-21, Colonia del Valle, Mexico City, 03100, Mexico. vichip2002@yahoo.com.mx
Complications of arthroscopic femoroacetabular impingement treatment: a review. [Review] [34 refs]

Philippon MJ. Stubbs AJ. Schenker ML. Maxwell RB. Ganz R. Leunig M.
Arthroscopic management of femoroacetabular impingement: osteoplasty technique and literature review. [Review] [64 refs]
American Journal of Sports Medicine. 35(9):1571-80, 2007 Sep.

Wettstein M. Zambelli PY. Theumann N.
[Femoro-acetabular impingement]. [Review] [30 refs] [French]
Revue Medicale Suisse. 3(105):884-9, 2007 Apr 4.

Philippon MJ. Schenker ML.
Arthroscopy for the treatment of femoroacetabular impingement in the athlete. [Review] [28 refs]
Clinics in Sports Medicine. 25(2):299-308, ix, 2006 Apr.

Wettstein M. Dienst M.
[Hip arthroscopy for femoroacetabular impingement]. [Review] [46 refs] [German]
Orthopade. 35(1):85-93, 2006 Jan.

Kelly BT. Weiland DE. Schenker ML. Philippon MJ.
Arthroscopic labral repair in the hip: surgical technique and review of the literature. [Review] [34 refs]
Arthroscopy. 21(12):1496-504, 2005 Dec.

Other reviews

Source – HTAi Vortal

AETNA. Clinical Policy Bulletin: femoro – acetabular surgery for hip impingement syndrome; 2008. http://www.aetna.com/cpb/medical/data/700_799/0736.html

Source – Provided as background

BlueCross BlueShield of North Carolina**.** Corporate Medical Policy. Arthroscopic surgery for femoroacetabular impingement. BlueCross BlueShield of North Carolina; 2009.

CIGNA medical coverage policy. Hip surgery for femoroacetabular impingement syndrome (FAI). CIGNA; 2009.

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Assisted Ventilation Bronchiolitis

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Question Reformulated

We identified a list of currently employed treatments for bronchiolitis. This request focuses on the use of assisted ventilation.

Reviews Identified

None identified.

Other Literature Identified

- Smith PG, el Khatib MF, Carlo WA. PEEP does not improve pulmonary mechanics in infants with bronchiolitis. American Review of Respiratory Disease 1993; 147: 1295-1298
- Steinhorn RH and Green TP. Use of extracorporeal membrane oxygenation in the treatment of respiratory syncytial virus bronchiolitis: The national experience, 1983 to 1988. Journal of Paediatrics 1990; 116: 338-342

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Comments

There appears to be very little existing research on different methods of assisted ventilation in infants with bronchiolitis. We identified no relevant reviews or trials. The paper by Smith et al described a case series of the use of positive end-expiratory pressure. This highlights some of the adverse effects of positive pressure ventilation (PPV) in children, which form the basis of the rationale for the use of CNEP, and other alternative methods of ventilatory support.

The other paper cited is a retrospective analysis of data from the United States National ECMO Registry and the authors suggest that this may be a useful alternative to PPV.

In summary, there is no reliable evidence at this point in time, which compares different methods of assisted ventilation in infants with bronchiolitis.

Additional information relevant to this request is available in the requests entitled Bronchiolitis/Bronchodilators, Bronchiolitis/Continuous Negative Extrathoracic Pressure (CNEP), Bronchiolitis/Ribavirin, Bronchiolitis/Immunoglobulin, Bronchiolitis/Steroids, Bronchiolitis/Antibiotics

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Atenolol Betablocker Hypertension

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The Problem Submitted for ARIF to Advise Upon:

What is the quality of a recent systematic review (Carlberg et al, 2004) assessing the effect of atenolol on cardiovascular morbidity and mortality in hypertensive patients?

Reviews Identified

- Carlberg B, Samuelsson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? Lancet 2004; 364:1684-89
- Volmink J, Bradley H, Maroney R, Mbewu A, Opie L. Betablockers for hypertension (Protocol) The Cochrane Database of Systematic Reviews 1998; Issue 4. Art No: CD002003

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Comments

Carlberg et al compare the effects of atenolol with placebo/no treatment and the effects of atenolol with other antihypertensive drugs.

They conclude that atenolol reduces hypertension when compared with placebo/no treatment but does not lead to improved cardiovascular outcomes. Furthermore they conclude that whilst atenolol has a similar impact on hypertension to other antihypertensive drugs it is less effective in improving clinical outcomes such as cardiovascular mortality and stroke.

A formal appraisal of the paper identified a number of issues that suggested the authors' conclusions concerning atenolol need to be treated with caution. A Cochrane review in progress (Volmink et al, 1998) may help to place the findings on atenolol within the broader context of RCT's on other betablockers used in the treatment of hypertension.

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Dyadic Developmental Psychotherapy Attachment Disorder 'Looked After' Children

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence on the effectiveness/cost effectiveness of dyadic developmental psychotherapy in the treatment of children with attachment disorders and particularly the effect on adoption rates amongst 'looked after' children?

'Looked After' children are those children cared for by local authorities.

Dyadic developmental psychotherapy involves the building of attachment between child and guardian through the utilisation of 'holding therapies', developing feelings of security and the involvement of the guardian.

Reviews Identified

No systematic reviews were identified.

Trials Identified

- Becker-Weidman. Dyadic developmental psychotherapy: an effective treatment for children with trauma-attachment disorders. URL: http://www.attach.org/protocals/CFDprotocals_files/cdf_research.htm [accessed 29 April 2003] - no longer accessible see - http://www.articlesbase.com/authors/arthur-becker-weidman,-ph.d./80088.htm
- Myeroff R, Mertlich G, Gross J. Comparative effectiveness of holding therapy with aggressive children. Child Psychiatry and Human Development 1999; 29(4):303-313

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Comments

We identified no systematic reviews on this topic.

We identified no studies that looked at the effect of dyadic developmental psychotherapy in 'looked after' children.

The two primary studies on dyadic developmental psychotherapy enrolled children already in a family environment. The studies differed in the delivery of the therapy in that one was an intensive 2-week course and the other was multiple sessions delivered over a year. Both studies enrolled small sample sizes and were subject to bias and confounding due to the nature of the study designs employed. Only one of the studies was published in a peer reviewed journal (Myeroff et al 1999). Therefore, although the results suggest that dyadic developmental psychotherapy reduces antisocial behaviour, the findings should be treated with caution.

Both the studies highlighted the need for robust further research on those populations already studied and other groups. We concur with this recommendation.

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Ritalin
Attention Deficit Hyperactivity Disorder

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The Problem Submitted for ARIF to Advise Upon:

What is the benefit of continuing treatment with Ritalin in adulthood for patients who have been treated with Ritalin (as children) for ADHD?

Reviews Identified

- Higgins ES. A comparative analysis of antidepressants and stimulants for the treatment of adults with attention-deficit hyperactivity disorder. Journal of Family Practice 1999;48(1):15-20
- Jadad AR, Boyle M, Cunningham C, Kim M, Schachar R. Treatment of attention-deficit/hyperactivity disorder. Rockville, MD, USA: Agency for Healthcare Research and Quality. Evidence Report/Technology Assessment Number 11 1999. 1-341. Summary available at www.ahcpr.gov/clinic/epcsums/adhdsum.htm
- Wilens TE, Biederman J, Spencer TJ, Prince J. Pharmacotherapy of adult attention deficit/hyperactivity disorder: a review. Journal of Clinical Psychopharmacology 1995;15(4):270-279

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Comments

The three reviews above examined the effectiveness of Ritalin treatment in adults with ADHD. The estimates of effectiveness of Ritalin in decreasing symptoms of ADHD ranged from 25-78% across all three reviews. There was substantial heterogeneity in the diagnostic criteria of ADHD in the included trials, dosage of Ritalin and methods of assessing outcomes in all three reviews. Another caution regarding the interpretation of these results is that all the included trials were small, with the largest trial enrolling only 51 patients. It was also unclear whether patients treated with Ritalin as adults had been treated with Ritalin previously as children or adolescents. Therefore the reviews do not specifically inform about the continuation of treatment with Ritalin into adulthood in patients diagnosed with ADHD as children, but provides some promising evidence for the effectiveness of Ritalin in reducing symptoms of ADHD in adult patients.

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Audiological Screening
Down's Syndrome

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The Problem Submitted for ARIF to Advise Upon:

What is the strength of the evidence that screening adults with Downs Syndrome for hearing impairment is of benefit and is cost-effective?

Reviews Identified

- Murdoch H. He can hear when he wants to! Assessment of hearing function for people with learning difficulties. British Journal of Learning Disabilities 1994; 22: 85

Other Studies Considered

- Prasha V. Screening of hearing impairment and associated effects on adaptive behaviour in adults with Down Syndrome. British Journal of Developmental Disabilities 1995; 41: 1126-1132
- Yeates S. The incidence and importance of hearing loss in people with severe learning disability: the evolution of a service. British Journal of Learning Disabilities 1995; 23:79-84
- Yeates S. Have they got a hearing loss? A follow up study of hearing in people with mental handicaps. Mental Handicap 1992; 20: 126-133
- Yeates S. Hearing in people with mental handicaps: a review of 100 adults. Mental Handicap 1989; 17: 33-37

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Comments

No systematic reviews of the effects/effectiveness of screening for hearing impairment in adults with Down's Syndrome were identified.

The reference by Murdoch H provides useful background information on issues needing to be considered in measuring hearing impairment.

The four other studies considered provide data on the prevalence of hearing impairment in populations who might potentially be targeted for screening. There is a marked variation which is most likely to be accounted for by:

- Differences in the populations examined.
- Differences in the methods used to detect hearing impairment.

In answering the question on the strength of the evidence to support audiological screening for adults with Down's Syndrome we must take into account that we could not identify:

- Any study indicating the overall effectiveness or cost effectiveness of a screening programme
- Any study indicating the test performance of the diagnostic/screening tests which might be employed (against a gold/reference standard)
- Any study indicating the effects of manoeuvres to ameliorate any hearing loss identified on the fraction of adults with Down's Syndrome

Thus, on the basis of our search, the strength of evidence must be considered weak, although the prevalent studies suggest that there is potential to improve health.

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Archived ARIF Request

Autoinflation
Glue Ear

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The Problem Submitted for ARIF to Advise Upon:

What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Question Reformulated

Due to the breadth of this question, we focused our attention on groups of interventions. The groups of interventions were antimicrobial drugs, steriods, antihistamines and decongestants, mucolytic agents, and auto-inflation.

This web page details our findings on autoinflation. Links to pages on the other groups of interventions can be found at the bottom of this page.

Reviews Identified

- Williamson I. Otitis media with effusion. In: Clinical Evidence 3. London: BMJ Publishing Group, 2000. Pp248-254
- Reidpath DD, Glasziou PP, Del Mar C. Systematic review of autoinflation for treatment of glue ear in children. BMJ 1999, 318, pp.1177-1178

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Comments

The review by Williamson is a systematic overview of treatments for glue ear and for the most part appears a concise and accurate synthesis of the evidence presented in other systematic reviews.

We identified one systematic review on the use of autoinflation (blowing up a balloon with the nose) for treatment of glue ear, Reidpath et al 1999. This was also the only review identified by the overview by Williamson.

In general this appears to be a well conducted review although the brief format of the report precludes assessment of some characteristics. The authors noted that the RCTs included in the review were of variable and low quality, were short term and for many characteristics were not comparable. Three of

the six included RCTs employed manufactured nasal balloons and in the short term, children treated by this method tended towards (n=1) or were significantly more likely (n=2) to show 'recovery' or improvement by tympanogram, than controls. Other methods (toy balloons/modified anaesthetic mask) showed no benefit over controls. A point to note is that the nature of the controls is not clearly stated in this review. The authors conclude that the evidence on treatment using autoinflation is conflicting but it may be of clinical benefit and that larger and better-conducted trials are required.

Although, the overview by Williamson accurately reports the findings of the review, it presents the potential clinical benefit of autoinflation using a nasal balloon more positively than the cautious overall approach taken by the original reviewers.

Additional information relevant to this topic is available in the other web pages on glue ear and these are on the following interventions: antimicrobial drugs, steroids, antihistamines and decongestants, and mucolytic agents.

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Automated Peritoneal Dialysis Renal Failure

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The Problem Submitted for ARIF to Advise Upon:

Are there any recognised criteria for the use of automated peritoneal dialysis and is it a cost-effective form of treatment for end stage renal failure?

Reviews Identified

- Wrenger E et al. Adequacy and quality of life with automated peritoneal dialysis. Peritoneal Dialysis International 1996; 16 Supplement 1: S153-S157
- Hiroshige K et al. Rapid decline of residual renal function in patients on automated peritoneal dialysis. Peritoneal Dialysis International 1996; 16(3): 307-315
- Blake PG. Targets in CAPD and APD prescription. Peritoneal Dialysis International 1996; 16 Supplement 1: S143-S146

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Comments

No systematic reviews were identified. We used research articles identified by a search on Medline of which the three listed were particularly useful to inform us about important issues needing to be considered in gauging the effects of APD relative to other methods of renal replacement, with the following conclusions:

1. This is a complex and highly technical subject. We do not have complete confidence that all the important issues have been identified in the literature we examined. Talking to "experts" in the field would be a very important source of additional information.
2. It seems that the way in which the equipment is employed is as important as the equipment itself.
3. In terms of use of APD it is worth trying to distinguish if APD is being used:
   a) when other methods of controlling uraemia are contraindicated, especially continuous ambulatory peritoneal dialysis (CAPD) because of hernias, poor sight ie providing an additional option where otherwise none would exist;
   b) as a first/second choice option in preference to other methods of replacing renal function, because it is believed that APD produces better outcomes that CAPD or haemodialysis (HD);

c) in combination with other methods of replacing renal function, especially CAPD because it is believed that "more dialysis", or "adequate" dialysis produces better outcomes.

The evidence required to consider whether each of the general uses listed above is appropriate, will differ, and I suspect that in the case of a) the only evidence required is that individuals who cannot use other methods of renal replacement do exist and that APD can control uraemia. However, for b) and c) there is a requirement to show benefit relative to an alternative and so it is in these situations that I would expect research on effectiveness, if it exists, to be most helpful.

In conclusion the appraisal of research identified does help us understand this issue better, but does little to tell us reliably relative to other forms of renal replacement. Further I am not sure that searching for further research will help clarify things; only doing a completely systematic review is likely to achieve this.

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Gastrointestinal Disease
Autism

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The Problem Submitted for ARIF to Advise Upon:

What is the extent of the association between autism and chronic gastrointestinal disease?

There has been the suggestion that chronic gastrontestinal disease and malabsorption may be causal factors in the development of autism. It is important therefore to ascertain the extent of any association between autism and chronic gastrointestinal disease.

Reviews Identified

No systematic reviews were identified on this topic.

Primary Studies Identified

- Black C et al. Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database. BMJ 2002; 325:419-421

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Comments

The aim of the case-control study by Black et al was to assess the frequency of chronic inflammation of the gastro-intestinal tract, food intolerance and recurrent gastrointestinal symptoms among children with a diagnosis of autism compared to children without autism. There was no evidence that children with autism were more likely to have defined chronic gastrointestinal disorders than children without autism.

A particular strength of this study is that symptoms of gastrointestinal problems would have been recorded at the time they were reported to the GP rather than being retrospectively recalled by parents and/or caregivers at a later date. This substantially decreases the potential for recall bias, often a problem in case-control studies.

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Gluten-Free Diets
Autism

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of gluten-free diets for autistic children?

Reviews Identified

No systematic reviews were identified.

Primary Studies Identified

- Sponheim E. Gluten-free diet in infantile autism. A therapeutic trial. Tidsskrift for Den Norske Laegeforening 1991;111(6):704-7

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Comments

We did not identify any systematic reviews on this topic. We did identify one very small trial in which seven children with autism were randomised to receive either receive a gluten-free diet for six months or a gluten-placebo. There was no association observed between gluten and behaviour typical for these patients. The main problem with this trial is the small sample size which limits the conclusions that can be drawn about the effectiveness of gluten free diets.

Further robust research is required in this area particularly in regarding additional issues such as compliance of patients to prescribed diets and the implementation of the dietary regime especially when the initial effects may be negative and may include stomach upsets, anxiety, dizziness, clinginess, and aches and pains. These may be precursors of a positive response, but it is worth noting that the effects of withdrawal are more noticeable in very small children (younger than four years of age). A trial period of three months is usually recommended and if the intervention has not shown any beneficial effect after that period of time, it is unlikely to do so.

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Sensory Integration Therapy Autism

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence on the effectiveness of sensory integrated therapy provided by occupational therapists to children with autism? In particular, is there any evidence for the most effective number of sessions or length of treatment?

Sensory integrated therapy involves using pieces of equipment to provide sensory awareness of one's own body and position. The aim is to encourage children to make adaptive responses to the stimuli in order to improve how the brain processes and organises sensory input.

Reviews Identified

- Lipson A, Edwards P, Logan GS. Occupational therapy and physiotherapy for developmental coordination disorder (Protocol for a Cochrane review). In: The Cochrane Library, Issue 2, 2003. Oxford: Update Software.

Trials Identified

- Humphries T, Wright M, Snider L, McDougall B. A comparison of the effectiveness of sensory integrative therapy and perceptual motor training in treating children with learning disabilities. Developmental and Behavioral Pediatrics 1992; 13(1): 31-40

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Comments

We identified no robust evidence for the effectiveness of sensory integration therapy for the treatment of autistic children.

The RCT by Humphries found some evidence for the improvement in motor planning and performance in children with learning disabilities and sensory dysfunction. However, these changes were not accompanied by improvements in a number of other functional outcomes relating to learning and academic performance.

In addition, we found no evidence relating to the frequency of treatment with sensory integration

therapy to produce benefits in children with autism or with learning disabilities.

A Cochrane Review is currently ongoing to evaluate physiotherapy and occupational therapy interventions for developmental coordination disorder, or equivalent conditions such as sensory integrative dysfunction, developmental dyspraxia, clumsy child syndrome and minimal brain dysfunction.

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Archived ARIF Request

Autologous Stem Cell Transplant
Stem Cell Transplant
Systemic Sclerosis

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of autologous stem cell transplantation for systemic sclerosis?

The requestor required a rapid response and therefore only the key article below was appraised.

Systemic sclerosis is a connective tissue disease precipitated by an altered immune function. T cell and fibroblast activation, together with the release of cytokines, leads to microvascular damage, increased collagen production and results in sclerosis (hardening of tissue). The disease is multisystem, predominantly affecting skin, gastrointestinal tract, heart, lungs, kidney and muscles. The effects are progressive and life expectancy may be reduced. Treatment is organ/symptom based but there is no intervention to prevent overall progression of the disease.

Autologous stem cell transplant involves the intravenous infusion of autologous (taken from the patient) stem cells collected from the bone marrow or peripheral blood, to re-establish hematopoietic function in patients with damaged or defective bone marrow or immune systems. The stem cells are treated prior to infusion to remove the potential for an auto-response to the patient. The patient is treated prior to infusion to deplete the immune system of auto-antibodies.

Reviews Identified

- Farge D, Passweg J, van Laar JM et al. Autlogous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR Registry. Annals of the Rheumatic Diseases 2004;63:974-981

Randomised Controlled Trials

Ongoing RCT:

- A multicenter, prospective randomized phase III study to compare efficacy and safety of high dose immunoablation and autologous hematopoietic stem cell transplantation with intravenous pulse therapy cyclophosphamide for the treatment of patients with severe systemic sclerosis. EBMT/EULAR Scleroderma Study Group. http://www.astistrial.com/

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Comments

The article by Farge et al, reports on the follow-up of patients enrolled in phase I-II studies using data in the European Bone Marrow Transplant/Rheumatism Registry. From the data presented autologous stem cell transplant appears to be a promising emerging intervention for systemic sclerosis. However, the current evidence of effectiveness should be treated with caution as it comes from uncontrolled studies with incomplete and/or limited follow-up of surviving patients. In addition, health related quality of life has not been measured. Further and more robust evaluation of the clinical effectiveness of autologous stem cell transplant is required. There is an on-going randomised controlled trial (RCT) due to end in 2008, which will hopefully address this need (see above). Moreover, this RCT indicates there is a willingness and an ability to conduct more robust research on this rare disease.

Due to the current absence of robust data we suggest that autologous stem cell transplant is regarded as a promising emerging, but still largely experimental, intervention for systemic sclerosis. If any patient is to receive this intervention they should do so as part of a robust evaluation of the effectiveness of the intervention and ideally as part of an RCT. Furthermore, patients should be made fully aware that it is an intervention under-investigation and fully understand the risks involved, and in particular treatment related deaths.

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Archived ARIF Request

Automated Implantable Cardioverter Defibrillators Cardiac Arrhythmias

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The Problem Submitted for ARIF to Advise Upon:

What is known about the effectiveness and cost-effectiveness of automatic implantable cardioverter defibrillators (ICD) in the management of ventricular arrhythmias?

Reviews Identified

None identified.

Trials Identified

- The antiarrhythmics versus implantable defibrillators (AVID) investigators. A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. New England Journal of Medicine 1997; 337: 1576-1583
- Moss AJ, Hall WJ, Cannom DS et al. (MADIT). Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. New England Journal of Medicine 1996; 335: 1933-1940
- Siebels J, Cappato R, Ruppel R et al. Preliminary results of the Cardiac Arrest Study Hamburg (CASH). American Journal of Cardiology 1993; 72: 109F-113F

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Comments

We identified no systematic reviews on this subject, but identified a number of trials which were either ongoing, or very recently published, at the time of writing:

- CIDS - The Canadian Implantable Defibrillator Study
- CASH - Cardiac Arrest Study Hamburg
- MADIT - Multicentre Automatic Defibrillator Implantation Trial
- AVID - Antiarrhythmic versus Implantable Defibrillators Trial
- MUSTT - Multicentre Unsustained Tachycardia Trial

The three trials cited are reports of the MADIT and AVID trials, which have recently been completed,

and one arm of the CASH trial, which was stopped early. The AVID and the MADIT trials are both reasonably well-conducted, large, multicentre trials, the results of which demonstrate improved survival in the ICD groups. However, certain methodological features of both studies could have resulted in an overestimation of the size of effect. The CASH trial, which is also a large, well-organised trial, reported early on that survival in the ICD arm was significantly better than that of the propafenone arm. This led the trial safety board to recommend the early stopping of this arm of the trial, but the amiodarone and metoprolol arms continue.

The overall pattern of results consistently demonstrates the superiority of ICD over drug treatments, even given the possibility that some overestimation of the size of effect may have occurred. What is not available, however, is good information on cost-effectiveness. The ICD is an expensive option and more certainty around the size of effect required before a judgment about cost-effectiveness can be made.

Robust conclusions about the effectiveness and cost-effectiveness of the ICD relative to drug therapy will have to await the full results of these trials.

This is an area prone to need for regular updating as new information is continually becoming available.

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Mycophenolate Mofetil for Behcet's disease

Synopsis

Question:	What is the clinical effectiveness of mycophenolate mofetil for patients with Behcet's disease?
Evidence Identified:	No systematic reviews, health technology assessments or on-going studies were identified. Three primary studies were identified which were somewhat relevant: Adler YD, Mansmann U, Zouboulis CC. Mycophenolate mofetil is ineffective in the treatment of mucocutaneous Adamantiades-Behcet's disease. Dermatology 2001;203(4):322-4 Neri P, Mariotti C, Cimino L, Mercanti L, Giovannini A. Long-term control of cystoid macular oedema in noninfectious uveitis with Mycophenolate Mofetil. International Ophthalmology 2009;29(3):127-33 Llinares-Tello F, Hernandez-Prats C, Munoz-Ruiz C, Selva-Otaolaurruchi J, Ordovas-Baines JP. Monitoring trough plasma concentrations of mycophenolate mofetil in patients with uveitis. Journal of Clinical Pharmacy & Therapeutics 2004;29(1):53-8
Comments:	Current evidence on the effectiveness of mycophenolate mofetil for Behcet's disease is very limited.
Date Completed:	June 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Mycophenolate Mofetil for Behcet's disease

Request completed: June 2010

Question

What is the clinical effectiveness of mycophenolate mofetil for patients with Behcet's disease who are intolerant of immunosuppressive treatment with methotrexate, cyclosporine and azathioprine?

Question clarification

Population	Patients with Behcet's disease who are intolerant of immunosuppressive treatment with methotrexate, cyclosporine and azathioprine
Intervention	Mycophenolate mofetil (MMF); MMF plus steroid
Comparator	Steroid, interferon, anti-TNFs or any other standard immunosuppressive agents other than methotrexate, cyclosporine or azathioprine
Outcome	Effects (including reducing inflammation, visual acuity, etc); side effects
Study design	Systematic reviews and health technology assessments

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol http://www.arif.bham.ac.uk/strategy.shtml. Primary studies were sought in CENTRAL, MEDLINE and EMBASE. On going studies were sought in ClinicalTrials.gov and Controlled-trials.com. Text and index terms were used to represent the population and the intervention. Sources were searched from their inception to May 2010. No language restriction was applied to the searches. The MEDLINE search can be found in Appendix A. The inclusion criteria for study search and selection were widened as the follows:

Population	Patients with Behcet's disease
Intervention	Mycophenolate mofetil (MMF) or MMF plus steroid
Study design	Systematic reviews; health technology assessments; primary studies of any type

Results

Full search results can be found in Appendix B.

No systematic reviews or health technology assessments were identified.

One guideline[1] for the management of Behcet's disease developed by the European League Against Rheumatism and published in 2008 was identified, however, in its recommendations mycophenolate mofetil was not stated for the management of Behcet's disease.

Four primary studies were identified (see Appendix B), three of which were somewhat relevant to the question. Of the three studies, one[2] was a case series study investigating the effectiveness and toxicity of MMF plus prednisolone in 30 patients with Behcet's disease. The primary outcome was the decrease in the disease activity index. However, the study was interrupted for ethical reasons due to inefficacy of MMF after the intermediate evaluation of the first six patients. The second study was a retrospective case series[3] investigating long-term safety and efficacy of MMF for the control of cystoid macular oedema in 19 patients, of which only three were affected by Behcet panuveitis. The third[3] monitored plasma concentrations of MMF in 12 patients with uveitis, of which only one had Behcet's disease. These three studies, with only a total of ten relevant patients, add little value to the question of this report. Table 1 below outlines the characteristics of the three studies.

An additional search for on-going studies based on the above criteria identified no studies.

Table 1. Outline of primary studies

Study	Study design	Population	Intervention	Outcome (or outcome measure)
Adler 2001[2]	Prospective case series	Patients with mucocutaneous Behcet's disease; n = 30 (targeted for recruitment)	MMF for 6 months + prednisolone for the first month	An improvement of the DAI was found after the first month but withdrawal of prednisolone led to quick relapses. As such, The study was interrupted for ethical reasons due to inefficacy of the compound after intermediate evaluation of the first six patients.
Neri 2009[3]	Retrospective case series	Patients with cystoid macular oedema (CMO) secondary to non-infectious uveitis, and unresponsive to traditional immuno-suppressants; n = 19 (only 3 had Behcet panuveitis)	MMF	All the 3 patients with Behcet's panuveitis had recurrences of CMO at the last follow-up (27-37th month)
Linares-Tello 2004[4]	Prospective case series	Patients with uveitis; n = 12 (only one had Behcet's disease)	MMF	Trough plasma concentrations of MPA; Visual acuity. (However the results were not reported separately for the one patient with Behcet's disease)
DAI: Decrease in the disease activity index according to a modified variant of the Iran Behcet's Disease Dynamic Activity Measure system. **CMO**: cystoid macular oedema. **MPA**: mycophenolic acid.				

Conclusions

No systematic reviews or health technology assessments were identified. The only available evidence appears to come from three case series studies including a total of ten patients with

Behcet's disease. As such, the evidence base for the treatment of these patients with MMF is very limited.

References

1. Hatemi G, Silman A, Bang D, Bodaghi B, Chamberlain A M, Gul A et al. EULAR recommendations on the management of Behcet disease. Ann Rheum Dis 2008;67:1656-1662. Available on http://ard.bmj.com/content/67/12/1656.full.pdf [Accessed: 27-05-2010]

2. Adler YD, Mansmann U, Zouboulis CC. Mycophenolate mofetil is ineffective in the treatment of mucocutaneous Adamantiades-Behcet's disease. Dermatology 2001;203(4):322-4

3. Neri P, Mariotti C, Cimino L, Mercanti L, Giovannini A. Long-term control of cystoid macular oedema in noninfectious uveitis with Mycophenolate Mofetil. International Ophthalmology 2009;29(3):127-33

4. Llinares-Tello F, Hernandez-Prats C, Munoz-Ruiz C, Selva-Otaolaurruchi J, Ordovas-Baines JP. Monitoring trough plasma concentrations of mycophenolate mofetil in patients with uveitis. Journal of Clinical Pharmacy & Therapeutics 2004;29(1):53-8

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 (mmf or cellcept).mp.
2 mycophenolate mofetil.mp.
3 or/1-2
4 behcet$.mp.
5 Behcet Syndrome/
6 4 or 5
7 3 and 6

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Appendix B – Literature search results

Systematic reviews

None identified

Primary studies

Source – MEDLINE (Ovid) 1950 – May week 2 2010

Neri P, Mariotti C, Cimino L, Mercanti L, Giovannini A.
Long-term control of cystoid macular oedema in noninfectious uveitis with Mycophenolate Mofetil.
International Ophthalmology. 29(3):127-33, 2009 Jun.

Llinares-Tello F, Hernandez-Prats C, Munoz-Ruiz C, Selva-Otaolaurruchi J, Ordovas-Baines JP.
Monitoring trough plasma concentrations of mycophenolate mofetil in patients with uveitis.
Journal of Clinical Pharmacy & Therapeutics. 29(1):53-8, 2004 Feb.

Adler YD, Mansmann U, Zouboulis CC.
Mycophenolate mofetil is ineffective in the treatment of mucocutaneous Adamantiades-Behcet's disease.
Dermatology. 203(4):322-4, 2001.

Source – EMBASE (Ovid) 1980 – 2010 week 20

Moghimi J, Daraee G.
A case report on dramatic response of refractory panuveitis of Behcet disease to short-term therapy with Infliximab followed by Cellcept.
Koomesh. 10(3)(pp 225-227+34), 2009

Guidelines

Source – NHS Evidence

G Hatemi, A Silman, D Bang, et al. EULAR recommendations on the management of Behcet disease. Ann Rheum Dis 2008 67: 1656-1662
http://ard.bmj.com/content/67/12/1656.full.pdf

Background information

Source – General internet searches

NHS Clinical Knowledge Service. Behcet's syndrome – a patient booklet.
http://www.cks.nhs.uk/patient_information_leaflet/behcets_syndrome_arc

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Archived ARIF Request

Bosentan
Sildenafil
Berapost
Iloprost
Pulmonary Arterial Hypertension

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in April 2006.

The Problem Submitted for ARIF to Advise Upon:

Critical appraisal of “Goal-orientated treatment and combination therapy for pulmonary arterial hypertension” Hoeper MM, Markevych I, Spiekerkoetter E. et al. European Respiratory Journal 2005;26(5) 858-863 in relation to assessment of study design and interpretation of the results particularly regarding the effectiveness of dual therapy relative to monotherapy.

Comments

The results from this study suggest that the prospective intervention group had better outcomes than the historical control group. However the results have to be treated with caution in that they do not originate from a randomised controlled trial. Differences in survival estimates may be due to the intervention but could also be due to bias inherent in the study design. On balance the study provides fair support for direction of effect (prospective treatment protocol better than historical), but poor evidence on the size of that effect.

As to whether combination therapy is superior to monotherapy, this study cannot answer this question because the intervention was monotherapy versus a treatment algorithm, of which only 43% of the participants in the algorithm went on to receive combination therapy.

What this paper makes clear is the assessment of this is not straight-forward and will almost certainly require detailed assessment, such as that currently being undertaken by NICE. The NICE guidance is currently expected to be completed in May 2008.

Request Carried Out: April 2006

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Archived ARIF Request

Biventricular Pacing
Severe Heart Failure

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of biventricular pacing in patients with severe heart failure who have not responded to other treatment?

Reviews Identified

No systematic reviews were identified.

Trials Identified

- Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert JC, Multisite Stimulation in Cardiomyopathies (MUSTIC) Study. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. New England Journal of Medicine 2001; 344(12): 873-80

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Comments

We identified no systematic reviews on this topic. Cazeau et al (2001) was a single blind randomised controlled crossover study that examined the clinical efficacy and safety of biventricular pacing in patients with severe heart failure due to chronic left ventricular dysfunction. There were statistically significant differences favouring active biventricular pacing over inactive pacing in distance covered in the 6-minute walk test and in quality of life. These findings should be treated with caution as the study was small (n=67) and losses to follow up were high.

Request Carried Out: March 2002

Updated: March 2006 - A Regional Evaluation Report (REP) was produced in January 2006.

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The Bobath Method Cerebral Palsy

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The Problem Submitted for ARIF to Advise Upon:

How effective is the Bobath method as a therapy for children with cerebral palsy?

Reviews Identified

- Guarna F et al. An evaluation of the hemiplegic subject based on the Bobath approach. Parts I-III. Scandinavian Journal of Rehabilitive Medicine 1988; 20: 1-11 & 13-16

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Comments

No systematic reviews have been identified. However, Guarna F et al gives background information on the nature of the Bobath approach.

Request Carried Out: July 1996

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Archived ARIF Request

Bone Anchored Hearing Aids (Bilateral)
Conductive Hearing Loss
Deafness

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The Problem Submitted for ARIF to Advise Upon:

What is the clinical and cost-effectiveness of bilateral bone anchored hearing aids (BAHAs) in comparison with unilateral bone anchored hearing aids?

The BAHA is a bone conduction hearing device that comprises a titanium screw, permanently implanted into the mastoid bone of the skull, attached to an external sound processor by means of a skin penetrating connector. As the device bypasses the middle ear and directly stimulates the cochlea, it has been recommended for individuals with conduction hearing loss or discharging middle ear infection.

Reviews Identified

No systematic reviews were identified.

Primary Studies

- Bosman AJ, Snik AF, van der Pouw CT, Mylanus EA, Cremers CW. Audiometric evaluation of bilaterally fitted bone-anchored hearing aids. Audiology. 2001; 40(3): 158-67
- Dutt SN, McDermott A-L, Burrell SP, Cooper HR, Reid AP, Proops DW. Patient satisfaction with bilateral bone-anchored hearing aids: The Birmingham experience. The Journal of Laryngology & Otology. 2002; 116, Suppl No 28: 37-46
- Dutt SN, McDermott A-L, Burrell SP, Cooper HR, Reid AP, Proops DW. Speech intelligibility with bilateral bone-anchored hearing aids: the Birmingham experience. The Journal of Laryngology & Otology. 2002; 116, Suppl No 28: 47-51
- Priwin C, Stenfelt S, Granstrom G, Tjellstrom A, Hakansson B. Bilateral Bone-Anchored Hearing Aids (BAHAs): An Audiometric Evaluation. Laryngoscope. 2004; 114(1): 77-84
- Snik AF, Beynon AJ, Mylanus EA, van der Pouw CT, Cremers CW. Binaural application of the bone-anchored hearing aid. Annals of Otology, Rhinology & Laryngology. 1998; 107(3):187-93
- van der Pouw KTM, Snik FM, Cremers CW. Audiometric Results of Bilateral Bone-anchored Hearing Aid Application in Patients With Bilateral Congenital Aural Atresia. The Laryngoscope. 1998; 108(4): 548-53

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Comments

Five small case series with sample sizes ranging from 3 to 25 were identified; one of which (Dutt et al, 2002) reported patient satisfaction and speech intelligibility in separate papers

The studies highlighted some promising outcomes for patients with a second bone anchored hearing aid (BAHA). Audiometric tests undertaken indicated patients fitted with a bilateral as opposed to a unilateral BAHA showed an improved ability to localise the source of sounds and achieve a better recognition of speech in quiet and noisy conditions. Furthermore a high level of patient satisfaction with a second BAHA was evident.

However we would caution against taking these results at face value as the study design adopted is methodologically weak. Without a control group there is a tendency to provide positive results which may or may not be associated with the intervention that is being examined. Also, as the studies listed were not identified as part of a systematic review, the possibility of publication bias cannot be ruled out.

In overall conclusion, based on the evidence identified, the clinical effectiveness of bilateral BAHAs is neither fully supported nor refuted. Given the potential future demand for second side BAHAs a systematic review of the clinical and cost effectiveness of bilateral BAHAs would be beneficial.

Request Carried Out: September 2005

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Bone Densitometry
Osteoporosis

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The Problem Submitted for ARIF to Advise Upon:

What is the contribution of bone densitometry in the prediction of osteoporosis fracture and diagnosing osteoporosis. In particular, how does it help identify populations at risk of osteoporosis?

Question Reformulated:

It is particularly useful in considering this complex question to consider the following elements:

Intervention:
Apparatus to measure bone density, particularly bone densitometers, recognising that other methods such as ultrasound and CT scanning are available.

Further, bone density measurement should be considered as a package in conjunction with available treatment options, ie HRT, bisphosphonates, vitamin D and calcium etc.

Population:

- persons at any risk of future osteoporosis induced fracture - "Population screening"
- persons at high risk of future osteoporosis induced fracture - "Selective screening"
- persons who have already developed osteoporosis induced fracture/s - "Disease management"

Reviews Identified

There is a wealth of evidence which can be considered in addressing the question posed. The following three citations represent a starting point only.

- Sheldon TA, Raffle A, Watt I. Why the report of the Advisory Group on Osteoporosis undermines evidence based purchasing. British Medical Journal 1996; 312: 296-297
- Barlow D, Cooper C, Reeve J et al. Department of Health is fair to patients with osteoporosis. British Medical Journal 1996; 312: 297-298
- Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. British Medical Journal 1996; 312: 1254-1259

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Comments

The first two references are not systematic reviews, but are useful in understanding the rationale for the two prevalent opposing points of view, that there should not or that there should be increased provision of bone densitometry.

The last reference is the most easily accessible systematic review of the available evidence indicating how well bone density performs in identifying those who will or will not develop an osteoporosis induced fracture at some point in the future.

It helps explain why there is clear international consensus that population screening of bone density is not viable at present. Because of the degree of overlap between the bone densities of those who do and those who do not subsequently fractures, the numbers of false positive results (persons thought to be at risk, who never develop fragility fractures) and false negative results (persons thought to be normal, who do develop fragility fractures) are felt to be too large to justify population screening.

The same phenomenon explains why there is also considerable doubt about the usefulness of bone densitometry in those who by virtue of age, medical history or co-existent conditions are thought to be at higher risk of developing an osteoporosis induced fractures. Notwithstanding the higher prevalence of the condition "osteoporosis leading to future fracture", the performance of bone density measurement is such that it will still lead to significant numbers of incorrect identifications (and inappropriate management decisions). In judging whether the balance of benefit and harm resulting is favourable, account needs to be taken of the effectiveness of available treatment. Doubts have been expressed on the effectiveness of such treatments, on which point evidence is available and will be fed back in on-going requests on the effectiveness of the bisphosphonates and HRT.

With regard to the use of bone density in disease management the systematic review identified does not help. However, in this population group the diagnosis is usually not in doubt and the role of bone density measurement is to monitor the effects of treatment.

This is an area prone to need for regular updating as new information is continually becoming available.

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Bosentan
Pulmonary Hypertension

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of bosentan for the treatment of pulmonary hypertension?

See ARIF related request - Bosentan/Sildenafil/Beraprost/Pulmonary Arterial Hypertension

Reviews Identified

No systematic reviews were identified.

Trials Identified

- Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, Badesch DB, Roux S, Rainisio M, Bodin F, Rubin LJ. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet 2001; 358(9288):1119-23
- Rubin LJ, Badesch DB, Barst RJ, Keogh A, Galie N, Black CM, Pulido T et al. Bosentan therapy for pulmonary arterial hypertension. New England Journal of Medicine 2002; 346 (12):896-903

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Comments

No systematic reviews were identified.

In both the above placebo controlled trials there appears to be some benefits for patients treated with bosentan demonstrated by increased exercise capacity, improvements in functional class of illness and increased time to worsening of clinical condition.

However, the findings of the studies should be treated with some caution, given that bosentan has only been evaluated in randomised controlled trials against placebos and with short duration of follow up (12 weeks). There are a number of on-going open label trials collecting long-term safety data on bosentan for pulmonary hypertension.

Please note this is a topic in need of frequent updating.

Request Carried Out: June 2002

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Botulinum Toxin type A (BTX-A)
Limb Spasticity, Cerebral Palsy

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The Problem Submitted for ARIF to Advise Upon:

Is BTX-A a safe and effective treatment for the relief of limb spasticity in cerebral palsy?

Reviews Identified

None identified.

Trials Identified

- Koman LA, Mooney JF, Smith BP et al. Management of spasticity in cerebral palsy with botulinum-A toxin: report of a preliminary randomised double-blind trial. Journal of Paediatric Orthopaedics 1994; 14: 299-303
- Corry IS, Cosgrove AP, Walsh EG et al. Botulinum toxin A in the hemiplegic upper limb: a double-blind trial. Developmental Medicine and Child Neurology 1997; 39: 185-193
- Corry IS, Cosgrove AP, Duffy CM et al. Botulinum toxin compared with serial stretching casts in the treatment of spastic equinus: a randomised prospective trial. Journal of Paediatric Orthopaedics 1998; 18: 304-311
- Flett PJ, Stern LM, Waddy H et al. Botulinum toxin A versus fixed cast stretching for dynamic calf tightness in cerebral palsy. Journal of Paediatric Child Health 1999; 35: 71-7

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Comments

We identified no published systematic reviews on this topic at the time of the request but did uncover a number of relevant primary studies. The studies cited above are all very small but fairly well-conducted trials that examine the effectiveness of BTX-A in reducing spasticity in a variety of muscle groups. The first two compare BTX-A with placebo and the second two with serial casting, as the current non-invasive treatment of choice. Bearing in mind the limitations of such small studies, the results suggest that BTX-A is more effective than placebo and at least as effective as serial casting, in improving gait and reducing muscle tone, without producing significant adverse effects.

Comparative data on the acceptability and costs of different treatments is required in order to make an overall judgement on the effectiveness of BTX-A. Reliable information of this nature was not available

at the time of this request. In addition, some questions were not addressed by the existing research such as the effect of repeated injections over a longer period.

In summary, it appears that BTX-A may represent a useful option in the management of spasticity due to cerebral palsy. However, at this stage it is difficult to obtain a clear picture of exactly what its place might be, particularly in relation to particular muscle groups, and other treatment options. Further research is clearly required.

Readers should note that this is an area prone to the need for regular updating as new information is continually becoming available. At the time of writing a ScHARR health technology assessment and a Cochrane review were both nearing completion.

Request Carried Out: March 1999

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Archived ARIF Request

pro-Brain Natriuetic Peptide Heart Failure

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The Problem Submitted for ARIF to Advise Upon:

What is the accuracy of pro-Brain Natriuretic Peptide (proBNP) in the diagnosis of heart failure?

Question Reformulated

When undertaking this request we became aware of the complexity of the nomenclature surrounding proBNP and the potential for confusion to which this gives rise. Therefore, we feel it important to outline our understanding of brain natriuretic peptide (BNP) biochemistry and the terms applied to the peptides involved, in order to ensure that this feedback contains no ambiguities. Pro-brain natriuretic peptide is released from cardiac ventricles and cleaved into two peptides, BNP and N-terminal pro-brain natriuretic peptide (NT-proBNP). Brain natriuretic peptide appears to have also been called B-type natriuretic peptide.

This request related to the diagnostic accuracy of a test for NT-proBNP.

Reviews Identified

No reviews were identified.

Primary Studies

- Hobbs FDR, Davis RC, Roalfe AK, Hare R,Davies MK, Kenkre JE. Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: cohort study in representative and high risk community populations. BMJ 2002;324:1498-1500

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Comments

No systematic reviews were identified and we identified only one study on the diagnostic accuracy of a test for NT-proBNP.

The study appears to be a generally well-conducted, although some aspects of the methods are not fully reported. The study found that the sensitivity of the test is high and indicates that the test is good at identifying those who have the condition. However, the specificity of the test is poor indicating that

the test is not good at correctly excluding people without the condition. However the method of analysing the test results was chosen to maximise sensitivity and thus identify those having the condition.

In conclusion the results indicate that NT-proBNP testing maybe a promising tool in the diagnosis of heart failure. However, the reliability of the test is still somewhat unclear due in part to the relatively small sample size(s) used in the study.

Request Carried Out: August 2002

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Archived ARIF Request

Temozolomide
Brain Tumours (Glioblastoma)

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of temozolomide in addition to surgery and radiotherapy for newly diagnosed glioblastoma multiforme?

NICE guidance already recommends the use of temozolomide for patients with recurrent malignant glioma. However, this guidance which is due to be reviewed in 2006, does not consider first-line use, particularly in combination with surgery and radiotherapy. This was because it was not licensed for this use when the original guidance was compiled. This still seems to be the case (BNF 49 March 2005)

Reviews Identified

No systematic reviews were identified.

Randomised Controlled Trials

- Stupp R, Mason WP van dan Bent MJ et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. New England Journal of Medicine 2005;352:987-96
- Athanassiou H, Synodinou M, Maragoudakis E et al. Temozolomide combined with radiotherapy versus radiotherapy alone in newly diagnosed glioblastoma multiforme. Journal of Clinical Oncology 2005;23(10):2372-2377

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Comments

It should be emphasised that the RCTs listed were not identified as part of a systematic review, so the possibility of publication bias needs to be seriously considered.

Both studies compare surgery + radiotherapy + temozolomide with surgery + radiotherapy as the first line treatment for glioblastoma. With the exception of lack of blinding, which would be difficult to achieve in this clinical situation, both studies are reasonably well conducted. The study by Stupp et al is much larger (573 in contrast to 110 patients) and its method of randomisation better reported. Both studies report benefit in terms of overall survival and progression-free survival with additional temozolomide.

The key outstanding question is whether the use is cost-effective, given that the drug cost of

temozolomide is substantial – NICE guidance in 2001 indicates £1,176 for a 5-day course; concomitant and adjuvant temozolomide used in a manner similar to the RCT by Stupp et al would generally require the equivalent of 6 or 7 courses for each patient.

Ideally commissioners should not use temozolomide until it has been licenced and its cost-effectiveness formally assessed. However, the two RCTs identified suggest that temozolomide is potentially useful as part of first line treatment.

A related request looks at the effectiveness of Gliadel Wafer implants in the treatment of recurrent glioblastoma multiforme (GBM).

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Archived ARIF Request

Gliadel Wafer
Carmustine Implants
Glioblastoma Multiforme (GBM)
Brain Tumour

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in April 2005.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of Gliadel wafer implants in the treatment of recurrent glioblastoma multiforme (GBM)?

GBM is the most frequent, and aggressive, primary brain cancer. Optimal therapy includes surgical resection, radiation therapy and systemic chemotherapy. With this treatment patients have a median survival of approximately one year. Carmustine is a type of chemotherapy used in GBM but it cannot penetrate the tissue of the brain easily. Implanting wafers of carmustine into the cavity left after surgery attempts to overcome this problem.

Reviews Identified

- Brophy J, Chen J. Use of carmustine implants (gliadel wafer) in patients with malignant glioma at The McGill University Health Centre. Montreal: Technology Assessment Unit of the McGill University Health Centre (MUHC) 2004: 28. Technology Assessment Unit of the McGill University Health Centre (MUHC)

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Comments

Brophy and Chen (2004) adopted a comprehensive search strategy reviewing the major bibliographic databases, health technology assessment and other relevant websites from 1990 to 2003, with no language restriction. A criticism of the review however was its general lack of transparency in terms of the methods employed. An unavoidable drawback of the review was the shortage of available studies in this area. However the reviewers did identify three randomised controlled trials with a total of 494 patients and provided a narrative summary of the results.

In overall summary the review indicated:

- A fairly consistent median survival benefit of approximately 6-8 weeks amongst patients receiving Gliadel wafer implants in comparison with placebo, regardless of whether the implants were used at

the time of recurrent surgery or administered at the time of initial resection.

- Firm conclusions regarding the overall safety of the technology were limited by the lack of data.
- No formal cost-effectiveness studies were identified. The authors performed a rough cost effectiveness assessment, assuming an average requirement of 7 wafers/patient plus an additional hospital stay of 4.5 days and an average 8-week extension to life, which suggested a cost-effectiveness ratio of approximately Canadian $100,000 per life year.

The balance between the benefits and costs associated with Gliadel wafer implants is finely poised. A definitive judgement should await a detailed assessment. In the interim we would agree with Brophy & Chen's suggestion that the available evidence does support limited use of Gliadel wafers decided on a case-by-case basis.

An ongoing NICE Health Technology Appraisal will assess the clinical and cost effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high grade gliomas (grades III & IV) as an adjunct to surgery and radiation. Treatment strategies using carmustine implants or temozolomide will also be compared with each other, evidence permitting. The final report is expected in June 2006.

A related request looks at the effectiveness of temozolomide in addition to surgery and radiotherapy for newly diagnosed glioblastoma multiforme.

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THE UNIVERSITY
OF BIRMINGHAM

THE BREAKSPEAR HOSPITAL

ARIF
(AGGRESSIVE RESEARCH INTELLIGENCE FACILITY)

October 2003

What is ARIF?

ARIF is an established specialist unit based at the University of Birmingham whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

What does ARIF do?

The core activity of ARIF is the provision of an "on demand" information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

ARIF also:

- Contributes to the production of systematic reviews and health technology assessments
- Provides support to researchers who are undertaking systematic reviews
- Provides advice on targeting literature searches for research evidence
- Disseminates important research findings
- Provides input into educational events
- Undertakes a variety of in-house research on different aspects of review methodology and getting research into practice
- Contributes to the work of the Birmingham Technology Assessment Group and is a key member of the West Midlands Health Technology Assessment Collaboration

Beyond the West Midlands

Although primarily aimed at the NHS in the West Midlands region, ARIF welcomes inquiries from outside this area and is committed to help on an informal basis as far as time and resources permit.

How can I find out more?

For further information about the unit, summaries of the results of information requests and other resources which you might find useful in making health care decisions more evidence-based, access the ARIF web site at:

http://www.bham.ac.uk/arif

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BREAKSPEAR HOSPITAL

WARNING

The following information is primarily designed to give readers a starting point to consider research evidence in a particular area. Readers should not use the comments made in isolation and should have read the literature suggested. This report stems from specific requests for information, and as such utilisation of the report outside of this context should be undertaken with caution. Readers should also be aware that more appropriate information might have become available since this report was compiled.

Summary

- The Breakspear Hospital is a clinical ecology unit offering alternative therapies for a wide variety of conditions
- ARIF has received a number of requests for assistance with identifying evidence on the effectiveness of care offered by the Breakspear Hospital over the past 7 years
- This report summarises the cumulated evidence on effectiveness, particularly systematic reviews and randomised controlled trials (RCT) gleaned from these requests, also highlighting areas which have not been investigated in depth
- Assessing the effectiveness of the Breakspear Hospital and its treatments is problematic
- There are no systematic reviews or RCTs on the effectiveness of provocation-neutralisation, one of its key therapies, in candidal hypersensitivity, chronic fatigue syndrome (CFS), multiple chemical sensitivities (MCS) and multiple allergies. It needs to be emphasised that this is an absence of evidence, not evidence of ineffectiveness. An urgent need for primary research is suggested.
- There are RCTs of provocation-neutralisation for less serious conditions such as hay-fever, asthma and eczema. Ideally these should be systematically reviewed, after which further primary research may still be the correct further course of action.
- A systematic review of the effectiveness of provocation-neutralisation for food allergies has recently been completed.
- Many other components of the treatments offered by the Breakspear Hospital remain uninvestigated by ARIF and it may be appropriate to proactively target some of these for further assessments of evidence on effectiveness.
- We have not established whether there are effective and cost-effective alternative treatments to those offered by the Breakspear for many conditions that they target. Such exercises may be helpful in assessing whether use of new therapies is reasonable.
- There has been one evaluation of a Breakspear-like unit in Germany. The findings of this need to be replicated, but the approach adopted may be a useful alternative to considering individually all the treatment/condition combinations offered by the Breakspear
- ARIF requests have also been done on enzyme-potentiated desensitisation (EPD) which although not a treatment offered by the Breakspear seems similar in some respects to provocation-neutralisation. The need for systematic reviews of the effectiveness of EDP for simple allergies eg asthma, hay-fever and eczema, and the need for primary research on EPD for CFS and multiple allergies is similar to the pattern observed for provocation-neutralisation.
- Guidance is particularly sought on priorities for further action at regional level on further ARIF requests and REP reports on the effectiveness of various aspects of care offered by the Breakspear

Aims of this report

ARIF has received several requests for information on the evidence of effectiveness of interventions given at the Breakspear Hospital (a clinical ecology unit) for a variety of conditions over the past 7 years. It is apparent that requests for patient referral to the Hospital have been received by Health Authorities and latterly Primary Care Trusts, and whether to fund such referrals is a dilemma which seems likely to continue. This report assimilates the information from these requests to provide a summary of the evidence base to act as a starting point for other commissioners of health care who need to make decisions about referrals in the future. As well as concluding on aspects of care offered at the Breakspear which we have investigated, we also identify aspects of care not investigated in depth, where further requests to ARIF may be particularly appropriate. We also attempt to identify areas where there is a particular need for further research, both systematic reviews and primary research. This report thus invites comments on:

a) The veracity of our conclusions in the areas which we have investigated in depth and whether any recommendations for practice should ensue
b) The relative importance of need for further investigation of the effectiveness of aspects of care offered by the Breakspear which we have not investigated in depth so far
c) Whether these areas for further investigation should be addressed by further ARIF requests, a REP report or should be directed to the NHS HTA programme as potential topics for further research

The Breakspear Hospital

The Breakspear Hospital is a privately owned and run day hospital specializing in the treatment of patients with allergies and environmental disorders, and in general terms can be described as a clinical ecology unit. The hospital is registered with the National Care Standards Commission as an independent hospital and is located in Hemel Hempstead, Hertfordshire. The hospital is part of the Breakspear Medical Group Ltd and an associated trust, the Breakspear Hospital Trust, provides some support for research and the treatment of less well-off patients. Further details about the hospital are available on their website (www.breakspearmedical.com) and in a guide to allergy and environmental medicine produced by the hospital (latest version, obtained May 2003, attached as Appendix 1).

Activities of the Breakspear Hospital

The Breakspear Hospital produces a guide for patients to allergy and environmental medicine (Appendix 1). ARIF have been supplied with copies of this guide in the past when requested to undertake evaluation of the effectiveness of an intervention provided at the hospital. The latest version of this guide (May 2003) has been used to present a table of the conditions which the hospital appears to treat and the treatments said to be most appropriate for these conditions (Table 1). One of difficulties in compiling this is ambiguity about whether interventions for specific conditions detailed in the guide are *actually* undertaken at the Hospital. The criterion we applied was that if the guide mentioned the intervention in the context of the condition, and it appeared to be an intervention that could be supplied by the Hospital, then it was assumed that it was given for the condition. For example, where surgical interventions are mentioned in the context of gastrointestinal problems these are not detailed in the table, as we know such surgery is not undertaken at the Hospital. Conversely, utilisation of healing frequencies for the treatment of electrical sensitivities is included in the table as it appears to be the type of intervention that may be given at the Hospital.

A further caveat is that experience with various requests submitted to ARIF suggests that treatments are individualised according to findings of various tests and therefore Table 1 should only be viewed as a general indication of what might be offered for a particular patient with a given condition. Further it is possible that particular types of treatments may actually be used for a broader range of conditions than indicated. It is also worth noting that the rationale for treating many conditions mentioned is that these disorders are partly caused or exacerbated by allergies to food or chemicals or other environmental factors.

In order to aid understanding of the table, a cross-reference is given to the page of the Breakspear Guide in Appendix 1 which describes the intervention in question. In later sections we also provide our own understanding about one particular technique offered by the Breakspear, the Miller technique or provocation-neutralisation, contrasting it with related techniques (enzyme potentiated desensitisation and immunotherapy) which do not seem to be offered by the Breakspear, with which there may be confusion.

Table 1. Conditions and corresponding interventions provided by the Breakspear Hospital

			Condition												
			Asthma	Cancer Prevention	Candida *	Chemical Sensitivities **	Coeliac Disease	Crohn's Disease	Electrical Sensitivity	Eczema	Food Allergy ***	Hyperactivity	Myalgic Encephalomyelitis (ME) ****	Migraine	Ulcerative Colitis
		Page reference in Guide (see Appx 1)	P29	P42 +2	P31	P16	P14	P15	P22	P42 +1	P10	P33	P35	P23	P15
Intervention	Detection/Diagnosis of Provocants ^	P6	●			●			●	●	●	●	●	●	
	Detoxification Programme	P18		●		●									
	Environmental Counselling	P30	●									●			
	Exclusion/ Special Diets ^	P12	●	●	●		●	●		●	●	●	●	●	●
	Exposure to Healing frequencies	P23							●						
	Immunoglobulin/ Immunovir/ Gammaglobulins	P35											●		
	Immune Enhancement	P42+2		●											
	Metabolic Detoxification (Ultraclear)	P21				●					●				
	Multiple Allergen Vaccine (MAV)	P27	●			●				●	●				
	Provocation-Neutralisation ^	P27	●		●	●				●			●	●	
	Stress Reduction	P25													
	Vitamin/Nutritional Supplements ^	P21	●		●	●				●	●	●		●	

● Intervention that the Guide to Allergies and Environmental Medicine appears to suggest is offered at the Breakspear Hospital for a given condition
* Assumed to encompass candidal hypersensitivty
** Assumed to encompass multiple chemical sensitivities and severe allergies/total allergy syndrome
*** Assumed to encompass severe allergies/total allergy syndrome
**** ME, also referred to as post-viral fatigue and chronic fatigue syndrome (CFS)
^ Mentioned as integral to holistic approach offered by Breakspear on p3

What work has ARIF undertaken in the context of the Breakspear Hospital

Since 1996 ARIF have undertake many requests relating to the referral of patients to the Breakspear hospital and similar facilities. Table 2 summarises those aspects of care (treatment/condition combinations) offered by the Breakspear for which ARIF has undertaken examination of the evidence of effectiveness. It also includes requests undertaken on a treatment similar to that offered by the Breakspear, enzyme potentiated desensitisation (EPD). Table 2 thus contains three key items:

- The treatments that are available at the Breakspear hospital (as per Table 1)
- The number and nature of the requests which ARIF has undertaken in response to pending referrals to the Hospital
- The number and nature of the requests which ARIF has undertaken on similar conditions / interventions combinations to those treated/available at the Breakspear Hospital.

Those ARIF requests falling within the range of Breakspear treatments have focussed on the effectiveness of provocation-neutralisation in the treatment of multiple chemical sensitivities/severe allergies and fatigue related syndromes (chronic fatigue syndrome/post-chemotherapy fatigue). These latter two types of condition are also the subject of several requests on the effectiveness of similar interventions (enzyme potentiated desensitisation).

The following sections of this report describe:

- The evidence of effectiveness of the above intervention/condition combinations
- The evidence of effectiveness of these interventions in other conditions
- Other interventions that maybe effective for fatigue syndrome and multiple chemical sensitivities

The format will be to provide detail on the quantity, quality and direction of effect of the available research information. Primarily ARIF undertakes such tasks utilising existing systematic reviews, searched for using documented search strategies covering a wide variety of databases including the Cochrane Library and MEDLINE. In the absence of systematic reviews ARIF will assess the evidence from primary studies, but clearly recognising that it has not systematically reviewed these and applying appropriate caution in their interpretation, particularly concerning the threat posed by publication bias.

Table 2. Topics on which ARIF has undertaken requests for information on evidence of effectiveness

		Condition														
		Asthma	Cancer Prevention	Candida *	Chemical Sensitivities **	Coeliac Disease	Crohn's Disease	Electrical Sensitivity	Eczema	Food Allergy ***	Hyperactivity	Myalgic Encephalomyelitis (ME) ****	Migraine	Ulcerative Colitis	Post Chemotherapy Fatigue *****	Gulf War Syndrome
Intervention	Detection/Diagnosis of Provocants	●			●			●	●	●	●	●	●			
	Detoxification Programme		●													
	Environmental Counselling	●									●					
	Exclusion/ Special Diets	●	●	●		●	●		●	●	●	●	●	●		
	Exposure to Healing frequencies							●								
	Immunoglobulin/ Immunovir/ Gammaglobulins											●				
	Immune Enhancement		●													
	Metabolic Detoxification (Ultraclear)				●					●						
	Multiple Allergen Vaccine (MAV)	●			●				●	●						
	Provocation-Neutralisation	●		●1	●4				●	2		●2	●		1	
	Stress Reduction															
	Vitamin/Nutritional Supplements	●		●	●				●	●	●		●		1	
	Enzyme Potentiated Desensitisation (EPD)				1											

● Intervention that the Guide to Allergies and Environmental Medicine appears to suggest is offered at the Breakspear Hospital for a given condition

* Assumed to encompass candidal hypersensitivty

** Assumed to encompass multiple chemical sensitivities and severe allergies/total allergy syndrome

*** Assumed to encompass severe allergies/total allergy syndrome

**** ME, also referred to as post-viral fatigue and chronic fatigue syndrome (CFS)

***** Although a subject of a request concerning the Breakspear, post-chemotherapy fatigue is not mentioned in their guide

Area covered by Table 1

Topics on which ARIF has undertaken requests for information on evidence of effectiveness concerning the Breakspear

Topics on which ARIF has undertaken requests for information on evidence of effectiveness not concerning the Breakspear

2 Indicates the number of requests undertaken by ARIF on this topic

Provocation-neutralisation (the Miller technique; low dose hyposensitisation)

Nature:
Provocation-neutralisation is a technique in which the Breakspear claims to have particular expertise. The purpose is to reduce the body's responses (especially allergic responses) to a range of agents in the diet and the environment (provocants). It comprises two stages: first testing, then neutralisation. Testing involves administering increasingly dilute solutions of suspected provocants until a dilution is found which causes relief of symptoms* – this dilution is the "neutralising dose". The neutralising dose is then the basis for a "vaccine" which is given repeatedly either by injection into the skin (intra-dermal) or under the tongue (sub-lingually). The vaccine may contain neutralising doses of up to 25 different provocants. The vaccines are claimed to have an 80% chance of "working well" and are claimed to have no adverse effects. Although not specifically mentioned in the literature from Breakspear, other texts [1] place emphasis on distinguishing between neutralisation techniques based on maximum tolerated dose and those based on prompting symptoms, which is then the basis for diagnosis. The latter is suggested to be unreliable. On the basis of the most recent brochure from the Breakspear the version of the provocation-neutralisation test used conforms to the accepted maximum tolerated dose technique.

The Miller technique needs to be distinguished from:
- allergen immunotherapy, allergen-injection immunotherapy (see Appendix 2)
- enzyme-potentiated desensitisation (EPD) or hyposensitisation (see next section)

In brief EPD appears to be similar to the Miller technique, with the exception that the provocant is mixed with a potentiator (ß-glucuronidase). The equivalent of the "vaccine" is then given intradermally or onto the scarified surface of the skin, restrained by a "cup". Traditional allergic immunotherapy involves sub-cutaneous injections of much higher doses of allergens, usually sequentially increased. There were great concerns about use of allergic immunotherapy in the 80's owing to reports of high levels of adverse events, some of which were severe, such as anaphylaxis [2].

Requests conducted:
The effectiveness of provocation-neutralisation is by far the most common request received by ARIF in relation to the care offered by the Breakspear. Table 3 summarises the timing of these requests, the question submitted, the target condition and whether we re-ran searches or merely fed-back information we already had on the topic.

* The description of provocation-neutralisation is primarily based on the descriptions provided by the Breakspear. It should be noted that absence of changes in skin wheals rather than relief of symptoms now appears to be the preferred means to determine the neutralising dose.

Table 3. Details of ARIF requests on provocation-neutralisation

	Question submitted	Breakspear specifically mentioned?	Condition targeted	New search?	Findings in brief
1/4/96	Requests "Evaluation of the research evidence for the diagnosis and treatment of multiple allergies by neutralising techniques and controlled environments"	No	Allergies and particularly multiple allergies	Yes; focus on allergy	No systematic reviews, but some useful background papers concerned with the use allergen-injection immunotherapy [1] [2]. One review indicates some trials of maximum tolerated dose provocation-neutralisation techniques in food allergy, allergic rhinitis and asthma [1]
18/6/97	What is the evidence on the effects/effectiveness of treatments for systemic allergies due to environmental toxins.	Yes	Systemic allergies	No	As for previous request
17/6/99	Requests information on "The management of patients with multiple chemical sensitivity", with particular reference to the "neutralisation" technique	Yes	Multiple chemical sensitivity (MCS)	Yes; focus on neutralisation, desensitisation and allergy	As for previous request
7/6/00	Advice requested on "Innovative treatment offered by the Breakspear Hospital". Provocation-neutralistaion specifically mentioned	Yes	Chronic fatigue syndrome (CFS), MCS and candidal hyper-sensitivity.	Yes; focus on neutralisation, desensitisation and allergy plus on any effective interventions for listed conditions plus. Searches include both reviews and primary studies. Request also includes check of references provided by Breakspear on provocation-neutralisation and chemical sensitivities.	No new directly relevant systematic reviews. Completed Cochrane review on allergen immunotherapy for asthma [3] and protocol for Cochrane review (now a completed review) on sublingual immunotherapy for allergic rhinitis [4] [NB immunotherapy ≠ provocation neutralisation] One new trial of use of provocation neutralisation for *identifying* food & chemical sensitivities. Breakspear reference list includes trials, but these are restricted to application of provocation-neutralisation techniques in asthma, allergic rhinitis and food sensitivity
13/7/01	Advice sought on effectiveness of provocation-neutralisation for CFS	Yes	CFS	Yes; focus on effective treatments for CFS	Comprehensive systematic review of potential treatments for CFS identified [5]. Provocation-neutralisation not highlighted; cognitive behavioural therapy and graded exercise were.
5/4/02	Follow-up to request 13/7/01. Further review of effectiveness of provocation-neutralisation for CFS, but extending conditions to include MCS. Appraisal of information provided by Breakspear supporting effectiveness of provocation-neutralisation	Yes	CFS and MCS	No. Appraisal of bibliography of articles on effectiveness of provocation-neutralisation, a report on MCS recognition and management and an article on motor-neurone disease	Breakspear reference list identical to that assessed for request 7/6/00. Trials claiming effectiveness of provocation-neutralisation restricted to asthma, allergic rhinitis and food sensitivity.
24/10/02	Requests update of request on effectiveness of Miller technique in treatment of allergies	No	Allergies and particularly multiple allergies	Yes; focus on provocation-neutralisation and allergies. Primary studies considered as well as reviews	No new directly relevant systematic reviews. No new trials.
18/01/03	Effectiveness of nutritional intervention, in the form of vitamins and minerals, and immunotherapy, in the form of desensitising vaccines, for post chemotherapy CFS	Yes	Post chemo-therapy chronic fatigue	Yes; focus on specified condition	Systematic review of potential treatments for cancer symptoms (pain, depression and fatigue) identified [6]. Interventions offered by Breakspear not highlighted as potentially effective.

Conclusions:
From this it is clear that we have assessed the effectiveness of provocation-neutralisation on several occasions, and from a number of different perspectives. We are confident that there are no adequate systematic reviews of effectiveness on the subject, irrespective of the target condition. The best background reviews we have identified, remain those from the original request in 1996:

- Effective allergy practice: a document on standards of care and management of the allergy patient. Southampton: British Society for Allergy and Environmental Medicine & The British Society for Nutritional Medicine, 1994. Pp18
- Position paper on allergen immunotherapy: report of a BASCI working party January-October 1992. Clinical and Experimental Allergy, 1993;23(Suppl 3, August):1-44.

Concerning primary studies, particularly RCTs, we are confident that there is no rigorous evidence of the effectiveness of provocation-neutralisation testing in the target conditions of most concern in the requests, namely chronic fatigue syndrome, post-chemotherapy fatigue, multiple allergies, total allergy syndrome, multiple chemical sensitivity and candidal hypersensitivity. It should be noted that this includes assessment of the evidence provided by the Breakspear.

Outstanding issues which we do not feel have been fully investigated are the use of provocation-neutralisation techniques for simpler allergies (ie hay-fever) atopic conditions (ie eczema and asthma) migraine and hyperactivity. Of these we have identified some RCTs investigating the effectiveness of provocation-neutralisation on hay fever and asthma. The results are mixed, suggesting a systematic review would be of great value, but the time and effort needing to be invested must be tempered by the fact that we have never received requests concerning the use of provocation-neutralisation techniques in these disorders.

A systematic review has been conducted on the effectiveness of provocation-neutralisation for food allergies. It was undertaken in collaboration with ARIF, taking into account the requests received and detailed in this report. The systematic review by Dretzke and Song will be considered at the same meeting this report is targeted at, and will be published thereafter incorporating any suggestions for change recommended. An important issue worth highlighting is that the definition of food allergies used in this systematic review overlaps with other conditions such as migraine and hyperactivity mentioned in the preceding paragraph. The systematic review included studies with patients with conditions where a food allergy was thought to be an underlying cause or exacerbating factor; this may not coincide with all clinicians' understanding of what is meant by food allergy.

Enzyme Potentiated Desensitisation

Nature:
Enzyme potentiated desensitisation (EPD) can also be easily confused with immunotherapy and provocation-neutralisation. EPD involves the administration, via skin injection (intra dermal), of an enzyme, ß-glucuronidase, and minute doses of mixed allergens. The enzyme is used at levels already present in the body and the allergens are used in quantities much less than in conventional desensitising treatments and immunotherapy. In response to allergy details in the patient history the EPD cocktails can contain a variety of inhalants, foods, and chemicals. EPD does not appear to be available at the Breakspear Hospital, but the requests on this topic are considered here because of the similarity with provocation-neutralisation and the fact that it was being suggested for similar conditions (MCS and CFS).

Requests:
Two requests have been received on the effectiveness of EPD. Their details are summarised in Table 4.

Table 4. Details of ARIF requests on enzyme potentiated desensitisation (EPD)

	Question submitted	Breakspear specifically mentioned?	Condition targeted	New search?	Findings in brief
1/9/01	"What is the effectiveness of EPD for treating severe allergies"	No	Severe allergies and Gulf War syndrome	Yes; focus on effectiveness of EPD. Reviews and primary studies considered	No systematic reviews. A number of RCTs, but none addressing severe allergies eg total allergy syndrome. RCTs do appear to address hay-fever, asthma, food-induced migraine, food-induced hyperkinetic syndrome and ulcerative colitis.
12/2/02	"How effective is homeopathic treatment based on EPD in the treatment of patients suffering from CFS"	No	CFS	Yes; focus on both effectiveness of EPD and effective treatments for CFS	No new systematic reviews or RCTs relative to previous request. None of the RCTs on EPD relate to CFS Best review of treatments for CFS remains the review undertaken by NHS Centre for Reviews and Dissemination [5]

Conclusions:
The requests have identified that there are no systematic reviews of the effectiveness of EPD, despite the fact that there a number of RCTs. These RCTs, like the pattern for provocation-neutralisation, focus on simple allergies such as hay-fever and asthma. The volume of RCTs was however much larger for EPD than provocation-neutralisation suggesting that there may be potential for a systematic review. Like provocation-neutralisation however, it should be noted that use of EPD for simple allergies has never been presented as a request for ARIF to consider.

It is very clear that there are no RCTs addressing the effectiveness of EPD for severe multiple allergies, Gulf war syndrome and CFS.

Other features of Breakspear treatment

It is worth stating that many aspects of the treatment offered by the Breakspear have not been examined including:

- Diagnostic procedures
- Detoxification programmes
- Metabolic detoxification programmes (including use of "Ultraclear")
- Environmental counselling
- Exclusion/special diets
- Exposure to healing frequencies
- Immunoglobulin/immunovir/gammaglobulins
- Immune enhancement
- Multiple allergen vaccine (MAV)
- Stress reduction (counselling, biofeedback and psychological assessment)
- Vitamin/nutritional supplementation

Although the last of these was examined in one request, it was not examined in great depth, the focus being on the identification of effective treatments for post-chemotherapy fatigue, and fatigue associated with cancer generally.

Effectiveness of Breakspear Hopsital treatment *in toto*

An important question running as a strong under-current in all the ARIF requests received is whether the whole package of care offered by the Breakspear Hospital is effective. Addressing this is difficult, as treatment from a wide-range of options is individualised not just to the presenting condition (of which there are many) but also to the individual findings in a person with a given condition. The treatment package is thus non-standardised, a corollary of which is that no two patients with say CFS are likely to receive exactly the same treatment. Answering the question - is the Breakspear Hospital effective? - could potentially be

addressed by systematically identifying evidence on effectiveness of all the interventions offered for the range of conditions which the Breakspear suggests might be applicable ie addressing the questions implicit behind all the cells in Table 2 marked with •. This is a huge undertaking, and one which we have not even come close to completing.

In this situation an attractive alternative source of evidence would be evaluations of the Breakspear Hospital as a unit. We have been alert to the possibility that the evaluations of clinical ecology units may be valuable in all the requests we have undertaken. One such evaluation has been identified. This is of a sister unit to the Breakspear in Germany, and is alluded to in some of the literature from the Breakspear. We obtained a copy of this evaluation in 2000 and undertook a translation of it from German. A copy of the abstract is included as Appendix 3.

The key features of this study are:

- That it is a pre-post study, where the measures prior to treatment/start of treatment effectively act as the "control" against which subsequent measures are judged
- There is no parallel control group who received no treatment, placebo or usual care
- In the absence of a control group, blinding of outcome assessment is impossible
- Both new out-patient and new in-patients were considered (n=95 & n=47)
- The most common conditions were chemical intolerances, food intolerances, multiple chemical sensitivity and chronic fatigue syndrome
- Loss to follow-up over the 12 month follow-up period was only just acceptable (31% in out-patients; 26% in in-patients)
- The outcomes of particular interest were:
    - Symptoms
    - Patient assessed quality of life, including SF36 and Nottingham Health Profile
    - Use of health care facilities
- The key results were
    - Improvements in quality of life between 0 and 6 months, some statistically significant
    - A trend towards reduction in use of health services in 12 months before treatment and in the 12 months after it, but not statistically significant

It is debatable whether the size of the benefits demonstrated are convincing on their own, particularly taking into account the openness to bias arising from the study design and the losses to follow-up. Further whether the differences in quality of life demonstrated are clinically significant is uncertain. The results although interesting, certainly need to be repeated, and ideally from the perspective of this report in a UK setting.

Availability of effective treatments beyond those offered by Breakspear

The findings accumulated over the course of all the ARIF requests are summarised in Table 5.

Table 5. Alternative effective treatments, other than therapies offered by the Breakspear Hospital, for the conditions it targets and conditions of interest in the ARIF requests received

Condition	Best systematic reviews identified	Effective alternative treatments suggested
Asthma	Not investigated in course of requests	Although not investigated many well established effective treatments eg inhaled steroids
Candidial hypersensitivity	No systematic reviews identified	Unknown
Chronic fatigue syndrome	Bagnall AM, Whiting P, Wright K, Sowden AJ. The effectiveness of interventions used in the treatment and management of chronic fatigue syndrome and/or myalgic encephalomyelitis in adults and children. York: The NHS Centre for Reviews and Dissemination, University of York, 2001.	• Cognitive behavioural therapy • Graded exercise
Coeliac disease	Not investigated in course of requests	Although not investigated some well established effective treatments eg gluten free diets
Crohn's disease	Not investigated in course of requests	Although not investigated some well established effective treatments eg corticosteroids
Electrical sensitivity	Not investigated in course of requests	Unknown and uncertainty about nature of condition
Eczema	Not investigated in course of requests	Although not investigated some well established effective treatments eg topical steroids
Food allergy	Not investigated in course of requests	Unknown
Gulf War syndrome	No systematic reviews identified	Unknown and uncertainty about nature of condition
Hyperactivity	Not investigated in course of requests	Unknown and uncertainty about nature of condition
Migraine	Not investigated in course of requests	Although not investigated some well established effective treatments eg drug therapy
Multiple allergies; total allergy syndrome	No systematic reviews identified	Unknown and uncertainty about nature of condition
Multiple chemical sensitivities	No systematic reviews identified	Unknown and uncertainty about nature of condition
Post-chemotherapy fatigue	Carr D, Goudas L, Lawrence D et al. Management of cancer symptoms: pain, depression and fatigue. Rockville: Agency for Healthcare Research and Quality (AHRQ). Evidence Report/Tech, 2002.	• Erythropoeitin where fatigue associated with anaemia • Exercise programmes and psycho-social interventions may also be of assistance
Ulcerative colitis	Not investigated in course of requests	Although not investigated some well established effective treatments eg corticosteroids

This analysis is clearly only partially complete. It emphasises however that the acceptability of new/alternative treatments, such as those offered by the Breakspear, on which there is absence of evidence, has to be judged in the context of the availability of alternatives. There is thus value in establishing clearly whether there are alternatives, and whether these are effective and cost-effective, if only to ensure that these treatments have been fully applied/attempted before alternative therapies are considered. The identification of a systematic review on treatments for CFS highlights this well, suggesting that cognitive behavioural therapy and graded exercise should be considered before therapies untested in CFS are resorted to. In contrast, for multiple chemical sensitivities and multiple allergies we have confirmed there are no clearly effective alternative treatments, and so provision of alternative therapies *may* be viewed more sympathetically. Although concerns about the nature of total allergy syndrome and multiple chemical sensitivity exist, it is undoubted that there are a group of patients for whom existing traditional medical treatments have little to offer. Attempting treatment with untested treatments in these circumstance may thus be reasonable, but only in the context of commitment to rigourous evaluation by the facilities undertaking them.

OVERALL CONCLUSIONS

- Assessing the effectiveness of the Breakspear Hospital and its treatments is problematic.
- There are no systematic reviews or RCTs on the effectiveness of provocation-neutralisation, one of its key therapies, in candidal hypersensitivity, CFS, MCS and multiple allergies. It needs to be emphasised that this is an absence of evidence, not evidence of ineffectiveness. An urgent need for primary research is suggested.
- There are RCTs of provocation-neutralisation for less serious conditions such as hay-fever, asthma and eczema. Ideally these should be systematically reviewed, after which further primary research may still be the correct further course of action. A systematic review of the effectiveness of provocation-neutralisation for food allergies has recently been completed.
- Many other components of the treatments offered by the Breakspear Hospital remain uninvestigated by us and it may be appropriate to proactively target some of these for further assessments of evidence on effectiveness.
- We have not established whether there are effective and cost-effective alternative treatments to those offered by the Breakspear for many conditions that they target. Such exercises may be helpful in assessing whether use of new therapies is reasonable.
- There has been one evaluation of a Breakspear-like unit on Germany. The findings of this need to be replicated, but the approach adopted may be a useful alternative to considering individually all the treatment/condition combinations offered by the Breakspear.
- ARIF requests have also been done on EPD which although not a treatment offered by the Breakspear seems similar in some respects to provocation-neutralisation. There are RCTs of EPD for hay-fever, asthma and eczema. Ideally these should be systematically reviewed, after which further primary research may still be the correct further course of action. There is however a clear absence of primary research on the use of EPD in CFS and multiple allergies, conditions where there may be pressure to use EPD because there are no clearly effective alternative therapies. The pattern for EPD is an exact parallel to that for provocation-neutralisation.
- Guidance is particularly sought on priorities for further action at regional level on the need for further ARIF requests and regional REP reports on the effectiveness of various aspects of care offered by the Breakspear.

Appendices

Appendix 1

The Breakspear Guide To Allergy and Environmental Medicine.
[pp 42 + addendum pp 2]

Appendix 2

Other approaches to treating allergy

Immunotherapy

Allergen immunotherapy is the repeated administration of specific allergens to patients with IgE-mediated conditions for the purpose of providing protection against the allergic symptoms and inflammatory reactions associated with natural exposure to these allergens. It involves giving gradually increasing doses of the allergen to which the person is allergic. The incremental increases of the allergen cause the immune system to become less sensitive to the substance, probably by causing production of a "blocking" antibody, which reduces the symptoms of allergy when the substances is encountered in the future.

There were great concerns about the use of immunotherapy in the 80's owing to reports of high levels of adverse events, some of which were severe, such as anaphylaxis [2]. Subsequently attempts have been made to reduce the potential for adverse events by administering the allergen orally or sub-lingually.

The technique of allergen immunotherapy should be differentiated from provocation-neutralization therapy on the basis of the much higher doses of allergens employed and from the process of desensitisation, which usually applies to the rapid progressive administration of an allergenic substance to render effector cells less reactive.

ARIF has not undertaken any requests on immunotherapy.

Skin prick testing

Skin prick testing can be performed to diagnose IgE mediated allergy- a soluble extract of the potential allergen is placed on to the skin and pricked through the epidermis. A wheal or flare, reaching a maximum in 10-15 minutes indicates a positive reaction. The main difference between skin-prick testing and provocation-neutralisation is that you use undiluted extracts in skin prick testing, expect a wheal as a reaction and not symptoms and is for IgE mediated allergies. A skin prick test is used for diagnosis only.

ARIF has not undertaken any requests on skin prick testing as described above.

Appendix 3

Abstract for:

Kohlman T, Kunze U, Ehlers J, Raspe H.

"Final report on the scientific study of environmental medicine care of inpatients and outpatients at the Nordfriesland Specialist Hospital" [translated from German]

Summary

This report outlines the procedure and results of a scientific study on environmental medicine care at the Nordfriesland Specialist Hospital.

Study aims
The main aim of the study was to describe illness progression in first-time inpatients and outpatients of the environmental medicine department of the hospital. Standardized written questionnaires were completed by patients in an effort to examine features of subjective health (symptoms related to environmental medicine, physical and mental signs, etc.) and to collect data on the social medicine consequences of illness (including the use of medical services, inability to work and retirement). Questionnaires were completed at the beginning of treatment, four to eight weeks later and after a further six months and twelve months (totalling four observations). Additional details regarding diagnoses, medical prognoses and diagnostic and therapeutic treatment were taken from medical notes.

Study sample
A total of 131 patients (87 outpatients and 44 inpatients) with complete data for the first observation (at the beginning of treatment) were included at the start of the study. Since some patients did not complete later questionnaires, the size of the sample became smaller, leaving the study with a sample of 101 patients with completed questionnaires for each of the four observations. There was no evidence of analyses being distorted as a result of the manner in which the sample was recruited.

The planned size of the sample — originally based on information regarding the number of patients in treatment — could not be achieved, despite doing everything time would allow. Basically, too many of the clinic's patients had either already received treatment or, during the recruitment process, had returned as inpatients.

Starting point
Based on medical diagnoses, the majority of patients included in the study fell into four diagnostic categories: chemical intolerances, food intolerances, multiple chemical sensitivity and chronic fatigue syndrome. Initial analyses were made at the beginning of patient treatment, using both patient questionnaires and medical notes. These analyses showed that the patients treated at the clinic suffered from considerable health problems. Before coming to the clinic in Bredstedt, the patients had sought a considerable amount of medical and social services. Moreover, in comparison with corresponding norms, they had clearly less favourable values for physical condition, mental condition and social impairment. However, with respect to those variables related to how patients deal with their illnesses cognitively (e.g. 'active coping') and those variables related to how patients monitor their attitudes about health and illness (social and fatalistic externalization), the patients in the sample showed little or no difference to other groups observed and, as such, there was no noticeable impairment in this regard.

Results over time
Over the course of the study, there was evidence of statistically significant and — relatively speaking — practically significant improvement in nearly all recorded criteria on subjective health. As expected, this improvement tended to be greater in the inpatient group and the clearest changes were found in the area of general complaints and mental impairment. With few exceptions, the positive effects observed between the first and second observations stabilized over the next twelve months.

In contrast, target variables in the field of social medicine tended to show a less uniform picture. No evidence could be found to suggest there were changes in the frequency of hospital stays or inpatient

rehabilitation measures or the number of days when employed patients were unable to work between the twelve-month period before treatment began and the twelve-month period thereafter. Yet there was evidence to suggest that there were fewer doctor consultations and less treatment by non-medical therapists from one period to the next. There was an increase in the frequency of operations, although this was not statistically significant.

The examination of potential predictors of progression showed that variables related to mental disposition (including health concerns and how patients were monitoring their attitudes about health and illness) can be instrumental in explaining later development (with 'unfavourable' values for these variables having a negative effect). Having very little significance here, if any at all, were demographic variables (such as age and sex) and doctor and patient expectations.

Conclusions

In summary, the results of the study show that there were statistically proven and — relatively speaking — significant, positive changes in progression indicators during and after both inpatient and outpatient treatment. These changes primarily involved aspects of subjective health and were less evident with regard to social medicine consequences of illness and patient use of medical services.

It is interesting to compare the results of the changes in health parameters over time presented here with the findings of studies on the therapeutic effects of medical rehabilitation (e.g. illnesses of the locomotor system or cardio-circulatory disorders). Such a comparison reveals that the changes observed in the Bredstedt patients are entirely in the same area as we find in medical rehabilitation.

The results, particularly with regard to the mental state of patients in treatment, and the documented influence which cognitive-emotional variables have on progression would suggest a greater need for psychosocial patient care. The clinic already has the staff required for this, yet closer cooperation with additional psychology staff — e.g. assistance provided by a behavioural therapist — could improve treatment even more.

Equally beneficial would be expanding and systematizing the patient documentation that already exists at the clinic. While recruiting the sample, it became apparent that a number of patients were not first-time patients. This suggests the need to maintain a constantly updated register. Using this register, reports could be written at regular intervals on how the structure of inpatients and outpatients being treated at the clinic develops, on how many patients are first time patients and how many have returned for treatment (especially the inpatients here) and, finally, on the nature of the relationship between inpatient and outpatient care in Bredstedt.

Moreover, an appropriate set of instruments ought to be chosen from those used in this study which — in addition to the symptoms list already used at the clinic — would routinely be used with all patients in treatment or with a sample group drawn on a regular basis and in accordance with set criteria. Conducting questionnaires with patients before treatment begins and at regular intervals thereafter would yield valuable information on the state and progression of patient health over time. In addition, such continual monitoring of quality development and the resulting longitudinal documentation of developments would provide the clinic with a broad empirical basis for future assessments of the medical care it provides.

References

[1] Effective allergy practice: a document on standards of care and management of the allergy patient. Southampton: British Society for Allergy and Environmental Medicine & The British Society for Nutritional Medicine, 1994. Pp18
[2] Position paper on allergen immunotherapy: report of a BASCI working party January-October 1992. Clinical and Experimental Allergy, 1993;23(Suppl 3, August):1-44.
[3] Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2003. Oxford: Update Software.
[4] Wilson DR, Torres Lima M, Durham SR. Sublingual immunotherapy for allergic rhinitis (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2003. Oxford: Update Software.
[5] Bagnall AM, Whiting P, Wright K, Sowden AJ. The effectiveness of interventions used in the treatment and management of chronic fatigue syndrome and/or myalgic encephalomyelitis in adults and children. York: The NHS Centre for Reviews and Dissemination, University of York, 2001.
[6] Carr D, Goudas L, Lawrence D et al. Management of cancer symptoms: pain, depression and fatigue. Rockville: Agency for Healthcare Research and Quality (AHRQ). Evidence Report/Tech, 2002.

	N9831 & B-31 Meta-analysis		HERA Study		FinHer Study	
Population	Women with HER2-positive early-stage breast cancer		Women with HER2-positive early-stage breast cancer		Women with HER2-positive early-stage breast cancer	
	Undergone breast surgery		Undergone locoregional therapy		Undergone breast surgery with axillary node dissection and sentinel-node biopsy	
	Node-positive disease or high risk node-negative disease		Node-positive disease or high risk node-negative disease with tumour size >1cm		Node-positive disease or high risk node-negative disease with tumour size ≥20mm and progesterone receptor negative	
	No evidence of metastases		No information on exclusions for metastases		No evidence of distant metastases	
	Normal LVEF. Many exclusions for cardiac problems.		No information on exclusions for cardiac disease		Excluded patients with severe hypertension and patients with cardiac disease	
Regimen of Trastuzumab	Trastuzumab for 52 weeks initiated concomitantly with paclitaxel. Starting dose of 4mg/kg given with first dose of pacitaxel. Subsequent doses of 2mg/kg every week.		Trastuzumab for 1 year. Starting dose of 8mg/kg (90mins infusion). Subsequent doses of 6mg/kg (90mins infusion) every 3 weeks.		Trastuzumab for 9 weeks initiated concomitantly with docetaxel or vinorelbine. Starting dose of 4mg/kg (90mins infusion) with first dose of docetaxel or vinorelbine. Subsequent doses of 2mg/kg (30mins infusion) every week before docetaxel or vinorelbine infusion.	
Adjuvant Treatment	Doxorubicin and cyclophosphamide followed by pacitaxel every week or every 3 weeks.		At least 4 cycles of neoadjuvant or adjuvant chemotherapy.		Docetaxel or vinorelbine followed by 3 cycles of fluorouracil, epirubicin and cyclophosphamide.	
Sample Size	3351		3387		232	
Quality Issues	Unblinded		Unblinded		Unblinded	
Median Follow-up	2 years		1 year		3 years	
Disease Free Survival	HR=0.46 CI=0.37-0.56 p<0.0001	RD (3yr)=11.8% CI=8.1-15.4 RD (4yr)=18.2% CI=12.7-23.7	HR=0.54 CI=0.43-0.67 p<0.0001	RD (2yr)=8.4% CI=2.1-14.8	HR=0.42 CI=0.21-0.83 p=0.01	RD (2yr)=7.7% No CI reported RD (3yr)=11.7% No CI reported
Overall Survival	HR=0.67 CI=0.48-0.93 p=0.015	RD (3yr)=2.5% CI=0.1-5 RD (4yr)=4.8% CI=0.6-9	HR=0.76 CI=0.47-1.23 p=0.26	RD (2yr)=0.9% CI=-3-5	HR=0.41 CI=0.16-1.08 p=0.07	RD (2yr)=1.7% No CI reported RD (3yr)=6.6% No CI reported
Distant Recurrence Free Survival	HR=0.47 CI=0.37-0.61 p<0.0001	RD (3yr)=8.8% CI=5.5-12.1 RD (4yr)= 15.9% CI=11.1-20.8	HR=0.49 CI=0.38-0.63 p<0.0001	RD (2yr)=7.8% CI=2-13	HR=0.29 CI=0.13-0.64 p=0.02	Not reported
Cardiac Safety	Cumulative incidence of CHF or death from cardiac causes for: B-31 Study: 4.1% (trastuzumab) vs 0.8% (control) N9831 Study: 2.9% (trastuzumab) vs 0% (control)		Symptomatic CHF inc. severe CHF =1.73% (trastuzumab) vs 0.06% (control) p<0.001		LVEF Difference (12 months)=1.7% in favour of trastuzumab group CI=-0.1-3.5 p=0.06	
			Disease in LVEF =7.08% (trastuzumab) vs 2.21% (control) p<0.001		LVEF Difference (36 months)=3.0% in favour of trastuzumab group CI=0.7-5.4 p=0.01	

Notes: HR=hazard ratio; RD=risk difference; CI=95% confidence interval; HER2-positive=amplification of the HER2/neu gene; LVEF=left ventricular ejection fraction; CHF=congestive heart failure

Archived ARIF Request

Screening in Those with Family History Breast Cancer

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in June 1998 and Update in May 2000.

The Problem Submitted for ARIF to Advise Upon:

What is the evidence base of the proposals made for the West Midlands Familial Cancer Initiative, particularly those concerning screening of individuals with a positive family history of breast cancer?

Question Reformulated:

What are the effects of annual mammography + breast self examination + appropriate treatment in those with a positive family history of breast cancer on that cancer's incidence, severity, mortality and morbidity?

An appropriately strong family history ranges from one first degree relative developing cancer under the age of 40 years to three close relatives on the same side of the family developing breast cancer at an average age below 60 years.

Reviews Identified

- Kerlikowske K et al. Efficacy of screening mammography. A meta-analysis. JAMA 1995; 273: 149-154

Additional useful background information also provided by:

- Pharaoh P et al. Managing women at high risk of breast cancer because of a family history. Assessing the evidence. Anglia and Oxford NHSE; Cambridge, 1997. Pp 15

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Comments

The first of the above is a systematic review. Although it indicates that rigorous research on the specific question of interest is not available, the summaries of research on related aspects of the prevention and early treatment of breast cancer are useful. Important findings include:

- Screening by mammography in the population at general risk has been demonstrated to reduce breast cancer mortality.

- However, neither having shorter screening intervals e.g. annual screening or adding breast self-examination seems to improve effectiveness, raising the question why the screening proposed for the West Midlands Familial Cancer Initiative incorporates these two features.
- Further, there is continuing uncertainty about whether the benefits of mammography screening apply to the 40-49 year age group. This is particularly important as it is this same age group where family history seems to confer greatest additional risk. Putting this uncertainty aside, we could surmise that if a small benefit does truly exist from mammographic screening for the 40-49 age group at general risk, this benefit would be greater for a higher risk group, such as those with a clear family history. Unfortunately, even this logical deduction is challenged by the possibility that increased radiation exposure from additional mammograms in a group who may be more susceptible to the effects of radiation could cause as many additional cancers as it saves.

Thus, annual mammographic screening of women under 50 with a positive family history should only be undertaken in the context of rigorous evaluation. In ARIF's view it has not been proved that annual mammographic screening for those with a positive family history will definitely guarantee an individual is less likely to suffer death from breast cancer than if they had not been screened.

This is an area prone to need for regular updating as new information is continually becoming available.

Request Carried Out: June 1998

Updated: May 2000 - This request was updated in response to the publication of a controversial review on the role of breast cancer screening programmes:

- Gøtzsche PC, Olsen O. Is screening for breast cancer with mammography justifiable? Lancet 2000; 355: 129-134

We undertook a detailed appraisal of this review and our main conclusion was that, although a definitive appraisal is prohibited by the omission of some important details of the methods of the review, it does make a few important points:

- The methods of previous systematic reviews and meta-analyses, which have contributed to the widespread introduction of mammographic breast screening programmes, are inadequate.
- There are also inadequacies in the methods of the existing trials.
- It is possible that treatment associated morbidity may offset any benefit in terms of reduced mortality.
- The pooled results for around half a million women fail to demonstrate a reduction in all-cause mortality.

The methodological limitations of the review are such that the analysis does not support the authors' conclusion that "Screening for breast cancer with mammography is unjustified." Nevertheless, the review clearly indicates that existing uncertainty around the value of breast screening by mammography has increased.

Given our original concerns about the effectiveness of annual mammography in those with a positive family history, this review only serves to reinforce the need for caution in implementation of enhanced screening in this group.

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Archived ARIF Request

Docetaxel (Taxotere)
Breast Cancer (advanced)

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Is docetaxel effective in the management of patients with advanced breast cancer?

Reviews Identified

- BMJ Publishing Group. Paclitaxel and docetaxel in breast and ovarian cancer. Drugs and Therapeutics Bulletin 1997; 35(6): 43-6

Trials Identified

- Chan S. Docetaxel vs doxorubicin in metastatic breast cancer resistant to alkylating chemotherapy. Oncology (Huntingt) 1997; 11(8S): 19-24
- Nabholtz J-M, Theurlimman B, Bezwoda WR et al. Docetaxel vs mitomycin plus vinblastine in anthracycline-resistant metastatic breast cancer. Oncology (Huntingt) 1997; 11(8S): 25-30

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Comments

The review identified provides a well structured account of the evidence-base for using this chemotherapeutic agent.

Based on appraisal of the fully published studies of the trials, previously only reported in abstract, it appears that there is evidence to support the effectiveness of this agent in advanced breast cancer.

This is an area prone to need for regular updating as new information is continually becoming available.

Request Carried Out: August 1998

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Health Promotion
Brief Interventions
Primary Care
Diet

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to diet?

The evidence supporting brief advice on giving up smoking provides the benchmark for an effective brief health promotion intervention par excellence - Lancaster T, Stead LF. Physician advice for smoking cessation. The Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No: CD000165.pub2. DOI: 10.1002/14651858.CD000165.pub2.

Reviews Identified

- Ammerman A, Pignone M, Fernandez L, Lohr K, Jacobs AD, Nester C et al. 18. Counseling to promote a healthy diet. In: Guide to Clinical Preventive Services, 3rd ed. Evidence Syntheses, formerly systematic evidence reviews, HSTAT, Health Services/Technology Assessment; 2000 [cited 29th June 2006]. Available from: http://www.ncbi.nih.gov/books/bv.fcgi?rid=hstat3.chapter.3509

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Comments

We did not locate any systematic reviews that focussed specifically on brief dietary interventions in primary care. However, in a well-conducted systematic review, Ammerman et al (2002) examined the effectiveness of all types of primary care counselling to promote a healthy diet, including brief advice.

Our formal appraisal of the review focused on the section Key Question No. 4: Efficacy of Primare Care Counseling and Dietary Behavior Change, examining the efficacy of primary care counselling and dietary behaviour change interventions, particularly the low-intensity interventions.

The review highlighted the complex nature of dietary counselling for patients in primary care. Any interpretation of the data is effected by numerous factors such as the risk status of the patients, the intensity of the intervention, the dietary elements targeted, and the outcome measures used. However,

even with this proviso, the review indicated brief advice (≤5 minutes) on dietary behaviour may have a small effect. This was based on the results of two trials (n=142 and n=2121) which assessed the effect of counselling in changing dietary fat and fibre intakes.

In conclusion research evidence to-date neither fully supports nor refutes the provision of brief advice in a primary care setting on dietary behaviour.

Request Carried Out: July 2005

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Health Promotion
Brief Interventions
Primary Care
Exercise
Physical Activity

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to increasing physical activity?

The evidence supporting brief advice on giving up smoking provides the benchmark for an effective brief health promotion intervention par excellence - Lancaster T, Stead LF. Physician advice for smoking cessation. The Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No: CD000165.pub2. DOI: 10.1002/14651858.CD000165.pub2.

Reviews Identified

- Lawlor DA, Hanratty B. The effect of physical activity advice given in routine primary care consultations: a systematic review. Journal of Public Health Medicine. 2001;23(3):219-26

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Comments

Lawlor and Hanratty (2001) aimed to determine the effect of advice given in routine primary care consultations on levels of physical activity. A formal appraisal of the review indicated it was well conducted with appropriate search strategy and quality assessments undertaken.

Eight trials involving 4747 participants were identified. Two were cluster randomised RCTs, the remaining 6 were non-randomised controlled trials. Four of the 6 trials which reported short-term outcomes (up to 8 weeks) found in favour of the intervention. None of the 4 trials with long-term follow-up (over 4 months) found a statistically significant effect. Unfortunately the results of the review were limited by the validity of the trials, in particular the selection bias inherent in a non-randomised control trial.

In conclusion the evidence base appears insufficient to either fully support or refute the effectiveness of

brief advice given in routine primary care consultations to promote more physical activity.

Request Carried Out: July 2005

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Archived ARIF Request

Health Promotion
Brief Interventions
Primary Care
Falls in Older People

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in October 2005.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to the prevention of falls amongst older people?

The evidence supporting brief advice on giving up smoking provides the benchmark for an effective brief health promotion intervention par excellence - Lancaster T, Stead LF. Physician advice for smoking cessation. The Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No: CD000165.pub2. DOI: 10.1002/14651858.CD000165.pub2.

Reviews Identified

- Gillespie LD, Gillespie WJ, Robertson MC, Lamb SE, Cumming RG, Rowe BH. Interventions for preventing falls in elderly people. The Cochrane Database of Systematic Reviews 2003, Issue 4. Art No: CD000340.DOI: 10.1002/14651858.CD000340

OtherEvidence

- National Institute for Clinical Excellence. Clinical practice guideline for the assessment and prevention of falls in older people. National Institute for Clinical Excellence Clinical Practice Guideline 21; November 2004
  http://www.nice.org.uk/nicemedia/pdf/CG021fullguideline.pdf

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Comments

No systematic reviews focusing on brief interventions in primary care settings to prevent falls in older people were identified.

The NICE (2004) clinical practice guideline for the assessment and prevention of falls in older people

provided a thorough appraisal of the risk factors for falls and the effectiveness of preventive programmes seeking to reduce these risks. The NICE (2004) report drew heavily on a Cochrane review of interventions for preventing falls in elderly people (Gillespie et al, 2003).

In summary the NICE (2004) report indicated that risk factors predictive of falling and measures taken to reduce these risks are wide ranging and can be quite complex. Factors most predictive of falling amongst community dwelling elderly people are a falls history, gait deficit, balance deficit, mobility impairment, fear of falling, visual impairment, cognitive impairment, urinary incontinence and home hazards. Preventive programmes based on these risk factors included exercise programmes, education programmes, medication review, environmental modification in homes, and nutritional and hormonal supplementation.

In conclusion the interventions most likely to be beneficial appeared to be multidisciplinary interventions targeting multiple risk factors. Also individually tailored interventions delivered by a health professional appeared to be more effective than standard or group delivered programmes. The effectiveness of brief primary care interventions remains unclear.

Request Carried Out: October 2005

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Archived ARIF Request

Health Promotion
Brief Interventions
Primary Care
First Intercourse Amongst Adolescents

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to advice on delaying the time of first intercourse?

The evidence supporting brief advice on giving up smoking provides the benchmark for an effective brief health promotion intervention par excellence - Lancaster T, Stead LF. Physician advice for smoking cessation. The Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No: CD000165.pub2. DOI: 10.1002/14651858.CD000165.pub2.

Reviews Identified

- DiCenso A, Guyatt G, Willan A, Griffith L. Interventions to reduce unintended pregnancies among adolescents: systematic review of randomised controlled trials. BMJ. 2002;324:1426-30

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Comments

We did not locate any systematic reviews that focussed specifically on brief interventions in primary care settings aimed at delaying time of first intercourse amongst adolescents. However DiCenso et al (2002) evaluated the effectiveness of primary prevention strategies in delaying sexual intercourse, improving the use of birth control, and reducing the incidence of unintended pregnancies amongst adolescents.

A formal appraisal of the review indicated it was comprehensive and generally well-documented. In summary the evidence presented indicated primary prevention strategies in these areas are generally offered as part of a long-term sex education programme often integrated within the school curriculum. Although these longer-term interventions are not the brief primary care interventions sought, we feel they are useful given the lack of evidence on the effectiveness of brief interventions.

RCTs undertaken to-date indicate longer-term primary prevention strategies are not effective in delaying the initiation of sexual intercourse, improving the use of birth control amongst young men and women, or reducing the number of pregnancies in young women or the partners of young men. The effectiveness of brief primary care interventions is unknown.

Request Carried Out: October 2005

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Health Promotion
Brief Interventions
Primary Care
Illicit Drug Use

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to the prevention/reduction of illicit drug use amongst young people?

The evidence supporting brief advice on giving up smoking provides the benchmark for an effective brief health promotion intervention par excellence - Lancaster T, Stead LF. Physician advice for smoking cessation. The Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No: CD000165.pub2. DOI: 10.1002/14651858.CD000165.pub2.

Reviews Identified

- White D, Pitts M. Educating young people about drugs: a systematic review. Addiction 1998;93(10):1475-87

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Comments

No systematic reviews focusing on brief interventions in primary care settings to delay/prevent drug use amongst young people were identified. However White et al (1998) evaluated the effectiveness of a broader range of interventions directed at the reduction/prevention of drug use.

A formal appraisal of the review indicated it was comprehensive and generally well-documented however an update would be beneficial. To-date research in this area has looked at longer-term group interventions predominantly based in schools. The intervention setting and delivery timescale therefore differ quite markedly from those of our target question. However, in the absence of more pertinent research, we feel this work is important as it usefully explores the effectiveness of the main strategies employed to delay/prevent drug use amongst young people.

In conclusion, the report indicated school based programmes had a small effect on illicit drug use in

terms of a delay in the onset of substance use by non-users and a reduction in substance use by current users, but any programme gains dissipate with time. The more positive interventions with longer-term impact were the more intense interventions (10 sessions or more) that were able to reinforce their messages with additional booster sessions. The effectiveness of brief primary care interventions remains unclear.

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Health Promotion
Brief Interventions
Primary Care
Safe Sex

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to safe sex?

The evidence supporting brief advice on giving up smoking provides the benchmark for an effective brief health promotion intervention par excellence - Lancaster T, Stead LF. Physician advice for smoking cessation. The Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No: CD000165.pub2. DOI: 10.1002/14651858.CD000165.pub2.

Reviews Identified

- Ward D, Rowe B, Pattison H, Taylor R. Behavioural Interventions To Reduce The Risk of Sexually Transmitted Infections In Genitourinary Medicine Clinic Patients: A Systematic Review. The West Midlands Health Technology Assessment Collaboration, Department of Public Health and Epidemiology, University of Birmingham. 2004 June. Report No 50

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Comments

We did not locate any systematic reviews that focussed specifically on brief interventions to promote safe sex in primary care settings. However Ward et al (2004) evaluated the effectiveness of behavioural interventions in reducing the risk of sexually transmitted infection (STI) or re-infection amongst patients attending genitourinary medicine (GUM) or sexual health clinics.

A formal appraisal of the review indicated it was well conducted. Although broader in scope than our target question the review did include some relatively brief behavioural interventions (<30mins) delivered to individuals in public STI and family planning clinics. The trials reported were mainly carried out in US urban sexual health clinics. The results were mixed.

In conclusion the evidence does not consistently support the use of behavioural interventions as a means of reducing STI rates. Nor does it provide consistent evidence that behavioural interventions can reduce the number of new sexual partners or their risk characteristics. However it does provide evidence that behavioural interventions are generally effective at increasing the proportion of subjects reporting consistent condom use. These findings would appear to refute the effectiveness of brief interventions equally.

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Health Promotion
Brief Interventions
Primary Care
Smoking Cessation

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of possible brief interventions (5-10 minutes) by healthcare professionals in primary care settings that promote a healthy lifestyle/lifestyle change with specific reference to smoking cessation?

The evidence supporting brief advice on giving up smoking provides the benchmark for an effective brief health promotion intervention par excellence (see Cochrane Review below).

Reviews Identified

- Lancaster T, Stead LF. Physician advice for smoking cessation. The Cochrane Database of Systematic Reviews 2004, Issue 4. Art No: CD000165.pub2. DOI: 10.1002/14651858.CD000165.pub2.

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Comments

This well-conducted systematic review identified 39 trials conducted between 1972 and 2003, including over 31,000 subjects. The results of a meta-analysis of 17 trials that compared brief advice with no advice/usual care and showed a small but significant increase in the odds of quitting (OR: 1.74, 95%CI: 1.48 to 2.05). Direct comparison of intensive versus minimal advice showed a small advantage in providing intensive advice (OR: 1.44, 95%CI: 1.24 to 1.67). Direct comparison also suggested a small benefit of follow-up visits.

The provision of brief advice in primary care has a small but significant effect on smoking cessation rates.

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Bronchodilators
Bronchiolitis

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Question Reformulated

We identified a list of currently employed treatments for bronchiolitis. This request focuses on the use of bronchodilators.

Reviews Identified

- Kellner JD, Ohlsson A, Gadomski AM, Wang EEL. Bronchodilators for bronchiolitis (Cochrane Review). In: The Cochrane Library, Issue 3, 1999. Oxford: Update Software.

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Comments

The Cochrane review is a good and up-to-date review. However, it does have some minor methodological limitations and, although it purports to have been updated recently, the update appears to have consisted only of a re-run of the MEDLINE search. The review includes 8 RCTs, and the total numbers of events are reasonable for most outcomes. The findings suggest that there are very modest benefits with treatment which may have been overestimated in some studies due to the inclusion of some children with asthma (recurrent wheeze), which is known to respond well to bronchodilators. It is also important to note that the review does not address the treatment of children with moderate or severe illness.

Additional information relevant to this request is available in the requests entitled Bronchiolitis/Continuous Negative Extrathoracic Pressure (CNEP), Bronchiolitis/Ribavirin, Bronchiolitis/Immunoglobulin, Bronchiolitis/Steroids, Bronchiolitis/Antibiotics, Bronchiolitis/Assisted Ventilation.

Request Carried Out: November 1999

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Continuous Negative Extrathoracic Pressure (CNEP) Bronchiolitis

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence base for the treatments of infants with bronchiolitis with Continuous Negative Extrathoracic Pressure (CNEP) ventilation?

Reviews Identified

- Thomson A. The role of negative pressure ventilation. Archives of Diseases in Childhood 1997; 77(5):454-458

Trials Identified

None identified.

Other Literature Identified

- Linney MJ. Negative pressure ventilation in bronchiolitis. Care of the Critically Ill 1997;13:161

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Comments

The review by Thomson is not a systematic review but a general narrative overview of negative pressure ventilation, which covers the use of CNEP in neonatal respiratory failure. This cites the only published randomised controlled trial of CNEP by Samuels et al (Paediatrics 1996; 98(6 Pt1): 1154-1160) which considers its role in neonatal respiratory distress syndrome.

The study by Linney appears to be the only published report of the use of CNEP in bronchiolitis. This is an abstract report of a small case series, the results of which, while promising, should be viewed with extreme caution. Although this paper does not make reference to any adverse effects, the trial of CNEP in neonates did record non-significant increases in cranial ultrasound abnormalities in the treatment group.

On the basis of this material, there appears to be little evidence at this point in time to support the use of CNEP in infants with bronchiolitis.

Additional information relevant to this request is available in the requests entitled: Bronchiolitis/Bronchodilators, Bronchiolitis/Ribavirin, Bronchiolitis/Immunoglobulin, Bronchiolitis/Steroids, Bronchiolitis/Antibiotics, Bronchiolitis/Assisted Ventilation.

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Immunoglobulin Bronchiolitis

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Question Reformulated

We identified a list of currently employed treatments for bronchiolitis. This request focuses on the use of immunoglobulin.

Reviews Identified

- Wang EEL, Tang NK. Immunoglobulin for preventing respiratory syncytial virus infection (Cochrane Review). In: The Cochrane Library, Issue 4, 1999. Oxford: Update Software.

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Comments

Respiratory Syncytial Virus (RSV) infection is the most important cause of bronchiolitis in infants. The Cochrane review on the use of immunoglobulin in the prevention of RSV infection is an up-to-date and well conducted systematic review.

Specifically, it considers the effectiveness of polyclonal RSV hyperimmune globulin and monoclonal antibody in the prevention of severe RSV infection in high-risk children. Outcomes used as surrogates for severe infection were the proportions of cases requiring admission to hospital, intensive care or mechanical ventilation, and case fatality rates. Despite some minor methodological limitations, the results of the review are probably reliable. Findings indicate that treatment is associated with reductions in hospitalisation rates and admissions to ICU. The results for mortality and mechanical ventilation, although also positive, were not statistically significant.

In summary, it seems likely that immunoglobulin may reduce morbidity and possibly mortality from RSV bronchiolitis in high-risk children.

Additional information relevant to this request is available in the requests entitled

Bronchiolitis/Bronchodilators, Bronchiolitis/Continuous Negative Extrathoracic Pressure (CNEP), Bronchiolitis/Ribavirin, Bronchiolitis/Steroids, Bronchiolitis/Antibiotics, Bronchiolitis/Assisted Ventilation.

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Ribavirin
Bronchiolitis

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Question Reformulated

We identified a list of currently employed treatments for bronchiolitis. This request focuses on the use of ribavirin.

Reviews Identified

- Randolph AG, Wang EEL. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract (Cochrane Review). In: The Cochrane Library, Issue 4, 1999. Oxford: Update Software

Trials Identified

- Rodriguez WJ, Gruber WC, Welliver RC et al. Respiratory syncytial virus (RSV) immune globulin intravenous therapy for RSV lower respiratory tract infection in infants and young children at high risk for severe RSV infections. Paediatrics 1997; 99: 454-461
- Long CE, Voter KZ, Barker WH, Hall CB. Long term follow-up of children hospitalized with respiratory syncytial virus lower respiratory tract infection and randomly treated with ribavirin or placebo. Pediatric Infectious Diseases Journal 1997; 16: 1023-1028

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Comments

Respiratory Syncytial Virus (RSV) infection is the most important cause of bronchiolitis in infants. The Cochrane review on ribavirin for RSV infection is a good review, but is potentially slightly out-of-date as it was last updated in February 1997. Most children were moderately or severely ill with lower respiratory tract infection or pneumonia, but only two of the eight included studies specifically stated that they included children with bronchiolitis.

The results of the review are inconclusive. Although the review itself has some methodological limitations, the main reason for this is that the included studies were generally small with insufficient power to provide statistically significant or reliable estimates of effect for the key outcomes.

We also identified two randomised controlled trials published since the review was last updated. They found no significant differences between the treatment and control groups, concluding that ribavirin is probably not effective in the treatment of infants with RSV infection.

Additional information relevant to this request is available in the requests entitled Bronchiolitis/Bronchodilators, Bronchiolitis/Continuous Negative Extrathoracic Pressure (CNEP), Bronchiolitis/Immunoglobulin, Bronchiolitis/Steroids, Bronchiolitis/Antibiotics, Bronchiolitis/Assisted Ventilation.

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Steroids
Bronchiolitis

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence base for the effectiveness of treatments for moderate to severe bronchiolitis in infants?

Question Reforumlated

We identified a list of currently employed treatments for bronchiolitis. This request focuses on the use of steroids.

Reviews Identified

None identified.

Trials Identified

- Leer JA, Green JL, Heimlich EM et al. Corticosteroid treatment in bronchiolitis. A controlled collaborative study in 297 infants and children. American Journal of Diseases in Childhood 1969; 117: 495-503
- Roosevelt G, Sheehan K, Grupp PJ et al. Dexamethasone in bronchiolitis: a randomised controlled trial. Lancet 1996; 348: 292-295
- van Woensel JB, Wolfs TF, van Aalderen WM et al. Randomised double blind placebo controlled trial of prednisilone in children admitted to hospital with respiratory syncytial virus bronchiolitis. Thorax 1997; 52: 634-637

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Comments

No reviews were identified, but several trials have been published on the use of steroids in bronchiolitis. We obtained several of these and all were of fairly good methodological quality, and of reasonable size. Although they all looked at different drugs, all but one of those we examined failed to detect any significant benefits associated with the intervention. It was difficult to single out any studies that were clearly of superior validity and those cited simply represent a sample of those available. The study by Leer et al is the largest trial with 297 participants. It was published in 1969 and as such may be slightly

out of date. A more up-to-date study of reasonable size is that by Roosevelt et al. The study by van Woensel was the only one to detect some benefits for treatment in terms of accelerating the rate of recovery.

A systematic review of trials on this intervention is required.

Additional information relevant to this request is available in the requests entitled Bronchiolitis/Bronchodilators, Bronchiolitis/Continuous Negative Extrathoracic Pressure (CNEP), Bronchiolitis/Ribavirin, Bronchiolitis/Immunoglobulin, Bronchiolitis/Antibiotics, Bronchiolitis/Assisted Ventilation.

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Archived ARIF Request

Buccal Nitrates
Heart Failure After Myocardial Infarction

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness and cost effectiveness of using buccal nitrates in primary care, in the management of patients with heart failure after a myocardial infarction?

Reviews Identified

None identified.

Trials Identified

- Verma SP et al. Nitrate therapy for left ventricular failure complicating acute myocardial infarction: a haemodynamic comparison of intravenous, buccal and transdermal delivery systems. Journal of Cardiovascular Pharmacology 1989;14:756-62
- Opasich C et al. Resting and exertional haemodynamic effects of buccal nitroglycerin: acute and chronic discontinuous treatment in post myocardial infarction patients with heart failure. European Heart Journal 1988;9:252

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Comments

No systematic or other reviews were found. The two primary studies identified almost certainly do not represent all research undertaken on this topic, nor can we guarantee that the studies obtained are representative. Not withstanding this it seems likely that most evidence on the effects of buccal nitrates is based on measurement of its haemodynamic effects alone and thus if a benefit at this level were demonstrated we would still need evidence of the effects on longer term outcomes. This is particularly so in view of the uncertainty about the role of nitrates generally post myocardial infarction suggested by studies such as ISIS-4 (Lancet 1995; 345: 669-685).

Also there is disagreement about whether buccal nitrates offer any advantages over other nitrate preparations given the comments, in the article by Verma et al.

On this basis, the grounds for prescribing buccal nitrate in heart failure in our opinion, seem tenuous.

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Archived ARIF Request

Buprenorphine Detoxification Opiate Addiction

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The Problem Submitted for ARIF to Advise Upon:

Is there any evidence on the effectiveness of buprenorphine in the management of detoxification for opiate addiction?

Reviews Identified

None identified.

Trials Identified

- Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for Opioid dependence. JAMA 1992; 267 (20): 2750-2755
- Strain EC, Stitzer ML, Liebson IA, Bigelow GE. A controlled trial of buprenorphine treatment for Opioid dependence. 1996; 16 (1): 58-67

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Comments

No reviews were identified. However, several relevant primary studies were identified. Both of the trials cited are good-sized, well-conducted, double blind, randomised controlled trials, the results of which are probably reliable. Their findings suggest that buprenorphine is at least as effective as methadone, and that it may be more effective in the longer term for some outcomes such as dependence and adverse events. Buprenorphine also has the additional benefit of blocking morphine receptors thus obviating the effect of self-administration of heroin during treatment.

In summary, a substantial and fairly robust literature exists around the use of buprenorphine as part of a detoxification programme for opiate addiction. It appears to be equally effective to methadone with some additional advantages pertaining to issues of safety, dependence and compliance.

Additional information relevant to this request is available in the request entitled "Dextropopoxyphene - Detoxification/Opiate Addiction"

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Archived ARIF Request

C1 Esterase Inhibitor Concentrate Hereditary Angioedema (HAE)

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence for using C1 Esterase Inhibitor Concentrate as a long-term prophylaxis in patients with severe Hereditary Angioedema (HAE).

Hereditary angioedema (HAE) is a genetic disorder passed down through families. Both males and females can be affected. It is rare, the prevalence being estimated to be between 1/10,000 to 1/50,000. There are two main types, Type I and Type II, the former being the most common representing 85% of patients. In both cases the symptoms of the disease are the same. Patients can have episodes of non painful and non pitting swelling in any part of the body, but most commonly in the extremities such as face, hands and feet. The airway, particularly the larynx can also be affected as can the intestine, both of which are usually treated in hospital. If the airway or larynx is affected the patient is in danger of suffocation, therefore they need to be treated in an intensive care setting where intubation/tracheostomy equipment is available. When swelling occurs in the abdomen this can also cause the patient to be admitted to hospital where they can be properly assessed as often the symptoms mimick an acute abdomen. Patients in hospital can also receive proper intravenous rehydration and pain relief. Patients vary in both the severity and frequency of the symptoms.

Patients receive three types of treatment; treatment for acute attacks, short-term prophylaxis, given to cover patients for planned medical procedures such as surgery which can often trigger an attack, and long-term prophylaxis (i.e. prevention) given to patients where swelling is frequent and interferes with the patients quality of life. Long-term prophylaxis is the focus of this request.

Reviews Identified

- Annonymous. C1 esterase inhibitor: new preparation. A major advance in emergency treatment of hereditary angioneurotic oedema. Prescrire International 2001;10(53):67-70
- De Serres J, Groner A, Lindner J. Safety and efficacy of pasteurized C1 inhibitor concentrate (Berinert P) in hereditary angioedema: a review. Transfusion and Apheresis Science. 2003;29(3):247-254
- Fay A, Abinun M. Current management of hereditary angio-oedema (C'1 esterase inhibitor deficiency) Journal of Clinical Pathology. 2002;55(4):266-270

Randomised Controlled Trials

- Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. New England Journal of Medicine. 1996;334(25):1630-1634

Other Evidence

- Martinez-Saguer I, Heller C, Fischer D, Ettingshausen CE, Kreuz W. Prophylactic treatment with pasteurised C1 inhibitor concentrate in patients with recurrent angioedema caused by hereditary and aquired C1 inhibitor deficiency. American Society of Hematology, Forty First Annual Meeting, New Orleans Dec 3-7, #1032-2339. 1999
- Bork K, Witzke, G. Long-term prophylaxis with C1-inhibitor (C1 INH) concentrate in patients with recurrent angioedema caused by hereditary and acquired C1-inhibitor deficiency. Journal of Allergy and Clinical Immunology 1989;83(3):677-682
- Agostoni A et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. Journal of Allergy and Clinical Immunology. 2004;114(3 Suppl 1):S51-131

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Comments

The reviews although not systematic provide a good structured account of the treatment of HAE. We identified one comparative trial, one prospective case series and one case study which use C1 esterase inhibitor concentrate as a long-term prophylaxis treatment in patients with uncontrollable or severe HAE.

The numbers of patients in these trials are small, however, the evidence from the primary studies when taken together, suggest that this is a promising, but still very much an experimental treatment for patients in whom standard treatments have failed or are contraindicated.

We would suggest that any patient who has this treatment should ideally do so as part of a robust evaluation of clinical effectiveness and safety, in order to add to the current evidence base.

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Archived ARIF Request

Clinical Nurse Specialists
Cancer

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The Problem Submitted for ARIF to Advise Upon:

What evidence is there that clinical nurse specialists are effective, particularly in the care of cancer patients?

Question Reformulated:

Two aspects of the question as stated deserve close attention:

- Intervention - What is meant by "clinical nurse specialist" and how does it relate to terms such as "nurse practitioner"?
- Population - That research on "clinical nurse specialists" working in other fields eg diabetes care, rheumatology, care of neonates may provide as useful information as that specifically on "clinical nurse specialists" caring for cancer patients.

Reviews Identified

General Background

- Brown SA et al. A meta-analysis of nurse practitioners and nurse midwives in primary care. Nursing Research 1995; 44(6): 332-339
- Bryant J. Neonatal nurse practitioners. Winchester: Wessex Institute of Public Health, 1995. Pp 10 (DEC report)
- Watson P et al. The mid-level practitioner: a review of the literature on nurse practitioner and physician assistant programmes. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham & Sheffield, 1996. Discussion Paper 96/102. Pp 161

Specific to Question

- Cancer Guidance Sub-group of the Clinical Outcomes Group. Improving outcomes in breast cancer: The research evidence. London: NHS Executive, Department of Health, 1996. Chapter 8. [See also: NHS Centre for Reviews & Dissemination. The management of primary breast cancer. Effective Health Care 1996; 2(6): 1-16]
- Cancer Guidance Sub-group of the Clinical Outcomes Group. Improving outcomes in colorectal cancer: The research evidence. London: NHS Executive, Department of Health, 1997. Chapter 3;

Chapter 1 also of relevance. [See also: NHS Centre for Reviews & Dissemination. The management of colorectal cancer. Effective Health Care 1997; 3(6): 1-12]

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Comments

There is not a clear bottom line from the reviews identified, which are all systematic in approach. Two points which do emerge are:

"Clinical nurse specialists" are not a standardised entity and attempts to define them have been difficult. It may thus be more useful to focus on roles or procedures which nurses with appropriate additional training and experience have undertaken effectively, rather than just attempting to decide whether "clinical nurse specialists" are effective.

It is not true to say that there is no research supporting the effectiveness of nurses taking on tasks outside traditional nursing responsibilities, particularly if they have been adequately trained. For two areas of cancer care, breast and colorectal cancer, where the research has been summarised, the research evidence is clearly limited in quantity and quality but specifically suggests beneficial roles in counselling, psychosocial support, administration of chemotherapy and palliative care. On its own this research is not conclusive, nor does it exclude the possibility that there are other useful roles. However, when other research on the general effects of nurses with extended roles is considered, repeated demonstration that nurses can undertake roles normally carried out by medically qualified staff with equivalent outcomes, strengthens the argument for their effectiveness, although still leaving many unanswered questions.

Request Carried Out: July 1998

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Cancer chemotherapy delivered in the community

Synopsis

Question:	What is the feasibility of delivering cancer chemotherapy to patients In the community?
Reviews Identified:	Adams P, Hardwich J, Embree V, Sinclair S, Conn B, Bishop J. Literature review. Models of cancer services for rural and remote communities. Sydney: Cancer Institute New South Wales, March 2009 Campbell ND, Ritchie LD, Cassidy J, Little J. Systematic review of cancer treatment programmes in remote and rural areas. British Journal of Cancer 1999;80(8):1275-1280 Boothroyd L, Lehoux P. Home-based chemotherapy for cancer: issues for patients, caregivers and the health care system. Montreal: Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) 2004: 77
Comments:	Much of the research is out of date and of variable quality and focus, therefore it is difficult to draw specific conclusions regarding best practice and effectiveness of giving chemotherapy in a community setting. It may be that there needs to be a diversity of approaches to tailor care to local conditions, which creates problems in evaluating the research. ARIF have strived to indicate the type of research available, which should point to literature sources that may help inform potential models of practice.
Date Completed:	November 2009

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

The feasibility of cancer chemotherapy being delivered to patients in the community.

Request completed: November 2009

Question

What is the feasibility of delivering cancer chemotherapy to patients in the community?

Population/setting	Two types of patients: • Patients who are essentially 'well' and receiving chemotherapy as an adjuvant treatment • Patients with metastatic disease receiving cancer chemotherapy **NB**: types of chemotherapy considered: oral, intravenous, intra muscular. Setting: setting should be generalizable to the UK **Exploratory questions**: any subgroups
Intervention	Standard chemotherapy but delivered (via a registered nurse) in the community in the following locations: • Home • General practice • Community hospital • Acute hospital trust • Mobile centres • Other? **Exploratory questions**: Any head - to - head trials e.g. home vs. general practice
Comparator	Standard chemotherapy delivered in specialist oncology centres.
Outcomes - clinical	Safety: • Patient safety – adverse events, hospital in - patient episodes • Staff safety – issues around preparing (compounding units), handling and transporting chemotherapy • Quality of life **Exploratory questions**: Patient compliance
Outcomes - cost	Cost effectiveness (Cost per Quality Adjusted Life Year - QALY) Perspective - societal and NHS Cost of implementation of service and service running costs
Study design	Systematic reviews and health technology assessments No date or language restrictions

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol http://www.arif.bham.ac.uk/strategy.shtml Text and index terms were used to represent the population and the intervention. Sources were searched from their inception to August 2009. No language restriction was applied to the searches. The MEDLINE search can be found in Appendix A. Studies were selected according to the inclusion criteria stated in the question.

Results

This report is based on three reviews: one overview[1] looking at cancer treatment in rural and remote areas, one systematic review that investigated the effectiveness of programmes in remote and rural areas[2] and another on the effectiveness of home based chemotherapy.[3] In addition three papers were identified providing background on the challenges of undertaking community cancer

chemotherapy.[4,5,6] . These papers have not been critically appraised. Full search results can be found in Appendix B.

Cancer treatment in rural and remote areas

Adams P, Hardwich J, Embree V, Sinclair S, Conn B, Bishop J. Literature review. Models of cancer services for rural and remote communities. Sydney: Cancer Institute New South Wales, March 2009

The aim of this review was to investigate current models of cancer service provision in rural and remote areas, in order to identify common elements of best practice. Models of cancer were defined as "*literature related to services provided to rural communities by a specialist doctor, as well as specialist services provided by a generalist provider such as a GP*". Services could be based in local hospitals, or in primary care and amongst others include outreach services, shared care and tele-health. Remote was defined according to travelling time rather than distance and specified as treatment over an hour away. This is probably a good working definition given that patients in rural areas around Birmingham may have a travel time over this due to traffic conditions and/or public transport difficulties. The review was published by the Cancer Institute in New South Wales (NSW), Australia, which is a NSW government agency dedicated to cancer and looks at examples from Australia, Canada and Scotland.

The search for publications, which was extensive, was undertaken in a systematic manner. In their search the authors contacted 'key informants' from Canada and Australia, but it is not clear how these were identified. Results are reported in a narrative format, therefore, the review cannot be classified as a systematic review.

The authors start with a description of services in Australia. Cancer care in rural and remote areas is co-ordinated by the Cancer Council of Australia, a government organisation, which facilitated the setting up of seven cancer services networks (CanNET) – arranged according to states - to develop delivery models to people in rural areas. The review authors give several examples of cancer services developed under this framework, but state that it is still too early (at the time of writing the review) to identify the optimal model of care. It may be worthwhile to refer to the most recent report that the CanNET scheme has produced to see if there are any relevant models of care. This can be accessed at: (http://www.canceraustralia.gov.au/media/14678/may_2008_cannet_national_workshop_report.pdf [accessed 5-11-09])

Two examples of chemotherapy provision are provided. In the first, patients in Dubbo, NSWs are prepared for a visiting oncologist by a designated primary care physician. The patients are

assessed as to whether they are well enough to receive chemotherapy by the physician who also coordinates relevant tests, MRIs and biopsies etc. In the second example, patients are treated with chemotherapy in the Alice Springs Hospital which has a small capacity facility for up to 10 patients. Day to day care is provided by a general physician and nursing unit manager. Overall, the treatment is supervised by a specialist oncologist based at the Royal Adelaide Hospital who visits every three months and holds a teleconference once a fortnight.

In Canada, cancer services in rural and remote communities are also coordinated according to state. Examples in four states - British Columbia, Ontario, Manitoba, and Saskatchewan are described. The services appear to be more established than in Australia. One of the states, British Columbia, is reported as having the best outcomes in Canada for cancer patients, although this statement doesn't specify the location of patient treatment. The cancer services in British Columbia, co-ordinated by the British Columbia Cancer Agency (BCCA), consist of four regional comprehensive cancer centres which provide a range of services. The BCCA also produce Cancer Management Guidelines, Cancer Drug Manuals, Chemotherapy Protocols, Evidence Based Guidelines as well as education for community health care professionals and outcome evaluation and research, facilitated by their interactive website. www.bccancer.bc.ca [accessed 29-10-09]. Community care is co-ordinated through the Community Oncology Network (CON), which is a collaborative voluntary partnership with community services including 19 Community Cancer Centres, six Community Cancer Services and 12 Consultative Clinics across British Columbia. CON also supports service delivery in 33 other community hospitals. When patients receive chemotherapy in the community the transferring oncologist has the responsibility to ensure that the accepting physician has the necessary knowledge, skill and ability to manage this care. They also must ensure that the community facility meets the BCCA standards. At a minimum these should have appropriately trained and competent staff (nurses, physicians and pharmacists) to administer and manage the cytotoxic and hazardous products. There must also be access to clinical diagnostic services, such as haematology, with the capability to provide all of the information required to monitor cancer therapy and to have these facilities available 24 hours per day in case of complications.

Cancer care in Ontario is organised into 14 Local Health Integrated Networks (LHIN) and monitored by Cancer Care Ontario. In the Champlain region, the LHIN has developed a chemotherapy home infusion pump programme, which helps patients in Eastern Ontario to avoid travel and overnight stays in larger centres. In another example, 13 outreach programmes were developed to provide chemotherapy in remote communities in north-western Ontario. In this, designated local health providers received clinical training at the regional cancer centre and continuing educational support was available via teleconferencing technology.

In Manitoba, cancer care is provided by two major cancer centres, four urban community centres and 15 rural community cancer programmes. A range of services utilizing all types of community health care staff are available, more information can be obtained from their website: www.cancercare.mb.ca [accessed 6-11-09]

Saskatchewan also has two major cancer centres which serve the north and south of the province. Both of these centres work in partnership with 16 community oncology programmes to deliver cancer treatment in the community. No specific reference is made to the delivery of chemotherapy. For further details see Appendix C.

The review also examines the service provision of cancer care in Scotland. The Scottish model does not target cancer care to patients in rural and remote areas specifically, and the review authors state that there are sparse details regarding the delivery of care to patients in these areas. They cite a paper by Smith and Campbell[1] which reports a survey of services. It found that for remote rural patients, services fell into three categories: central clinics at a cancer centre; shared outreach oncology clinics with chemotherapy provision; and shared care outreach oncology clinics without chemotherapy provision. They found a high level of variation of services and made four recommendations to ensure quality of care: local expertise and back up from central oncologists; continuing professional development of staff; better and faster communication through standardisation of processes and more information on the cost effectiveness of outreach programmes.

The review authors conclude that the success and sustainability of outreach services depends on many factors including: integration and coordination of the outreach services within a total system of care; an adequate number of specialists to ensure that the service is supported and viable; adequate demand for the specialist service; adequate stable funding; regular evaluation of the service and its outcomes; regular and predictable visit schedule; prior planning of visits; involvement of primary care providers to learn about the specialised care being provided and to maintain continuity of care and treatment of the patient.

The research in this area is somewhat dated, few service models have been evaluated and there are just a small number of references to the administration of cancer chemotherapy. However, this review does suggest that giving cancer chemotherapy is not an isolated procedure and depends upon a management framework to ensure both patient and staff safety and effectiveness. It also suggests that there may be other approaches that could help patients in rural and remote areas, such as practical assistance to get to specialist centres. The diversity of schemes shows that there

[1] Smith SM, Campbell NC: Provision of oncology services in remote and rural areas: a Scottish perspective. European Journal of Cancer Care, 13: 185-192, 2004

is no one model to fit all locations but without formal evaluation it is difficult to know what works and what doesn't.

Effectiveness of programmes in remote and rural areas

Campbell ND, Ritchie LD, Cassidy J, Little J. Systematic review of cancer treatment programmes in remote and rural areas. British Journal of Cancer 1999; 80 (8):1275-1280

This review had a UK focus, and aimed to assess the effectiveness of programmes providing cancer treatments to those living in remote and rural areas. The review is dated, however, it has been included in this ARIF feedback to gain insight into the type and amount of evidence already reviewed in this field. Further details can be found in Appendix D.

Overall, the review appears to be well conducted. Searches were from 1978 to 1997 with appropriate databases searched. Fifteen publications are described. All but three papers were from the USA, with two from Australia and one from the UK. A mix of study methodology was utilised by the included studies. Rural hospital initiatives, shared care with central clinics, shared care with outreach clinics and shared care with tele-oncology clinics were assessed.

All of the studies for rural hospital initiatives were cross - sectional, two were from Australia, and two from the USA. The first two studies were audits of patient care and in both, patients outcomes were comparable to patients in specialist centres. The third study was an audit of a provincial radiation oncology service (Byram 1996), whilst the fourth was an audit of a joint rural hospital cancer programme involving two hospitals (Smith 1997). The provincial radiation oncology service audit concluded that patient access to this service had improved, and the joint cancer programme in two rural hospitals found that the majority of physicians felt it was worthwhile and that more patients were receiving appropriate care.

The sample sizes were small, for example Tulloh and Goldsworthy 1997 included a sample of just 28 patients over a three year period and Callaghen 1990 included just 168 patients over a 20 year period. This may have consequences for keeping skills and knowledge up to date. The study by Byram 1996 had the opposite problem and was over subscribed, treating 820 patients rather than the expected 500 patients in a provincial radiotherapy oncology service.

Assessment of shared care with central clinics was undertaken in one controlled clinical trial (Kisker 1980) which also had a cost study associated with it (Strayer 1980). In this study in the intervention group (n=24) specialists were responsible for diagnosis and assigning treatment with the GP taking responsibility for the remaining care, whereas in the control group all of the care was

undertaken by the specialists (n=22). No differences in outcomes or adverse events were found, however, the sample size may have been too small to detect an effect. The review authors concluded that this study demonstrated feasibility rather than safety.

Assessment of shared care with outreach clinics was undertaken by one controlled clinical trial, two before and after studies, and three cross sectional studies. Just one study by Howe 1997 had measured relevant and reliable outcomes. This was based in Illinois, USA, and compared an intensive rural oncology outreach programme (involving five hospitals) with an educational programme (involving four hospitals) and a specialist urban hospital. It included patients with breast cancer and the study ran from 1990 to 1991. At baseline the level of care reaching National Cancer Institute Guidelines for both rural arms of the trial were 58% compared to the specialist urban hospital at 79%. At the end of the trial the level of care meeting guideline standards for the intensive rural oncology outreach programme was 63%, for educational rural this was 55% and for specialist urban this was 71%. There was a statistically significant difference between specialist urban compared to educational rural.

Assessment of shared care with tele-oncology clinics was undertaken in two cross sectional studies Allen & Hayes 1995, Doolittle 1997. The study by Allen and Hayes, was a survey of patient and physician satisfaction. Overall, satisfaction was "*reasonably high*" but it declined in patients once they had a face – to - face consultation. Doolittle and colleagues undertook a cost survey from a healthcare service perspective. They found that the average cost per telemedicine consultation was $812 US dollars, for '*fly in*' outreach it was $897 US dollars and traditional clinic visits were £149 US dollars. Even without start up costs, once running at full capacity, telemedicine was still more expensive than traditional clinic visits coming in at $301 US dollars per visit.

Overall, the author of the review concluded [2] that the generalisability to the UK was limited particularly in studies undertaken in Australia. They felt that the following should be highlighted for further research:

- *"existing studies of shared care are not conclusive and effects on patient's health, quality of life, and survival require further description".*
- *"it is not known whether rural practitioners are motivated to take on the responsibility of shared care oncology, nor how safe it would be in the hands of less enthusiastic practitioners".*
- *"the benefits and disadvantages of tele-oncology over central clinics need to be evaluated"*

ARIF would concur with the authors: overall there seemed to be a paucity of information, with low numbers of studies, low numbers within the studies and weak methodology. The low numbers of patients within the studies that undertook cross sectional surveys, may be an artefact of the study

[2] Salient points, the conclusion in the text is very long

methodology, or it could be that there is a low incidence of cancer within the rural communities. Incidence of cancer within local communities would be something to consider when planning/modelling a service of community chemotherapy. A new review may well be needed given that this review was published in 1999.

Effectiveness of home based chemotherapy

Boothroyd L, Lehoux P. Home-based chemotherapy for cancer: issues for patients, caregivers and the health care system. Montreal: Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) 2004: 77

This report is both a systematic review and a clinical interview. Its aim was to examine the issues surrounding home chemotherapy for cancer in order to make health policy recommendations. The systematic review aimed to assess the evidence concerning effectiveness, safety, patient preference and satisfaction, patient quality of life, and costs of home chemotherapy for patients in outlying areas receiving cancer care. It is the only review that has concentrated on the specific delivery of chemotherapy rather than delivery of cancer services to the community.

The methodology and reporting of the review were poor. Study selection, data extraction process, details on quality assessment of the included studies and information on the study characteristics were either not reported or insufficient. Searches were up to August 2002. A total of 32 studies, including seven randomised controlled trials (RCTs), seven controlled studies, 16 uncontrolled studies and two cost models were included. Details regarding study characteristics and summary results of the reviewed studies can be found in Appendix E.

The twenty eight relevant studies were published between 1980 and 2002, all had small sample sizes, ranging from 20 to 87 (median 42) in the seven RCTs, 14 to 188 (median 20) in the five controlled studies, and 16 to 170 in the 16 uncontrolled studies[3]. Of the six RCTs, three were crossover trials. Patients included had various cancers, and the majority were adults. Home chemotherapy in the review was defined as any type of administration of cancer chemotherapeutic agents at home (intravenous, subcutaneous, oral, etc.), with or without on-site supervision by a nurse. The comparators were mainly hospital settings (including day hospital, outpatient facility and day-ward); although some were based in general practice (one RCT - McCorkle, 1989), institution and institution plus home setting (one controlled study Brown 1997). Outcomes reported were in the categories of 'clinical efficacy', 'cost', 'safety', 'quality of life', and 'preference and/or satisfaction'. (See Appendix E for details).

[3] For one study (DeMoss, 1980) where home treatments were provided by visiting nurses the number of patients was reported as ">70". The review authors stated that by the time the article was written, the home treatments had been delivered to "more than 70 patients".

Three RCTs, two controlled studies and thirteen uncontrolled studies reported outcomes on safety and toxicity for the patients. One death was reported due to arrhythmia in the home setting in one RCT, however, the general trend was that there were no severe complications found in the home setting, nor was there a significant difference between home and non-home care settings. The authors concluded that it appears that home chemotherapy can be provided safely.

Patient quality of life (QoL) was reported in two RCTs, one controlled and three uncontrolled studies. The RCTs found there were no significant differences between home and non-home settings. In the controlled study QoL significantly favoured home setting compared to the inpatient setting. The authors' conclusion was: the evidence regarding quality of life for patients receiving home chemotherapy is limited by the small number of controlled studies and participants; the RCTs identified do not show a beneficial effect on quality of life; however, positive effects for both paediatric patients and their parents are supported by a controlled crossover study of home treatment for childhood cancer. Findings in uncontrolled studies are generally positive.

Six RCTs, four controlled and seven uncontrolled studies reported preference/satisfaction of patient/carer. Significantly greater preference for home setting was found in three RCTs compared with either day hospital or day-ward; home setting all tended to have better preference or better patient compliance in two RCTs. In the other studies satisfaction and preference were measured in various ways and the outcomes were diverse. Some of the measures, e.g. measuring the satisfaction as the rate of discontinuation with home care program (Lowenthal 1996), or as improvement in mental health, social dependency, symptom distress or health perception (McCorkle 1994) may be inappropriate.

Twelve studies reported cost. In one study the analysis was from a societal perspective, one was from a system perspective, one from a third party payer and one from a patient and/or third party payer perspective. The rest were either from a hospital or a patient perspective. None of these were UK based. Results on the cost of home care varied in the studies. One small controlled study (Close 1995) on paediatric patients reported significant cost savings for hospitals and families with home therapy compared with inpatient treatment.

Overall, the results from the studies on costs of home care were somewhat equivocal. The authors concluded that *"where home chemotherapy replaces inpatient treatment, convincing evidence of cost savings for hospitals and families arises from only one paediatric study. In studies where home chemotherapy replaces outpatient treatment, the mixed findings and variable study quality prevent a conclusion on the cost implications. Home chemotherapy causes cost shifting within the health care system from hospitals to home care organizations."*

Overall, evidence from the review was insufficient and poor quality. Conclusions on home delivery of cancer chemotherapy cannot be drawn regarding safety, toxicity, quality of life, preference or satisfaction of patients and caregivers, and cost within the home setting.

Conclusions

Much of the research is out of date and of variable quality and focus therefore it is difficult to draw specific conclusions regarding best practice and effectiveness of giving patients chemotherapy that they would normally receive in a hospital setting, within the community. It may be that there needs to be a diversity of approaches to tailor care to local conditions, which creates fundamental problems in evaluating such research. ARIF have strived to give an idea of the type of research available, which hopefully will point to literature sources that may help inform potential models of practice.

The following should be considered:

- Much of the research is out of date.
- Difficult area to study, lots of variables and confounders.
- Limited study designs.
- Poor reporting makes it difficult to interpret and limits the usefulness of the data in planning community chemotherapy services.
- Cancer incidence/prevalence - implications: cost per person treated, staff skill maintenance if low incidence/prevalence.
- Patient characteristics – variety of treatment and monitoring regimes.
- Infrastructure – costs of building and maintenance treatment delivery infrastructure.
- Funding issues – drug costs, delivery costs, monitoring costs. Variety of different perspectives can be taken e.g. NHS perspective, societal perspective.

References

1. Adams P, Hardwich J, Embree V, Sinclair S, Conn B, Bishop J. Literature review. Models of cancer services for rural and remote communities. Sydney: Cancer Institute New South Wales, March 2009
2. Campbell ND, Ritchie LD, Cassidy J, Little J. Systematic review of cancer treatment programmes in remote and rural areas. British Journal of Cancer 1999; 80 (8):1275-1280.
3. Boothroyd L, Lehoux P. Home-based chemotherapy for cancer: issues for patients, caregivers and the health care system. Montreal: Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) 2004: 77
4. Chahed S, Marcon E, Sahin E, Feillet D, Dallery Y. Exploring New Operational Research Opportunities within the Home Care Context: The Chemotherapy at Home. Health Care Management Science, June 2009, v 12, iss 2, pp 179-91 1900.
5. Kelly D et al. Achieving change in the NHS: a study to explore the feasibility of a home-based cancer chemotherapy service. International Journal of Nursing Studies 2004; 41(2):215-224.
6. Smith SM, Campbell NC, Provision of oncology services in remote and rural areas: a Scottish perspective. European Journal of Cancer Care. 2004, 13, 185-192.

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 exp chemotherapy, adjuvant/
2 chemotherapy.mp.
3 medical oncology/
4 or/1-3
5 community health services/
6 home care services/ or home infusion therapy/
7 rural health services/
8 family practice/
9 (community or home$ or remote or rural or countryside or mobile).ti,ab.
10 (general practice or primary care).ti,ab.
11 cancer outreach.ti,ab.
12 8 or 6 or 7 or 10 or 9 or 5
13 4 and 12
14 11 or 13
15 limit 14 to "reviews (specificity)"

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Appendix B – Literature search results

Systematic Reviews

Source – Cochrane Library (DARE) 2009 Issue 3

Campbell ND, Ritchie LD, Cassidy J, Little J. Systematic review of cancer treatment programmes in remote and rural areas. British Journal of Cancer 1999; 80 (8):1275-1280

Source – Cochrane Library (HTA database) 2009 Issue 3

Boothroyd L, Lehoux P. Home based chemotherapy for cancer: issues for patients, caregivers and the health care system. Montreal: Agence d'evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) 2004: 77

Literature overview

Source – Internet searches

Adams P Hardwick J , Embree V, Sinclair S, Conn B, Bishop J Literature review. Models of cancer services for rural and remote communities. Sydney: Cancer Institute New South Wales; March 2009
http://www.cancerinstitute.org.au/cancer_inst/publications/pdfs/web09-83-02_literature-review-models-of-cancer-services-for-rural-and-remote-communities.PDF

Projects

Source – Internet searches

NHS Institute for Innovation and Improvement. Cancer chemotherapy in the community.
http://www.institute.nhs.uk/index.php?option=com_mtree&task=viewlink&link_id=3068&Itemid=1876
https://www.institute.nhs.uk/images/documents/NHS%20Live/cancer%20chemotherapy.pdf

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Appendix C – Critical Appraisal of:

Adams P, Hardwich J, Embree V, Sinclair S, Conn B, Bishop J. Literature review. Models of Cancer Services for Rural and Remote Communities. Sydney: Cancer Institute NSW, March 2009

Aim	P5. "*To understand the current models of cancer service provision in rural and remote areas, by exploring the overall structure & function of cancer services" and to identify common elements of best practice*".
Notes	Australian focus. Authors suggest that "*common elements of successful outreach services are:* • *Integration & coordination of the services within a broader system of care, usually involves collaboration and agreement between rural and metropolitan programs for provisions of service, including shared-care models.* • *An adequate number of specialists to ensure that the service is viable.* • *Adequate demand for the specialised service.* • *Adequate stable funding linked to patient demand.* • *An established quality system including regular evaluation of the value of the service and in the cancer outcomes it produces.* • *Regular, predictable visit scheduled by specialists with contingency planning.* • *Involvement of* primary care providers in education, the continuity of care & treatment of the patient".
Population	Patients with cancer living in rural and/or remote areas (also indigenous people)
Intervention	Defined as "literature related to services provided to rural communities by a specialist doctor, as well as specialist services provided by a generalist provider such as a GP was reviewed". Cancer services &/or cancer specialised services. Setting = local hospitals, GP services. ("outreach services, shared care, telehealth, service models".
Control	
Outcome	Equitable services, effective cancer care.
Quality of Review	Semi-systematic review. Looks OK in the systematic parts, extensive search strategy recorded, which could be useful information for the requester.
Search date	Undertook several searches MEDLINE, APAIS Health, ATSI Health, Meditext, Cochrane Database of Systematic Reviews, Rural and Remote Health. Also sought information from 'grey' literature – included health departments in NSW, Victoria, Queensland, South Australia, Western Australia, and the Northern Territory (i.e. all of the Australian states) plus cancer related organisations such as the Cancer Institute NSW. They also searched NHS Scotland (www.show.scot.nhs.uk) which is probably the most relevant for us. The authors also contacted '*key informants'* (see page 5) from Canada and Australia. Dates of search not given, nor reasons for choosing '*key informants'* or '*grey literature areas'*.
Data analysis	Descriptive
Number of studies included	Unsure.
Effectiveness – results	Models of cancer services. Australia – 2001 Clinical Oncological Society of Australia (COSA) hosted a 'cancer in the bush summit, hosted in Canberra. Attended by multi-disciplinary groups in oncology, health officials with the aim to discuss the development of rural cancer service models from a national perspective. Eight potential planning issues identified. • "*Equitable travel and accommodation scheme to support rural/remote cancer patients.* • *Improved patient support, including the provision of breast cancer nurses national and a cancer nurse demonstration project.* • *National coordination and funding of training.* • *Workforce planning, considering recommendations of Australian Health Workforce Advisory Committee and special needs of rural cancer patients.* • *The establishment of networks and national accreditation and the development of a regional cancer demonstration project.*

- *Further research to examine rural outcomes in survival, access, psychological support and quality of life in rural and remote Australia.*
- *Medicare Benefits Schedule (MBA) item numbers for rural services and tele-oncology.*
- *Addressing issues of national priority, including making specific cancer drugs available on the Pharmaceutical Benefits Scheme and addressing the Radiation Oncology Strategic Plan and National Cancer Control Initiative utilisation strategy*".

2002 Baume P. Department of health and aging – radiotherapy, hub and spoke organisational framework.
2006 COSA undertook a mapping exercise to gain a comprehensive picture of regional & rural oncology services across Australia in a publication "Mapping Rural & Regional Oncology Services in Australia (COSA 2006).
From this they made the following recommendations.

- Formal recognition of the problem of regional disparity.
- Building regional oncology centres of excellence.
- Establishing a national quality assurance framework.

Short-term capacity building measures such as: investment in clinical data systems to audit, monitor and plan oncology services; investment in psychosocial support services for people in rural and remote areas, who have been shown to have significantly inequitable access to such services; support for distance education, mentoring and innovative models such as telemedicine in remote areas; improved coordination of government-funded travel and accommodation schemes for cancer patients and their families in remote areas."
2007 Based on the findings of the COSA mapping exercise Underhill et al (2006) and Begbie and Underhill (2007) advocate the development of regional cancer centres of excellence to enhance access to high quality cancer services in rural areas.
2007 Cancer Forum Journal of the Cancer Council of Australia – devoted this issue to regional and rural cancer care – explores progress since the last cancer in the Bush series in 2001.
2007 Australian Government through Cancer Council of Australia made significant investment in the development of service delivery models through cancer services networks (CanNET) National Demonstration programme. (NB: model for CanNET drawn from the Scottish Managed Clinical Networks system). **There are 7 CanNET projects**, one in each state and the Northern Territory of Australia. Most recent report can be found at:
(http://www.canceraustralia.gov.au/media/14678/may_2008_cannet_national_workshop_report.pdf accessed 5-10-09)

- Models of cancer services of (excluding Tasmania – as it "does not have the extent of remoteness found in other states or a large Aboriginal population – *ARIF comment – does this suggest that there may be difficulties in generalisability of the information from Australia?*), NSW, Victoria, Queensland, South Australia and the Northern Territory are described in details in Appendix C of the review.

ARIF comment: the data from Australia is more descriptive than analytical. Unsure/doubtful if the problems Australia have are generalisable to the UK, given the vastness of the country, and the differences in the density of the population and the differences in the health service with greater use of private companies to provide care.

Canada
The review authors describe models of cancer service care for rural and remote communities according to location. It describes the services offered in four provinces (British Columbia, Ontario, Manitoba and Saskatchewan) and one territory (the North-West Territories). All are co-ordinated by a lead cancer agency, with the exception of North West Territories buy in services from Edmonton, Alberta.

British Columbia
The first province of British Columbia is described as having the best outcomes in Canada for cancer patients. Cancer services are centralized through a body called the British Columbia Cancer Agency (BCCA), which supports four regional comprehensive cancer centres which provide a range of cancer services. The BCCA also co-ordinates community care through the Community Oncology Network, which has members from community cancer services, consultative clinics and other community hospitals, the Community Physician Oncology Network and the Surgical Oncology Network. The BCCA produce Cancer Management Guidelines, Cancer Drug Manual, Chemotherapy Protocols, Evidence Based Guidelines as well as education for community health care professionals and outcome evaluation and research, facilitated by their interactive website www.bccancer.bc.ca [accessed 29-10-09].

"The CON network is a collaborative voluntary partnership with community services including 19 Community Cancer Centres, 6 Community Cancer Services and 12 Consultative Clinics across British Columbia". In addition CON also supports service delivery in 33 other community hospitals. "*BCCA oncologists who transfer care to the community to receive chemotherapy have the responsibility to ensure that the accepting physician has the necessary knowledge, skill and ability to manage this care and that the community facility meets the BCCA standards as defined by the CON model. These standards outlining infrastructure and processes necessary for a comprehensive community cancer care program are found at the BCCA website*".
"*CON facilities must have at a minimum appropriately trained and competent staff (nurses, physicians and pharmacists) to administer and manage the cytotoxic and hazardous products used to treat cancer. As well, they must also have access to clinical diagnostic services, such as haematology, with the capability to provide all of the information required to monitor cancer therapy. Additionally these communities are required to have the capabilities to respond to complications of therapy 24 hours per day*".

Ontario
Compared to British Columbia above cancer service organisation seems a bit more loosely tied together. Its quality assurance is administered by Cancer Care Ontario (CCO) who oversee and performance manages all cancer services. At a community level there are regional cancer programmes that link health care professionals, organisations, patients and decision makers across a spectrum of cancer services from prevention to treatment. On top of the regional cancer programmes are Regional Cancer programmes who are responsible for creating an annual cancer service plan and forging networks of cancer services in Local Health Integrated Networks (LHIN) (of which there are 14). The regional cancer programmes access CCOs planning expertise, policy leadership, cancer information and the provisional standards and programmes. ***ARIF comment: more ad hoc than British Columbia.***

Manitoba
CancerCare Manitoba (CCMB) is a province wide agency which has legislated responsibility for cancer prevention, detection, care, research and education. There are 2 major cancer centres situated within major teaching hospitals, 4 urban community centres with oncology programmes and 15 rural community cancer programmes which are detailed on their website www.cancercare.mb.ca [accessed 29-10-09]
Community oncology (Community Cancer Programmes Network (CCPN) is established in 15 rural Manitoba communities. This is a longstanding programme and provides cancer treatment, follow up care to people living outside the city of Winnipeg, and will shortly expand to 16 sites. Each CCPN consists of a team of family physicians, nurses, pharmacists and may include others such as social workers and dieticians. As an example in 2005/06 over 14, 000 outpatient visits occurred at these sites avoiding 5.2 million km of travel by remote cancer patients. There are some innovative models described such as tele-oncology (2002); Uniting primary care and oncology: The UPCON Network in Winnipeg, which is a collaborative partnership between 12 Winnipeg family practice clinics/primary health care centres and CCMB, its role is to promote and support the shared care of the cancer patient. Finally there are 'clinical partnerships' where family physicians participate in a half day of education/discussion with CCMB specialists to discus areas of mutual concern such as the patient experience of navigating through CCMB services.

Saskatchewan
Like Manatoba, there are two major cancer centres. Health services across the province are linked by 16 Community Oncology Programmes (COPs) based in regional hospitals. Their primary aim is to provide cancer care and treatment near to cancer patients home communities. Funding is from regional budgets. There is a regional agency – the Saskatchewan Cancer Agency (SCA) but staff from this act as coordinators to support COPs programme staff, develop training programmes and certification programmes. See www.saskcancer.ca [accessed 2-11-09]

Scotland
'Cancer in Scotland: Action for Change (Scottish Executive 2001) is Scotland's cancer strategy. The model is based on 'managed clinical networks (MCN)' with the aim to deliver support to cancer patients regardless of location. MCN are based on '*linked groups of health professionals and organisations from primary, secondary and tertiary care, working in a co-ordinated manner, unconstrained by existing professional and health board boundaries, to ensure equitable provision of high quality clinically effective services throughout Scotland".* They are different from hub and spoke models as described in the Australian schemes, in that the "*the interests of the network*

	theoretically dominate those of individual hospitals" further details can be found in an NHS circular (Scottish Executive: promoting the development of managed clinical networks in NHS Scotland. NHS Circular: HDL (2002) 69, Edinburgh 2002). The cancer strategy has also led to the setting up of tumour specific MCNs across Scotland: West of Scotland Cancer Network (WoSCAN); South East Scotland Cancer Network (SCAN) and North of Scotland Cancer Network (NoSCAN). The Scottish model does not target cancer care to patients in rural and remote areas specifically, and the review authors state that there are sparse details regarding the delivery of care to patients in these areas. They cite a paper by Smith and Campbell (Smith SM, Campbell NC: Provision of oncology services in remote and rural areas: a Scottish perspective. European Journal of Cancer Care, 13: 185-192, 2004) who undertook a survey of services. They found that for remote rural patients services fell into 3 categories: central clinics at a cancer centre; shared outreach oncology clinics with chemotherapy provision; and shared care outreach oncology clinics without chemotherapy provision. They found a high level of variation of services and made four recommendations to ensure quality of care: local expertise and back up from central oncologists; continuing professional development of staff; better and faster communication through standardisation of processes; more information on the cost effectiveness of outreach programmes. Models of specialised services. The review authors describe several models that could be employed to get cancer services to patients in rural and remote areas. These are: Integrated and managed care pathways Outreach programmes Shared care Role of primary care and Tele-health Much of the research in this area is dated, and there are few specific references to the administration of cancer chemotherapy.
Cost effectiveness results & adverse events	Not studied.
Conclusions	Page 26 "*The most common forms of service delivery currently applied in rural and remote areas, include outreach programmes, shared care and tele-health. Although evidence of the efficacy of outreach programmes, shared care and tele-health for long-term improvements in health outcomes is not yet available, they are all used and promoted in Australia, Canada and Scotland in rural and remote communities. They are justified on the grounds that they provide equitable access and have been shown to increase utilisation rates among patients. Successful use of shared care, tele-health and outreach in rural/remote service delivery assumes the existence of a broader specialised system as well as local primary care providers working collaboratively with the specialised services to ensure continuity of care for the patient. The success and sustainability of outreach services depends on many factors including: integration and coordination of the outreach services within a total system of care; an adequate number of specialists to ensure that the service is supported and viable; adequate demand for the specialist service; adequate stable funding; regular evaluation of the value of the service and its outcomes; regular and predictable visit schedule; prior planning of visits; involvement of primary care providers to learn about the specialised care being provided and to maintain continuity of care and treatment of the patient*.
ARIF comment	Unsure re: generalisability – tend to define remote areas as areas where treatment is over an hour away, which is probably a good definition in that in remote areas, there is often little traffic therefore travelling times are much quicker. The review authors did not include Tasmania as "it does not have the extent of 'remoteness' found in other states or a large Aboriginal population" p7.

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Appendix D – Critical Appraisal of:

Campbell ND, Ritchie LD, Cassidy J, Little J. Systematic review of cancer treatment programmes in remote and rural areas. British Journal of Cancer 1999; 80 (8):1275-1280

<table>
<tr><td>Aim</td><td>"To review the literature about programmes providing cancer treatment in remote and rural areas and to identify evidence of effectiveness and problems".

"Specific questions asked were;
• Can they achieve similar survival rates to specialist centres
• Can they deliver appropriate treatment to more rural patients (not sure what this means)
• Do patients and physicians find them satisfactory
• What are their problems (including cost implications)"?</td></tr>
<tr><td>Notes</td><td>Inclusion criteria were;
• If they described (or cited a paper that described) a programme providing cancer treatment in rural areas
• Reported a study which aimed to evaluate the programme's effectiveness or identify problems
• Came from industrialized countries.
All types of evaluation were included as long as the results (including data) were presented.</td></tr>
<tr><td>Population
Intervention
Control
Outcome</td><td>See above.</td></tr>
<tr><td>Quality of Review</td><td>Well conducted review (although there are a few typos).</td></tr>
<tr><td>Study design</td><td>Any study design was included.</td></tr>
<tr><td>Search date</td><td>Searches from 1978 to 1997 – MEDLINE, EMBASE, CINAHL AND HEALTHSTAR databases.</td></tr>
<tr><td>Number of studies included</td><td>12 papers (on 9 programmes) were from USA, two from Australia, and one from the UK.</td></tr>
<tr><td>Trial characteristics</td><td>Interventions classified as:
• Rural hospital initiatives – 4 cross sectional studies
• Shared care with central clinics – 1 study with 2 publications (1 CCT, 1 cost study)
• Shared care with outreach clinics – 1 CCT, 2 B&A, 3 cross sectional
• Shared care with tele-oncology clinics – 3 cross sectional</td></tr>
<tr><td>Effectiveness – results</td><td>Rural hospital initiatives – 4 cross sectional studies
<table>
<tr><th>Study ID</th><th>Intervention</th><th>Characteristics</th><th>Results</th></tr>
<tr><td>Tulloh & Goldsworthy 1997
Victoria, Australia</td><td>General surgeon - audit.</td><td>Breast cancer
28/275 pts
3 year period</td><td>Breast conservation = 17/25
Chemotherapy = 12 pts, initially at specialist centre then by nurse/GP under supervision of a specialist
4 pts died, 1 metastases,</td></tr>
<tr><td>Callaghen 1990
Iowa, USA</td><td>Surgeon audit</td><td>Colorectal cancer – 71% stage C or D
168 cases
20 year period</td><td>2 pts died within 30 days
4 pts got wound infections
5 yr survival at 50%, node free disease 81%</td></tr>
<tr><td colspan="4">The review authors say that in "accompanying commentaries the results achieved by Tulloh and Callaghan were thought equal to series from specialist centres (Field 1990, Furnival 1997)
ARIF note – very small numbers in each study, what is the prevalence of cancer in rural communities in the UK - would have cost implications if the prevalence was low?</td></tr>
<tr><td>Byram 1996
Victoria, Australia</td><td>Provincial radiation oncology service</td><td>All cancer types
1009 pts
1st year experience</td><td>Main problem identified was over subscription of the facility (820 pts treated vs. 500 predicted)</td></tr>
<tr><td>Smith 1979
Washington State</td><td>Hospital cancer programme</td><td>All cancer types
2 programme + 5 other hospitals</td><td>Majority of physicians thought the programme was worthwhile.
Cancer surveillance data suggested</td></tr>
</table></td></tr>
</table>

USA		(4843 pts, 90 physicians, 22 consultants surveyed	that more pts were treated locally and there were some indications for better management e.g. more pts with prostate cancer received radiotherapy.

Shared care with central clinics – 1 study with 2 publications (1 CCT, 1 cost study)

Study ID	Intervention	Characteristics	Results
Kisker 1980 Iowa, USA Strayer 1980 Iowa, USA	Shared care – specialists = diagnosis and assigning treatment, remaining care by GPs	All cancer No time frame given 24 = shared care vs. 22 = specialist care	No differences between the groups re: febrile episodes, infections, toxicity, blood results or protocol compliance. Main problem = low sample size. Review authors say this demonstrated feasibility but not safety.

Shared care with outreach clinics – 1 CCT, 2 B&A, 3 cross sectional

Study ID	Intervention	Characteristics	Results
Howe 1997 Illinois, USA	Intensive rural oncology outreach programme – 5 hospitals, compared to an educational programme – 4 hospitals vs. specialist urban hospital	Breast cancer 817 cases 1990 to 1991	Baseline – level of care reaching National Cancer Institute Guidelines Both rural = 58% Urban = 70% Outcome Outreach rural = 63% Education rural = 55% Urban = 71% P<0.01 in comparison of urban vs. educational rural
Smith 1996 Virginia, USA	Rural oncology outreach programme	Breast cancer? Chart audit 2 yrs before, 3 years after.	Massive increase in the use of chemotherapy delivered locally (0% to 100%), tumour size recorded in 59% of cases compared to 29% pre-outreach and breast conservation rose to 70% compared to 20% p=0.004 pre-outreach. Patient numbers increased to 330%. Review authors cite many problems with this study and are dubious regarding whether the findings can be solely attributable to the outreach programme.
Hammond 1987 Montana, USA	To increase clinical trial accruals from rural areas using a community (more than 10,000 people) clinical oncology programme.	Any cancer Before and after hospital admission audit.	Overall patient accrual increased by 25%. *ARIFcomment: not sure of the relevance of this finding?*
White 1996 Michigan, USA	Advanced practice cancer nurses acting as satellite clinics to specialist cancer care.	Any cancer 170 cases	"They identified common knowledge deficits" - *ARIF comment – not sure what relevance this is either?*
Grose 1995 Stockport, UK	Urological community nurse	1 nurse, 464 procedures 1 year audit	Nurse conducted 33 mitomycin instillations for bladder cancer, and assisted in management of one patient with terminal prostate cancer, whose catheter was prone to blocking.
Guy 1988 Ohio, USA	Assessment of financial viability of patients attending 2 rural outreach clinics	94 pts of which 77 had cancer	Outreach clinics served less affluent populations with less capacity to pay.

Shared care with tele-oncology clinics – 3 cross sectional

Study ID	Intervention	Characteristics	Results
Allen & Hayes 1995a & b N Carolina, USA	Telemedicine oncology outreach* Questionnaire survey on a. pt satisfaction b. physician satisfaction *pts accompanied by oncology nurse who acted as a surrogate examiner.	39 pts 3 oncologists (based on 34 consultations)	For both pts and physicians satisfaction was "reasonably high", but pt satisfaction declined after in-person follow up.
Doolittle 1997 N. Carolina, USA	Cost study - health service perspective Looked at telemedicine clinic; a fly in outreach clinic; traditional city clinic	103 tele-oncology and 81 outreach visits 1 year	"Average cost per telemedicine visit = $812, outreach oncology = $897, traditional clinic visits = $149 The estimated cost for telemedicine included start up costs, once running at full capacity = $301.

Conclusions	Long conclusion: salient points are • Relevance to UK limited particularly between Australia and UK. The review authors end their conclusion with the following list of priorities for further research: • "*existing studies of shared care are not conclusive and effects on patient's health, quality of life, and survival require further description".* • *"it is not known whether rural practitioners are motivated to take on the responsibility of shared care oncology, nor how safe it would be in the hands of less enthusiastic practitioners".* • *"the benefits and disadvantages of tele-oncology over central clinics need to be evaluated*"
ARIF comment	Paucity of information, with low numbers of studies, low numbers within the studies and poor methodology.

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Appendix E – Critical Appraisal of:

Boothroyd L, Lehoux P. Home based chemotherapy for cancer: issues for patients, caregivers and the health care system. Montreal: Agence d'evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS) 2004: 77

Aim	To assess the evidence concerning effectiveness, safety, patient preference and satisfaction, patient quality of life, and costs of home chemotherapy for cancer.
Notes	The authors conducted a systematic review of literature for evidence concerning effectiveness, safety, patient preference and satisfaction, patient quality of life, and costs of home chemotherapy for cancer. They also examined organizational, access, and patient choice issues. The review was supplemented with semi-structured interviews with service providers at selected institutions for cancer care. The goal of the interviews was to collect perspectives on the benefits, barriers, facilitating factors, and challenges in providing home chemotherapy. Data extracted here by ARIF were of the literature review.
Population	Patients in outlying areas receiving cancer care
Intervention	Home chemotherapy, defined as any type of administration of cancer chemotherapeutic agents at home (intravenous, subcutaneous, oral, etc.), with or without on-site supervision by a nurse. (Literature search was restricted to chemotherapy for cancer *control and cure,* rather than end-of-life cancer cares where chemotherapy can have a role in palliation of pain and other symptoms).
Control	Non-home chemotherapy
Outcome	Clinical outcomes (such as survival rates, remission rates, and tumour control); safety; psychosocial issues; quality of life for patients and their caregivers; patient preference and satisfaction; costs
Quality of Review	The electronic databases MEDLINE, CancerLit and PubMed were searched up to August 2002. The Current Contents database and reference lists of retrieved articles and documents were also searched. Inclusion/exclusion criteria were applied for study selection, but the criteria were not explicit and complete. Study selection and data extraction process was not reported. No quality assessment for the included studies. No sufficient details reported on the characteristics of the included studies and baseline characteristics of the patients in each study. Data synthesized descriptively. Overall the quality/reporting of the review was poor.
Study design	Not specified for inclusion. But included were 'RCTs', 'cost models', 'controlled studies' and 'uncontrolled studies'.
Search date	Up to August 2002.
Data analysis	Descriptive
Number of studies included	The review did not clearly report how many studies in total, and of each of the above study design types, were included in the review, except that it was stated that eight RCTs were identified. Studies were reported by several outcome categories, i.e. studies regarding 'clinical efficacy', 'cost', 'safety', 'quality of life', or 'preference and satisfaction'. ARIF worked out that a total of 33 studies, including 8 RCTs, 7 controlled studies, 16 uncontrolled studies and 2 cost models were included in the review. Of these, one RCT and two controlled were inappropriate or irrelevant to the request. (see the following table below) **Studies examining safety and toxicity (Table 3 page 27):** • 3 RCTs • 2 'controlled studies' • 13 'uncontrolled studies' **Cost studies (Table 2 page 15):** • 4 RCTs (all crossover) • 2 'cost models' • 3 'controlled studies' • 3 'uncontrolled studies' **Studies regarding quality of life (QoL):** • 2 RCTs (all crossover)

	• 1 ‘controlled studies’ • 3 ‘uncontrolled studies’
Trial characteristics	See table below
Effectiveness – results & adverse events	Safety and toxicity data were presented in the Table 3 (page 27). In this table, of the four RCTs listed one found 1 death due to arrhythmia with home chemotherapy, the rest showed either no significant complication with the home chemotherapy or no significant differences between the comparisons. In the controlled and uncontrolled studies overall no major toxicity or major side effects that were irreversible with home chemotherapy.
Conclusions	Evidence is insufficient on effectiveness, cost implications, and the patient’s perspective, particularly in comparison with outpatient settings. The home delivery model cannot wholly replace outpatient treatment, especially in the rural setting, but can be a safe and acceptable option for some cancer patients who choose it, particularly those receiving simple continuous infusion therapies.

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Archived ARIF Request

Chronic Pain
Intractable Pain
Cancer Pain
Neuralgia

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in July 1997.

The Problem Submitted for ARIF to Advise Upon:

What interventions should a pain clinic be offering?

Question Reformulated

What reviews of research evidence are available on the effects/effectiveness of interventions for chronic pain, intractable pain, cancer pain and neuralgia?

Reviews Identified

Over 30 potentially relevant reviews were identified. A list of these is available from ARIF on request. Further work may be pending if greater specification of interventions of particular concern can be identified by the requester.

Request Carried Out: July 1997

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Archived ARIF Request

Haemodialysis and CAPD
Chronic Renal Failure

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence on the effectiveness of different methods of renal replacement therapy, other than renal transplant?

Reviews Identified

- MacLeod A et al. Effectiveness and efficiency of methods of dialysis therapy for end stage renal disease: systematic reviews. Health Technology Assessment 1998;2(5)

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Comments

The review is a well-conducted systematic review, the results of which are probably reliable. It actually addresses six individual questions which were carefully selected on the basis of their economic implications and known wide variations in practice. These questions were:

- Haemodialysis
  - synthetic versus cellulose-based membranes
  - bicarbonate versus acetate buffered dialysate
  - short-duration versus standard duration
- CAPD (continuous ambulatory peritoneal dialysis)
  - Y-set versus standard spike delivery systems
  - CCPD (continuous cycler-assisted peritoneal dialysis) versus CAPD
- Haemodialysis versus CAPD

The review found that the quality of the included studies was often poor and that there was a paucity of robust RCTs. However, when drawing their conclusions the authors took careful account of this, as well as any clinical and statistical heterogeneity between the individual studies.

Its results indicate that:

- At the moment cellulose membranes are probably appropriate for general use but that synthetic

membranes may be cost-effective in certain patients, but this situation may change as costs fall in the future

- Bicarbonate dialysate produces less unwanted effects than acetate dialysate at a similar cost
- There is no evidence that short-duration dialysis decreases mortality and it may increase morbidity
- Y-set delivery systems significantly reduce the incidence of peritonitis
- Although expensive, CCPD may be cost-effective in specific situations
- There is insufficient evidence to draw reliable conclusions on the relative effectiveness of haemodialysis and CAPD

Additional information relevant to this request is available in the requests entitled "Automated Peritoneal Dialysis - Renal Failure" and "Early Referral - Chronic Renal Failure".

Request Carried Out: October 1998

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Hyperbaric Oxygen Therapy
Carbon Monoxide Poisoning

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence for hyperbaric oxygen in the management of patients with acute carbon monoxide poisoning?

Reviews Identified

- Tibbles PM, Perrotta PL. Treatment of carbon monoxide poisoning: a critical review of human outcome studies comparing normobaric oxygen with hyperbaric oxygen. Annals of Emergency Medicine 1994;24(2):269-276
- Hyperbaric oxygen therapy. Winchester: Development and Evaluation Committee, Wessex Institute of Public Health, 1994

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Comments

Although both reviews contribute to answering the question, the approach adopted in the article by Tibbles P M et al is more systematic, as evidenced by the fact that they seem to have uncovered additional, more up to date material. The willingness to accept research evidence open to bias is clearly different between the DEC report and the review by Tibbles PM et al. From the evidence presented in the reviews the most we can indicate is that there is genuine uncertainty, even in severe cases of carbon monoxide poisoning about the effects and effectiveness of hyperbaric oxygen therapy.

This is an area prone to need for regular updating as new information is continually becoming available.

Request Carried Out: January 1997

Updated: January 2003 - Since doing this request we have been asked for a list of more recent reviews. We have not done any appraisals therefore the list below is for information only:

- Juurlink DN, Stanbrook MB, McGuigan MA. Hyperbaric oxygen for carbon monoxide poisoning (Cochrane Review). In: The Cochrane Library, Issue 4, 2002. Oxford: Update Software.
- Coulthard P, Esposito M, Worthington HV, Jokstad. Interventions for replacing missing teeth: hyperbaric oxygen therapy for irradiated patients who require dental implants (Cochrane Review). In:

The Cochrane Library, Issue 4, 2002. Oxford: Update Software.

- Ward SE, Thomas N, Mander C. The use of hyperbaric oxygen in the management of patients with oral cancer Sheffield: Trent Institute for Health Services Research, 2000 (Guidance Note for Purchasers 00/03)
- Saunders P. Hyperbaric oxygen therapy in the management of carbon monoxide poisoning, osteoradionecrosis, burns, skin grafts and crush injury Birmingham: University of Birmingham, West Midlands Development and Evaluation Service, 2000, Report No. 23
- Feldmeier JJ, Hampson NB. A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: evidence based approach Undersea and Hyperbaric Medicine 2002;29(1):4-30
- Coulthard P, Esposito M, Worthington HV et al. Therapeutic use of hyperbaric oxygen for irradiated dental implant patients: a systematic review Journal of Dental Education 2003;67(1):64-8

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LUCAS Device Cardiac Arrest

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The Problem Submitted for ARIF to Advise Upon:

Is the Lucas device effective/cost effective particularly in the context of an ambulance service?

The Lund University Cardiopulmonary Assist System or LUCAS device is a gas driven cardiopulmonary resuscitation device that provides automatic chest compression and active decompression during cardiac arrest. It can be driven by either oxygen or air and produces 100 compressions per minute. Maximum depth of depression is 5cm and maximum compression and decompression forces are 500 and 410 N respectively. [reference Steen 2005]

Reviews Identified

None identified.

Randomised Controlled Trials

None identified.

Other Evidence

- Steen S, Sjoberg T, Olsson P, Young M. Treatment of out-of-hospital cardiac arrest with LUCAS, a new device for automatic mechanical compression and active decompression resuscitation. Resuscitation 2005;67:25-30

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Comments

This paper describes a pilot study in which the LUCAS device was installed into 3 emergency cars in two cities in southern Sweden. Using this platform, 100 consecutive patients treated with the LUCAS device were followed up for 1 month post cardiac arrest. The trial started on 20th March 2002. Out of the 100 patients 31(31%) achieved a return to spontaneous circulation, but only 7 (7%) survived to 30 days. Six of the surviving patients had had a witnessed cardiac arrest and were in VF, the seventh had a witnessed cardiac arrest and was in asystole. All of the patients who survived for more than 30 days received treatment with the LUCAS-CPR device within 15 minutes of the ambulance staff being called. The paper discusses 2 cases where the LUCAS device was successfully used during transport to

hospital with one of these patients entering angiography still undergoing treatment with the LUCAS device.

Without a comparator it is difficult to assess the effectiveness of the LUCAS device and whether it is superior to manual CPR. Given the current evidence we can only conclude that this is still an experimental device. The paper by Steen 2002 states that there are prospective randomised controlled trials planned.

Please note that this summary is not a systematic review. There may be other potentially relevant evidence not mentioned above. We are however, confident that there are unlikely to be any published randomised controlled trials.

Request Carried Out: January 2006

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Cardiac Rehabilitation
Cardiac Disease

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The Problem Submitted for ARIF to Advise Upon:

Is cardiac rehabilitation an effective and cost-effective service?

Question Reformulated

Further discussions with the enquirer identified 5 specific questions which arose from the initial broad question:

- What should be the content of cardiac rehabilitation programmes aimed at patients post-myocardial infarction?
- What is the role of exercise testing in determining whether or not patients are suitable for cardiac rehabilitation?
- Is there any evidence to suggest whether hospital or community based programmes are the most effective?
- Are there any structural or process issues which must be considered when setting up a cardiac rehabilitation service which would increase the possibility of providing cost-effective care?
- What are the characteristics of patients who would benefit the most?

Further work was undertaken by ARIF on the role of risk stratification and exercise testing. Details of this can be found in the additional request entitled Cardiac Rehabilitation / Risk Stratification / Cardiac Disease

Reviews Identified

- US Department of Health and Social Services. Cardiac Rehabilitation. Agency for Health Care Policy and Research. Clinical Practice Guideline Number 17. http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat
- Dolan-Mullen P, Mains DA and Velez R. A meta-analysis of controlled trials of cardiac patient education. Patient Education and Counselling 1992;19:143-162
- Oldridge NB et al. Cardiac rehabilitation after myocardial infarction. JAMA 1988;260(7):945-950

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Comments

Several relevant reviews were identified. The most systematic and comprehensive of these was the AHCPR Clinical Practice Guideline which summarises a large body of evidence supporting the general effectiveness of cardiac rehabilitation. It contains information which addresses all of the specific sub-questions posed, bar exercise testing as a means of risk stratification. The main strength, and weakness, of the document is its breadth. Because it formulates its recommendations without the use of summary statistics or meta-analysis, it is difficult to determine the consistency of these results.

In this way the other two reviews are helpful as they provide more precise estimates of the effect of cardiac rehabilitation from different perspectives. Both are good systematic reviews, the results of which can be trusted. Taken together all three suggest that cardiac rehabilitation is beneficial across a range of outcomes for people with heart disease.

This is an area prone to need for regular updating as new information is continually becoming available.

Request Carried Out: September 1997

Update: The following review updates the summaries of research indicated above but does not introduce new evidence which would change the advice given.

- NHS Centre for Reviews and Dissemination. Cardiac Rehabilitation. Effective Health Care 1998; 4(4)

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Cardiac Rehabilitation (Risk Stratification, Exercise Testing) Cardiac Disease

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This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in September 1996.

The Problem Submitted for ARIF to Advise Upon:

Is there any evidence on the role of risk stratification, and in particular by exercise tests, for cardiac rehabilitation?

Reviews Identified

- North of England Stable Angina Guideline Development Group. North of England evidence bases guidelines development project: summary version of evidence based guideline for the primary care management of stable angina. BMJ 1996; 312: 827-832
- Gibbons et al. Exercise Testing Guidelines. Journal of the American College of Cardiology 1997; 30(1): 260-315

Other Literature Identified

- American College of Physicians, Health and Public Policy Committee. Cardiac Rehabilitation Services (Position Paper). Annals of Internal Medicine 1988; 15th October: 671-673
- Greenland P and Chu J. Efficacy of Cardiac Rehabilitation Services with emphasis on patients after myocardial infarction. Annals of Internal Medicine 1988; 15th October: 650-663

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Comments

No systematic reviews were identified which directly addressed the question of risk stratification prior to cardiac rehabilitation. However, a number of relevant papers were identified, the majority of which were position statements. The most useful of these are the American College of Physicians position paper and the article by Greenland and Chu.

The general consensus of all these documents was that all eligible patients, irrespective of risk, can potentially benefit from cardiac rehabilitation and this is supported by evidence from randomised controlled trials. No adverse events have been observed in low risk patients but the safety of such programmes in high risk patients remains unclear. The rational position, in the absence of specific and robust evidence against risk stratification, is to ensure that patients are stratified by risk prior to

commencement on a scheme and that exercise programmes should be tailored accordingly, on the grounds of safety.

The two reviews identified are fairly reliable systematic reviews which confirm the value of the exercise test in the assessment of cardiac risk.

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Sevelamer Hyperphosphataemia Dialysis

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in July 2003.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of sevelamer (Renagel®) for the treatment of hyperphosphataemia in patients on haemodialysis?

Of particular interest in this request was the effectiveness of sevelamer in avoiding the adverse effect of hypercalcaemia observed when hyperphosphataemia is treated with calcium binders.

Reviews Identified

No systematic reviews were identified.

Trials Identified

- Chertow GM, Burke S K, Raggi P, and Treat to Goal Working Group. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney International 2002; 62(1):245-252.

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Comments

No systematic reviews were identified on this topic.

The trial by Chertow et al (2002) compared sevelamer and calcium binders in the treatment of hyperphosphataemia in 200 patients receiving haemodialysis. After follow-up of 52 weeks, levels of serum phosphorus were equivalent in the two groups. Serum calcium concentrations were significantly lower in the group receiving sevelamer (p=0.02). In addition, calcium concentrations in the coronary arteries and aorta had increased significantly from baseline values in the calcium-treated subjects but not in the sevelamer treated subjects.

An important question is the extent to which the benefits of sevelamer treatment (particularly in the prevention of side effects associated with the use of calcium binders) are outweighed by the higher costs of treatment.

Request Carried Out: July 2003

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Electrodiagnostic Techniques
Pre-surgical Assessment
Carpal Tunnel Syndrome

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the usefulness of electrodiagnostic techniques as a prognostic tool in pre-surgical assessment of patients with carpal tunnel syndrome?

Carpal tunnel syndrome results from compression of the median nerve in the carpal tunnel and is characterised by painful paraesthesiae of the fingers and hand. It is a consequence of the tight packing of tendons and the median nerve in the carpal tunnel such that any swelling is likely to cause compression of the nerve.

Reviews Identified

- Jordan R, Carter T, Cummins C. A systematic review of the utility of electrodiagnostic testing in carpal tunnel syndrome. British Journal of General Practice. 2002;52(481):670-3
- Carter T, Jordan R, Cummings C Electrodiagnostic techniques in the pre-surgical assessment of patients with carpal tunnel syndrome? University of Birmingham: Department of Public Health The West Midlands DEC report [Report No: 18] InterTASC No.25;1999 http://www.rep.bham.ac.uk/2000/electrodiag.pdf

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Comments

Our standard ARIF searches identified only one systematic review and no more recent reviews or primary studies relevant to the question appear to have been published since then. The review concludes that despite the limited quality of the evidence, in cases of clear-cut clinical CTS, electrodiagnosis is not warranted either as a diagnostic test, where clinical symptoms are well defined, or as a predictive indicator of surgical outcome. It may still be useful in cases where the clinical diagnosis is not clear.

Request Carried Out: July 2006

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Ceramic Joint Implants
Metatarsophalangeal Joint Disease
Forefoot Disease

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in January 2002.

The Problem Submitted for ARIF to Advise Upon:

What is the evidence of effectiveness of ceramic joint implants in the treatment of metatarsophalangeal joint disease?

Reviews Identified

No systematic reviews were identified.

Primary Studies Identified

- Werner D. A ceramic prosthesis for hallux rigidus. The Foot 2001;11:24-27

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Comments

Our searches did not identify any systematic reviews on this topic.

The report by Werner is a case series comprising 40 procedures on 35 patients. There are a number of weaknesses both inherent in the study design employed and the way in which the study was subsequently conducted. These give rise to uncertainty around its findings that mean that we are unable to say that the study provides proof of the effectiveness of ceramic implants for metatarsophalangeal joint disease.

The author acknowledges that there are limitations with this study and states that further studies are required.

This is a topic prone to require updating as new information becomes available.

Request Carried Out: January 2002

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Archived ARIF Request

Conductive Education
Cerebral Palsy

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in May 1996.

The Problem Submitted for ARIF to Advise Upon:

Does conductive education for the treatment of cerebral palsy achieve better long term results than conventional treatment?

Reviews Identified

- Hurr JJ. Review of research on therapeutic interventions for children with cerebral palsy. Acta Neurologica Scandinavica 1995; 91(6): 423-432
- Bower E, McLellan DL. Evaluating therapy in cerebral palsy. Child Care, Health and Development 1994; 20 (6): 409-419
- Khaw CWH, Tidemann AJ, Stern LM. Study of hemiplegic cerebral palsy with a review of the literature. Journal of Paediatrics and Child Health 1994; 30(3): 224-229.
- Robinson RO et al. Conductive Education at the Peto Institute, Budapest. British Medical Journal 1989; 299: 1145-1149

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Comments

No systematic reviews were identified.

The first three reviews suggested give little information on the effectiveness of conductive education, but would inform a purchasing decision by indicating the range of interventions in addition to conductive education which should also be considered in the treatment of cerebral palsy. The fourth review article gives some useful background information on the nature of conductive education.

The most rigorous piece of original research identified was: Bairstow P et al. Evaluation of Conductive Education for children with cerebral palsy. Parts I & II. London: HMSO, 1993.

This prospective trial with matched controls purported to show no effect of conductive education, but our appraisal of the method is in accord with other critics of this piece of research, suggesting that failure to demonstrate an effect was as likely to arise from the way the study was performed as conductive education truly being ineffective. The correct conclusion is thus still that the effectiveness of conductive education is unproven. We understand that randomised trials of the "principles of conductive

education" are in progress in Australia.

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Cervical Screening

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The Problem Submitted for ARIF to Advise Upon:

What evidence is there on the effects/effectiveness of 3 year and 5 year screening intervals for cervical cancer?

Reviews Identified

- Noorani HZ. Assessment of techniques for cervical cancer screening. Ottawa, Ontario, Canada: Canadian Coordinating Office for Health Technology Assessment, 1997. pp33
- Cervical screening interval. Winchester: Wessex Institute of Public Health Medicine, 1995. (DEC Report No 46)

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Comments

Both the reviews are of direct relevance to the stated problem. However, readers should be warned that both the reviews are not completely systematic and are based on literature using study designs which are very susceptible to bias.

Even given the caution required in interpretation, ARIF would concur with the general conclusions of the DEC report suggesting that appropriate targets for improving the effectiveness of the cervical screening programme may not lie in reducing screening interval but in initiatives to improve the quality of smears and the coverage of the programme. One issue not mentioned in the DEC report is the use of automated slide processing. Research evidence on the likely effects of these three general alternatives is available, and the report by Noorani is a good place to start in assessing it.

Request Carried Out: September 1997

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Chelation Therapy
Peripheral Vascular Disease

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Is chelation therapy effective for the treatment of peripheral vascular disease?

Reviews Identified

- Canadian Co-ordinating Office for Health Technology Assessment (CCOHTA). Chelation therapy and atherosclerotic coronary artery disease. Ottawa: CCOHTA 1993 (Technology Brief Issue 6.0)
- Ernst E. Chelation therapy for peripheral arterial occlusive disease. A systematic review. Circulation 1997;96(3):1031-1033

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Comments

Both reviews are reasonably robust but do have some important limitations. The CCOHTA review considers coronary artery disease, not peripheral vascular disease, and Ernst provides insufficient methodological detail to allow a reliable judgment on validity.

Both reviews conclude that there is no reliable evidence to support the effectiveness of chelation therapy. The tone of the review by Ernst is so vehemently opposed to the treatment that it appears to lack objectivity. Given this fact and the limited generalisability of the CCOHTA review, we decided to examine some of the included studies ourselves.

Our assessment of the evidence confirms that chelation therapy does not appear to offer any benefits over placebo in the treatment of peripheral vascular disease. Benefits demonstrated in uncontrolled studies are not substantiated by randomised controlled trials. Equally, however, anecdotal evidence of serious side effects is not supported by evidence from any of the trials.

Request Carried Out: May 1999

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Presentation to chest pain services with particular regard to the South Asian population and those from deprived communities

Synopsis

Question:	To gain an understanding of the current knowledge base regarding chest pain presentations to both primary and secondary care services.
Reviews Identified:	Cooper A, Calvert N, Skinner J, Sawyer L, Sparrow K, Timmis A et al. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. Full guideline. Final draft - January 2010 London: National Clinical Guideline Centre for Acute and Chronic Conditions; 2010.
Comments:	NICE are due to publish guidelines on the management of patients presenting with chest pain of cardiac origin. The guidelines have taken into account two studies that have examined whether patients from Asian origin have atypical chest pain, and whether this should be considered during patient assessment. Both studies found that Asian patients were younger and more likely to have diabetes. Weak evidence suggests that there were more Asian patients with atypical symptoms than Caucasians, although, this uncertainty is not reflected in the draft NICE guidelines Section 1.2.1.6 page 10, line 22. We have contacted NICE to get clarification regarding their guidelines in respect of Asian patients. This is also an area that needs further research.
Date Completed:	March 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Presentation to chest pain services with particular regard to the South Asian population and those from deprived communities.

Request completed: March 2010

Aim

To gain an understanding of the current knowledge base regarding chest pain presentations to both primary and secondary care services.

Question Clarification

1. Are patients with chest pain who present to primary and secondary healthcare services treated differently depending upon ethnicity (South Asian) and deprivation.
   Study designs: cross sectional surveys, or cohort.

2. If there is a difference, why that is:
   a. Is this difference due to physiological differences (resulting in atypical presentation of signs and symptoms).
   b. Or is it due to social/cultural differences.
   c. Or is it due to access difficulties.
   Study design: qualitative, physiological

3. Does this difference (if it exists) lead to suboptimal care.
   Study design: cross sectional survey, mortality rates, and morbidity rates.

4. Are there any interventions that improve outcomes in this population?
   Study design: interventional study design, RCT, CCT, and cohort.

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol http://www.arif.bham.ac.uk/strategy.shtml Text and index terms were used to represent the population and factors of interest. Sources were searched from database inception to 12 February 2010. No language restriction was applied to the searches. The MEDLINE search can be found in Appendix A.

Studies identified were tabulated according to whether they could answer any of the questions posed above. The ARIF search protocol is not designed to systematically identify primary studies, although often these are identified ad hoc, which can give a rough idea of the size and stability of current research evidence. In this case, these were tabulated as the requester wanted to gain a feel for how much research there was on this topic. It must be stressed that any primary studies that are identified could be subject to publication bias.

Critical appraisal was undertaken on the relevant reviews identified.

Results

This report is based on evidence from one systematic review[1] and a draft NICE guideline[2]. In addition, eight primary studies[3] [4] [5] [6] [7] [8] were identified and tabulated. Full search results can be found in Appendix B.

Whilst the review was well conducted the searches were undertaken in 2001, limiting its usefulness. It would however, make a good basis for a new review. A précis of the review can be found in Appendix E. Efforts were concentrated on the critical appraisal of the NICE guideline* as it was the most up to date and pertinent to the question.

Chest pain of recent onset : Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. Full guideline. Final draft - January 2010 London: National Clinical Guideline Centre for Acute and Chronic Conditions; 2010[2] http://www.nice.org.uk/nicemedia/pdf/ChestPainFullGuideline.pdf [accessed 3rd March 2010]

This guideline produced by NICE is aimed at physicians/healthcare workers from both primary and secondary healthcare settings in England and Wales who have a responsibility in the evaluation of patients presenting with acute chest pain of cardiac origin.

This guideline is still in a draft format and is due to be published towards the end of March 2010.

The guideline is wide ranging, but there are no specific references to patients who live in deprived areas. The guideline does however consider patients from different ethnic backgrounds. Specific guideline recommendations can be found in section 1.2 (page 9) and section 1.2.1 (page 6). Evidence statements pertaining to Asian patients are presented in section 4.2.3.1 (page 109), with

* Only information used in the guideline in regards to ethnicity and deprivation were sought and critically appraised.

the evidence that was used to make these statements presented in section 4.2.3.2 (pages 110 to 120). Section 4.2.3.4 (page 121) presents an '*evidence to recommendations*' statement. Evidence for this part of the guideline was taken from two publications. [Teoh] [Barakat]. There are four evidence statements regarding Asian patients, which are:

Section 4.2.3.1 page 109, line 9 to 27.

Evidence statement 7.

"*One cohort study in patients presenting with an acute coronary syndrome (ACS) found that Asian patients were younger and more likely to be diabetic compared to Caucasians (Teoh M, Lalondrelle S, Roughton M et al 2007)*".

Evidence statement 8.

"*One cohort study in patients presenting with ACS found that Asian patients were more likely to report frontal upper body discomfort, pain on the rear of their body and greater intensity of pain over greater area of body than Caucasians. (Teoh M, Lalondrelle S, Roughton M et al 2007)*."

Evidence statement 9.

"*One cohort study in patients presenting with ACS found that Bangladeshi patients were younger, more often male and more likely to be diabetic and to report a previous MI compared with Caucasians. (Barakat K, Wels Z, Ramdhany S, et al 2003)*"

Evidence statement 10.

"*One cohort study in patients presenting with acute MI found that Bangladeshi patients were less likely to report central pain, less likely to report classic descriptions of the character of the pain (heaviness, tightness, weight, pressure, band-like, gripping) and more likely to offer non-classic descriptions of the character of the pain (sharp, stabbing, pinching, burning) compared with Caucasians. (Barakat K, Wels Z, Ramdhany S, et al 2003)*"

From the four evidence statements, it does appear that there are some differences between Asian and Caucasian chest pain symptoms, however, the actual guideline recommendation does not seem to reflect this and states:

Section 1.2.1.6 page 10, line 22

"*Do not assess symptoms of an ACS differently in ethnic groups. There are no major differences in symptoms of an ACS among different ethnic groups*."

The evidence to recommendations section is also somewhat contradictory and states:

Section 4.2.3.4 page 121 to 122 lines 25 to 31

"*One well conducted cohort study and a second study that may have spectrum bias (because recruited patients had been selected as those with Q wave acute myocardial infarction (MI) (Barakat) indicated that Asian patients may present with more atypical symptoms compared with Caucasian patients and that Asian patients are more likely to be younger, to be diabetic and have a prior MI. The GDG concluded that whilst there may be differences between different ethnic groups in the symptomatic presentation of ACS/MI these are small*".

It is difficult to know why there is a disparity between the evidence presented in the NICE evidence statements and guideline. To resolve this, the original publications were critically appraised. [Teoh] [Barakat]

Teoh M, Lalondrelle S, Roughton M, Grocott-Mason R et al. Acute coronary syndromes and their presentation in Asian and Caucasian patients in Britain. Heart. 2007; 93 (2):183-188.[9]

This was the larger study with 2905 patients recruited (604 Asian, 2301 Caucasian). Its aim was to find out if the two groups had different symptoms when experiencing ACS. Overall it was a well conducted study. Patient characteristics between the Asian and Caucasian groups differed in age, with the Asian group being younger, and more likely to be diabetic. Higher numbers were diagnosed with angina (51%) when compared with Caucasians (37%), conversely, less were diagnosed with MI (49% versus 63% respectively). (See Appendix C for further details).

Regarding symptom presentation the Asian group were more likely to present with a higher intensity of chest pain which covered a larger area of the body and experienced more frequently discomfort over the back of the upper thorax.

There are areas of uncertainty regarding the results. Firstly, there may have been confounding factors, with more Asian patients being diagnosed with angina; could this subtly alter the type of pain experienced, compared to patients who have myocardial infarction? In addition, more Asian patients had diabetes which may also have altered pain sensations. It would also have been helpful if the study had reported confidence intervals around the relevant outcomes such as discomfort, so that readers could assess whether the results are clinically as well as statistically significant.

Barakat K, Wells Z, Ramdhany S, Mills PG et al. Bangladeshi patients present with non-classic features of acute myocardial infarction and are treated less aggressively in east London, UK. Heart. 2003; 89(3): 276-279.[10]

This was a much smaller study, but still set in the UK. Patients were included if they had a Q wave MI. As with the study above, Asian patients tended to be younger and more likely to have diabetes. The 'door to needle time' was much longer with a mean delay of 42 minutes for the Asian group compared with 26 minutes for the Caucasian group.

Caucasian patients were more likely to have central chest pain and more classic descriptions of chest pain, whilst Asian patients were more likely to have atypical descriptions of chest pain. The main drawback of this study was the sample size, particularly for the nature of the symptoms presented. This was only determined in 63 patients (Asian 32, Caucasian 31), therefore the usefulness and reliability of the findings are severely limited. (See Appendix D).

Overall, the critical appraisal of both studies that NICE included in their guideline evidence statements suggests that there is some uncertainty regarding the differences in symptom presentation in Asian and Caucasian patients. However, the uncertainty, does not rule out the possibility that there may be ethnic differences in symptom presentation that could cause a delay within the Asian treatment pathway compared to Caucasian patient. Thus the statement in the NICE guidelines Section 1.2.1.6 page 10, line 22 that there are no differences may be a bit too strong.

So far, the literature identified has concentrated on just one aspect of the question posed i.e. Do patients from the South Asian population and from deprived areas in the UK, present atypical symptoms when experiencing chest pain related to acute coronary syndromes? The other studies that were identified from the ARIF search may well enable more questions to be answered.

Study	*Potentially Answers*
Galdas P, Cheater F, Marshall P. What is the role of masculinity in white and South Asian men's decisions to seek medical help for cardiac chest pain? *Journal of Health Services Research and Policy* 2007; **12(4)**: 223-229 (October 2007)[3]	Question 2
Richards HM, Reid ME , Watt GCM. Socioeconomic variations in responses to chest pain: qualitative study. *BMJ* 2002; **324 (7349**): 1308-1310[4]	Question 2
Ben Shlomo Y, Naqvi H, Baker, I Ethnic differences in healthcare-seeking behaviour and management for acute chest pain: secondary analysis of the MINAP dataset 2002-2003 *Heart* 2008; **94(3)**: 354-359[5]	Question 1, 2 & 3
Ben Shlomo Y, Rai H , Chaturvedi N. Lay diagnosis and health-care-seeking behaviour for chest pain in south Asians and Europeans. *Lancet* 1997; **350 (9091)**: 1578-1583[6]	Question 2
Richards H. Social and gender variation in the prevalence, presentation and general practitioner provisional diagnosis of chest pain. *Journal of Epidemiology and Community Health* 2000; **54 (9)**: 717-718[7]	Question 1
Adamson J, Ben-Shlomo Y, Chaturvedi N, Donovan J. Ethnicity, socio-economic position and gender – do they affect reported health care seeking behaviour? *Social Science & Medicine* 2003; **57:** 895-904[8]	Question 2

Conclusions

NICE are due to publish guidelines on the management of patients presenting with chest pain of cardiac origin. The guidelines have taken into account two studies that have examined whether patients from Asian origin have atypical chest pain, and whether this should be considered during patient assessment. Both studies found that Asian patients were younger and more likely to have diabetes. Weak evidence suggested that there were more Asian patients with atypical symptoms, although, this uncertainty is not reflected in the new NICE guidelines. It is an area which needs more research.

References

1 Hewitt A, Kainth A, Pattenden J, Sowden A, Duffy S, Watt I et al. Predictors of delay in seeking medical help in patients with suspected heart attack and interventions to reduce delay: a systematic review. 141. York : Centre for Reviews and Dissemination (CRD) ; 2004

2 Cooper A, Calvert N, Skinner J, Sawyer L, Sparrow K, Timmis A et al. Chest pain of recent onset : Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. Full guideline. Final draft January 2010 London: National Clinical Guideline Centre for Acute and Chronic Conditions ; 2010

3 Galdas P, Cheater F, Marshall P. What is the role of masculinity in white and South Asian men's decisions to seek medical help for cardiac chest pain? J Health Serv Res Policy 2007; 12(4):223-229.

4 Richards HM, Reid ME, Watt GC. Socioeconomic variations in responses to chest pain: qualitative study. BMJ 2002; 324(7349):1308.

5 Ben-Shlomo Y, Naqvi H, Baker I. Ethnic differences in healthcare-seeking behaviour and management for acute chest pain: secondary analysis of the MINAP dataset 2002-2003. Heart 2008; 94(3):354-359.

6 Chaturvedi N, Rai H, Ben-Shlomo Y. Lay diagnosis and health-care-seeking behaviour for chest pain in south Asians and Europeans. Lancet 1997; 350(9091):1578-1583.

7 Richards H, McConnachie A, Morrison C, Murray K, Watt G. Social and gender variation in the prevalence, presentation and general practitioner provisional diagnosis of chest pain. J Epidemiol Community Health 2000; 54(9):714-718.

8 Adamson J, Ben-Shlomo Y, Chaturvedi N, Donovan J. Ethnicity, socio-economic position and gender- do they affect reported health-care seeking behaviour? Soc Sci Med 2003; 57(5):895-904.

9 Teoh M, Lalondrelle S, Roughton M, Grocott-Mason R, Dubrey SW. Acute coronary syndromes and their presentation in Asian and Caucasian patients in Britain. Heart 2007; 93(2):183-188.

10 Barakat K, Wells Z, Ramdhany S, Mills PG, Timmis AD. Bangladeshi patients present with non-classic features of acute myocardial infarction and are treated less aggressively in east London, UK. Heart 2003; 89(3):276-279.

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 chest pain.mp. or exp Chest Pain/
2 clinic$.mp.
3 1 and 2
4 asian.mp.
5 deprived.mp.
6 Ethnic Groups/ or ethnic$.mp.
7 (minorities or minority).mp.
8 underprivileged.mp.
9 (underserved or under-served).mp.
10 (poor or poverty).mp.
11 or/4-10
12 3 and 11
13 limit 12 to "reviews (sensitivity)"
14 limit 12 to "reviews (optimized)"
15 limit 12 to "reviews (specificity)"
16 chest pain$.mp.
17 (access$ or present$ or use$ or usage or promot$ or market$ or adverti?$).tw.
18 16 and 17
19 11 and 18

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Appendix B – Literature search results

Systematic Reviews

Source – Cochrane Library 2010 Issue 1 (DARE)

Mant J, McManus R J, Oakes R A, Delaney BC, Barton PM, Deeks J J et al. Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care (Provisional abstract) Health Technology Assessment 2004; 8(2):1-170 http://www.hta.ac.uk/fullmono/mon802.pdf

McManus RJ, Mant J, Davies MK, Davis RC, Deeks JJ, Oakes RA et al . A systematic review of the evidence for rapid access chest pain clinics (Structured abstract) *International Journal of Clinical Practice* 2002 ; **56(1)**: 29-33

Source – Cochrane Library 2010 Issue 1 (HTA)

Hewitt AK, Kainth A, Pattenden J, Sowden A, Duffy S, Watt I et al. Predictors of delay in seeking medical help in patients with suspected heart attack, and interventions to reduce delay: a systematic review (Structured abstract) York: Centre for Reviews and Dissemination (CRD); 2004: 141 http://www.york.ac.uk/inst/crd/CRD_Reports/crdreport26.pdf

Guidelines

Source – Internet searches

Cooper A, Calvert N, Skinner J, Sawyer L, Sparrow K, Timmis A et al. Chest pain of recent onset : Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin Full guideline Final draft London: National Clinical Guideline Centre for Acute and Chronic Conditions ; January 2010
http://www.nice.org.uk/nicemedia/pdf/ChestPainFullGuideline.pdf

Primary studies

Source – MEDLINE (Ovid) 1950 – February week 1 2010

Zaman MJ, Junghans C , Sekhri N, Chen R, Feder GS, Timmis AD et al. Presentation of stable angina pectoris among women and South Asian people *Canadian Medical Association Journal* 2008; **179(7)**: doi:10.1503/cmaj.071763
http://www.cmaj.ca/cgi/content/full/179/7/659

Sekhri N, Feder GS, Junghans C, Hemingway H, Timmis AD. How effective are rapid access chest pain clinics? Prognosis of incident angina and non-cardiac chest pain in 8762 consecutive patients *Heart* 2007; **93**: 458-463 http://heart.bmj.com/content/93/4/458.full.pdf

Source – HMIC (Ovid) January 2010

Galdas P, Cheater F, Marshall P. What is the role of masculinity in white and South Asian men's decisions to seek medical help for cardiac chest pain? *Journal of Health Services Research and Policy* 2007; **12(4)**: 223-229 (October 2007)

Richards HM, Reid ME , Watt GCM Socioeconomic variations in responses to chest pain: qualitative study. *BMJ* 2002; **324 (7349**): 1308-1310
http://www.bmj.com/cgi/content/full/324/7349/1308

Ben Shlomo Y, Naqvi H, Baker, I. Ethnic differences in healthcare-seeking behaviour and management for acute chest pain: secondary analysis of the MINAP dataset 2002-2003 *Heart* 2008; **94(3)**: 354-359 http://heart.bmj.com/content/94/3/354.short

Ben Shlomo Y, Rai H, Chaturvedi N. Lay diagnosis and health-care-seeking behaviour for chest pain in south Asians and Europeans. *Lancet* 1997; **350 (9091)**: 1578-1583 http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(97)06243-0/abstract

Richards H. Social and gender variation in the prevalence, presentation and general practitioner provisional diagnosis of chest pain. *Journal of Epidemiology and Community Health* 2000; **54 (9)**: 717-718 http://jech.bmj.com/content/54/9/714.abstract

Source – Internet searches

Khunti K, Sarami SJ. Improving the delivery of coronary care for ethnic minorities *Heart* 2003;**89:**479-480 doi:10.1136/heart.89.5.479 http://heart.bmj.com/content/89/5/479.full

Adamson J, Ben-Shlomo Y, Chaturvedi N, Donovan J. Ethnicity, socio-economic position and gender - do they affect reported health-care seeking behaviour? *Social Science and Medicine* 2003; **57(5)**: 895-904

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6VBF-47T893R-6&_user=122868&_coverDate=09%2F30%2F2003&_rdoc=1&_fmt=high&_orig=search&_sort=d&_docanchor=&view=c&_searchStrId=1204670088&_rerunOrigin=google&_acct=C000010083&_version=1&_urlVersion=0&_userid=122868&md5=8e0be14601946de431bccc7e9b3dd066

Sekhri N, Feder GS, Junghans C, Hemingway H, Timmis AD. Rapid-access chest pain clinics and the traditional cardiology out-patient clinic QJM Advance Access originally published online 14 February 2006 *QMJ* 2006; **99(3):** 135-141 http://qjmed.oxfordjournals.org/cgi/content/abstract/99/3/135

Sekhri N, Feder GS, Junghans C, Hemingway H, Timmis AD. How effective are rapid access chest pain clinics? Prognosis of incident angina and non-cardiac chest pain in 8762 consecutive patients *Heart* 2007; **93**: 458-463 http://heart.bmj.com/content/93/4/458.full.pdf

Tod AM, Read C, Lacey A, Abbott J. Barriers to uptake of services for coronary heart disease: qualitative study *BMJ* 2001 July 28; **323(7306)**: 214. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC35276/

Richards HM, Reid ME, Watt GCM. Socioeconomic variations in responses to chest pain: qualitative study *BMJ* 2002**;** 324(7349)**:** 1308. http://ukpmc.ac.uk/articlerender.cgi?artid=477843

Background information

Source – DOH website

National Service Framework for Coronary Heart Disease London: Department of Health ; 2000 http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4094275

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Appendix C – Critical appraisal of :

Teoh M, Lalondrelle S, Roughton M, Grocott- Mason R et al. Acute coronary syndromes and their presentation in Asian and Caucasian patients in Britain. Heart. 2007; 93 (2):183-188.[6]

<table>
<tr><td>Aim</td><td>To assess if Asian and Caucasian patients living in Britain, have different symptoms when they are experiencing an ACS.</td></tr>
<tr><td>Methods</td><td>Consecutive patients were recruited from November 2001 to November 2005. Patients were asked to describe the pain intensity (using a scale of 1 to 10, with 10 being the worst pain ever experienced). They were also asked to describe the character of the pain i.e. stabbing, shooting pain, dull ache, heavy weight on chest, burning and squeezing pain. The location of the pain was also ascertained using a schematic diagram of the front and back of the upper body.</td></tr>
<tr><td>Quality</td><td>The quality of the study was good. Consecutive cases were recruited for the study. In addition the investigators tried to ensure that all patients received the same verbal instruction and that each had the same chances of understanding the questions asked (with interpreters etc).</td></tr>
<tr><td>Number of subjects</td><td>In total 2,905 patients were recruited of which 604 (21%) were Asian and 2301 (79%) were Caucasian. Just one Asian and 31 Caucasian patients did not complete the survey.</td></tr>
<tr><td>Patient characteristics</td><td>Statistically significant differences were found in the following patient characteristics:

<table>
<tr><td></td><td>Asian (%)</td><td>Caucasian (%)</td><td>P value</td></tr>
<tr><td>Age</td><td>60.6 (12.7)</td><td>68.9 (13.9)</td><td><0.001</td></tr>
<tr><td>Diabetic</td><td>262 (43)</td><td>398 (17)</td><td><0.001</td></tr>
<tr><td>MI diagnosed</td><td>294 (49)</td><td>1439 (63)</td><td><0.001</td></tr>
<tr><td>Non ST elevation</td><td>109 (18)</td><td>173 (40)</td><td><0.001</td></tr>
<tr><td>Angina</td><td>310(51)</td><td>851 937)</td><td><0.001</td></tr>
<tr><td colspan="4">No differences in gender distribution, ST segment elevation, left bundle branch block.</td></tr>
</table>

The study authors stated that Asian patients tended to be younger and were more likely to have diabetes.</td></tr>
<tr><td>Chest pain symptom presentations</td><td>There were also statistically significant differences between Asian and Caucasian in how they presented with chest pain:

<table>
<tr><td>Symptoms</td><td>Asian (%)</td><td>Caucasian (%)</td><td>P value</td></tr>
<tr><td>Frontal discomfort</td><td>565 (94)</td><td>1975 (86)</td><td><0.001</td></tr>
<tr><td>Posterior discomfort</td><td>278 (46)</td><td>562 (25)</td><td><0.001</td></tr>
<tr><td>Classical distribution</td><td>545 (90)</td><td>1887 (82)</td><td><0.001</td></tr>
<tr><td>Silent pain</td><td>35 (6)</td><td>299 (13)</td><td><0.001</td></tr>
<tr><td>Intensity of discomfort Median (range)</td><td>7.5 (0-10)</td><td>7 (0-10)</td><td>0.002</td></tr>
<tr><td>Maximum discomfort</td><td>148(25)</td><td>459 (20)</td><td>0.02</td></tr>
<tr><td>Area of discomfort Median (range)</td><td>5 (0-19)</td><td>4 (0-24)</td><td><0.001</td></tr>
</table>

The study authors concluded that Asian patients tended to report a higher intensity of chest pain that covered a larger area of their body and experienced more frequent discomfort over the rear of their upper thorax than Caucasian patients.</td></tr>
<tr><td>Comment 1</td><td>There may however, be confounding factors that have affected these results. Differences in the numbers of patients presenting with angina versus MI may have accounted for the variation in symptoms. The presence of diabetes may also have altered pain sensation.</td></tr>
</table>

Comment 2	In addition it would have been helpful to have seen the CI reported around important outcomes such as discomfort, so that the readers could see whether the results are clinically as well as statistically significant.
ARIF conclusions	Given these factors, there is a large degree of uncertainty surrounding the results of this study. However, the uncertainty does not rule out ethnic differences in symptom presentation that could cause a delay within the Asian treatment pathway compared to Caucasian patients, particularly the timely administration of thrombolytic therapy. Therefore the statement in the NICE guideline: Section 1.2.1.6, page 10 line 22 "*Do not assess the symptoms of an ACS differently in ethnic groups. There are no major differences in symptoms of an ACS among different ethnic groups*" may be too strong, and that the uncertainty should be considered.

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Appendix D – Critical appraisal of:

Barakat K, Wells Z, Ramdhany S, Mills PG et al. Bangladeshi patients present with non-classic features of acute myocardial infarction and are treated less aggressively in east London, UK. Heart. 2003; 89(3): 276-279.[10]

<table>
<tr><td>Aim</td><td>The aim of this study was to compare presentation of Q wave acute myocardial infarction (Q wave AMI) between patients of Bangladeshi origin and patients of European origin.</td></tr>
<tr><td>Methods</td><td>The setting was in the coronary care unit of an East London teaching hospital. The study ran between May 1998 to April 2001, but only gathered data on the character, interpretation, and initial response of the presenting symptoms between June 2000 and April 2001</td></tr>
<tr><td>Quality</td><td>Overall of fair quality, it is unclear if patients were recruited consecutively therefore selection bias is a potential problem. The NICE review group felt that the study had spectrum bias as the study only included patients with Q wave AMI, but this could also be an advantage, in that all the patients have the same pathology and so any differences are more likely to be due to different racial physiology or different social constructs in interpreting the pain from Q wave AMI.</td></tr>
<tr><td>Number of subjects</td><td>Total number recruited: 108 Bangladeshi and 263 White.
Number included symptom assessment: 32 Bangladeshi, 31 White</td></tr>
<tr><td>Patient characteristics</td><td>Statistically significant differences were found in the following patient characteristics:
<table>
<tr><td></td><td>Bangladeshi (%) n=108</td><td>White (%) n=263</td><td>P value</td></tr>
<tr><td>Age</td><td>63(12)</td><td>68 (19)</td><td><0.0001</td></tr>
<tr><td>Risk factors</td><td></td><td></td><td></td></tr>
<tr><td>Diabetic</td><td>54 (50)</td><td>40(15.2)</td><td><0.0001</td></tr>
<tr><td>Family history of IHD</td><td>14 (13)</td><td>77 (29.3)</td><td>0.0005</td></tr>
<tr><td>Tx on admission</td><td></td><td></td><td></td></tr>
<tr><td>Aspirin</td><td>49(45.4)</td><td>90 (34.2)</td><td>0.04</td></tr>
<tr><td>Beta blocker</td><td>24 (22.2)</td><td>31 (11.8)</td><td>0.011</td></tr>
<tr><td>ACE inhibitors</td><td>27 (25)</td><td>42 (16)</td><td>0.042</td></tr>
<tr><td>Tx Delay</td><td></td><td></td><td></td></tr>
<tr><td>Door to needle time</td><td>42.5 mins (78)</td><td>26 mins (47.7)</td><td>0.012</td></tr>
</table></td></tr>
<tr><td>Chest pain symptom presentations</td><td>The main findings regarding the character and interpretation of the symptoms are:
<table>
<tr><td></td><td>Bangladeshi (%) n = 32</td><td>White (%) n = 31</td><td>OR (95%CI)</td><td>p value</td></tr>
<tr><td>Central chest pain</td><td>13 (40.6)</td><td>27 (87.1)</td><td>0.11 (0.03, 0.38)</td><td>0.0006</td></tr>
<tr><td>Classic descriptions of chest pain</td><td>8 (25)</td><td>18 (58.1)</td><td>NR</td><td>NR</td></tr>
<tr><td>Atypical descriptions of chest pain</td><td>24 (75)</td><td>13 (41.9)</td><td>0.25 (0.09, 0.74)</td><td>0.0118</td></tr>
</table>
Classic descriptions = heaviness, tightness, weight, pressure, band-like gripping.
Atypical descriptions = sharp, stabbing, pinching and burning</td></tr>
<tr><td>ARIF conclusions</td><td>The study authors concluded that the atypical presentation of AMI symptoms by Bangladeshi patients may explain the delay in “door to needle time” experienced by this group of Bangladeshi patients under study. However, the major drawback to this study is that the nature of the chest pain was only measured in just 32 Bangladeshi and 31 white patients. This severely limits the reliability and usefulness of the findings. Again it suggests uncertainty.</td></tr>
</table>

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Appendix E – Critical appraisal of:

Hewitt AK, Kainth A, Pattenden J, Sowden A, Duffy S, Watt I et al. Predictors of delay in seeking medical help in patients with suspected heart attack, and interventions to reduce delay: a systematic review (Structured abstract) York: Centre for Reviews and Dissemination (CRD); 2004.[1]

Aims	To undertake two systematic reviews 1. "To identify the factors associated with patient decision time (referred to as patient delay)" in seeking medical help (specifically thrombolytic therapy) for an AMI 2. "How effective are interventions that aim to reduce the time from the onset of signs and symptoms of an AMI to seeking medical help/arrival at hospital?"
Quality	This was a well conducted systematic review, which used appropriate methodology. Unfortunately it is rather old, with the literature searches up to 2001.
Review of factors/predictors	
Methods	For question 1, several factors that delayed patients with signs and symptoms were investigated. These were grouped as follows: socio-demographic factors; psychosocial; access to/use of services; clinical knowledge; symptoms/evaluation of symptoms; attempts at self treatment. Results were reported according to these groupings, using a multivariate analysis. The primary outcome measured was time from signs and symptoms to time to call for appropriate medical help.
Number/type of studies included	Eleven studies were included of which six referred to ethnicity [Ashton KC, Martiny W, Bleeker JK, Alonzo AA, Ell K, Crawford SL]. Unfortunately, the results were not given using ethnicity or deprivation as subgroups therefore the following is a subgroup of all of the pertinent results.
Results	Multivariate analysis was undertaken on the following outcomes: Psychosocial = equivocal.* Socio-demographic = gender = 3/7 trials females delay was longer than males in seeking appropriate medical assistance. Age = 2/6 trials older age associated with longer delay. Ethnicity = 3/3 trials no delay associated with ethnicity. Social and economic status 4/4 equivocal results.* Access/use of services = factors reducing delay were event occurring during the day rather than at night and use of paramedic transport. Factors increasing delay recent consultation with a doctor. Health insurance and site/type of hospital were equivocal. Geographical location and transport difficulties had no effect on delay. Knowledge = two factors investigated, one was "calling the correct agency", which was unexpectedly related to longer delay. The other factor MI knowledge had no effect on delay. Clinical = Equivocal results for history of heart symptoms, chronic illnesses and previous MI. Although interestingly previous CCU admission was associated with delay in one study in contrast to previous MI, which reduced the time to delay. Does this suggest that there are other factors i.e. fear of false alarms plays a part? The presence of pulmonary oedema seems to be a recurring theme which shortens delay. Smoking was equivocal. Symptoms/evaluation of symptoms = symptom attribution (e.g. heart, indigestion other) and perceived seriousness of symptoms had an effect on delay with shorter delay if patients attributed symptoms to heart problems and perceived them to be serious. Pain scores were equivocal, but acute pain onset appeared to shorten the delay in seeking help. An increasing level of incapacitation e.g. patient collapse led to shorter delays. Attempts at self treatment = found equivocal results, one study found that resting to relieve pain was associated with delay, but when patients attributed the symptoms to heart pain (by ingesting heart medication for relief) delay was shortened. Total of factors = 96.

* equivocal = contradictory results (e.g. equal number of trials finding positive and negative relationships with similar independent variables)

Summary	Overall, it appears that if patients/carers perceive symptoms to be serious or attribute them to heart symptoms, then they shorten the time to delay. If symptoms are not associated with heart problems or not perceived to be serious in nature then there are significant delays. Delay is also shorter in patients who have risk factors for heart disease e.g. diabetes, smoking or who have had a previous MI. Symptoms that are not perceived to be associated with heart problems appear to be atypical symptoms, e.g. mild pain over a 24 hour period, breathlessness. Current and previous contact with medical practitioners who do not recognise the past or present illness episodes as an MI also appears to be a factor associated with delay.
Comment	The results from this section of the review should be viewed as hypothesis generating rather than as firm conclusions, as the study design and conduct was poor. No data specifically aimed at South Asian or deprived communities.
Review of interventions	
	For question 2, the effectiveness of interventions (not specified) to reduce time from onset of signs and symptoms of AMI to receiving appropriate treatment were sought. Study designs included randomized controlled trials (RCTs), controlled clinical trials (CCTs) and before and after studies. Primary outcomes were patient delay and also time taken to travel to the hospital (pre-hospital delay). Excluded were studies that measured patients 'intention to act' and studies that evaluated a change in delivery of health services such as mobile coronary care units.
Number/type of studies included	Two RCTs, one CCT and eight before and after studies were included.
RCT characteristics	Both RCTs were conducted in the USA and had investigated mass media campaigns. Meischke (Call fast, Call 911) also included a patient and physician educational programme and Luepker (the REACT trial) included mail shots. Both were of fair quality, with deficits in how allocation was concealed at randomisation and blinding of outcome assessors. Both trials lost 30% of follow up data. These three deficits have a tendency to exaggerate the effectiveness of interventions.
RCT results	Time to delay in the 'Call fast, Call 911' found no statistically differences in delay time between intervention and control groups. The REACT trial did find that delay time for the intervention group decreased from 140 minutes at baseline to 130 minutes at end of trial. The mean delay trend fell by 4.7% per year (95% CI -8.6 to -0.6%). However, the delay time in the control group also declined from a baseline of 140 minutes to 126 minutes with a mean delay trend of -6.8% per year (95% CI -14.5 to -1.6%). The difference between the groups was not statistically significant.
CCT characteristics & results	The CCT was conducted in Nottingham. The intervention was to offer symptomatic patients the chance to telephone a help line situated in a hospital CCU, to check if their symptoms were AMI and to advise them of the best cause of action. The trial was of low quality. At baseline, just 23% of patients in the Nottingham Heartwatch Study, who were a definite or probably MI, called for help within 30 minutes of symptom onset, whereas after the intervention this rose to 44% in the intervention group. The control group remained at the baseline level of 25%. This difference was statistically significant ($p<0.05$).
Before and after Studies	None of the eight before and after studies had been conducted in the UK, two were from the USA, two from Germany, and one from Canada, Australia, Sweden and Switzerland, therefore generalisability is probably a problem. Descriptions of the interventions are given in detail in the appendices of the review. Five studies sought outcomes measuring pre-hospital delay, two sought outcomes measuring patient delay and one measured both. Of the studies that looked at pre-hospital delay, five found a statistically significant reduction in the number of hours of delay, which was generally reduced by one hour. All of these used media interventions. The remaining study with pre-hospital delay outcomes found no

	difference, but this study used ‘patient education’. Of the three studies which examined patient delay, one found a significant reduction from 86 minutes to 60 minutes with the other two studies not finding a difference.
Summary of intervention studies	Overall evidence for effective interventions is weak, due to the study designs employed. Most of the positive results come from studies employing a before and after methodology, which doesn’t eliminate confounding factors nor temporal changes outside the intervention. The only controlled trial to show a statistically significant result was the CCT undertaken in Nottingham, which again does not eliminate that the result may have been due to baseline differences between the intervention and control groups.
ARIF conclusions	This was a well conducted systematic review. However, it is out of date, and has found only a limited number of studies, many with weak study designs addressing the questions. It has some use in hypothesis generation for new primary research and would also serve as a good base on which to plan a new systematic review.

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Archived ARIF Request

Nocturnal Mechanical Ventilation
Neuromuscular Disorders
Chest Wall Disorders

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in June 2001.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of nocturnal mechanical ventilation in relieving symptoms of hypoventilation in patients with neuromuscular and chest wall disorders?

Reviews Identified

- Annane D, Chevrolet JC, Chevret S, Raphael JC. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders (Cochrane Review). In: The Cochrane Library, Issue 1, 2001. Oxford: Update Software.

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Comments

The purpose of the above review was to examine the efficacy of nocturnal mechanical ventilation in relieving hypoventilation-related symptoms in patients with neuromuscular and chest wall disorders. The review generally appears to be comprehensive, systematic and well conducted. Four trials were included with a total number of 51 patients.

There appears to be a weak but consistent trend favouring nocturnal mechanical ventilation compared to no ventilation to improve hypoventilation-related clinical symptoms, nocturnal mean oxygen saturation and daytime hypercapnia in the short term. One trial that assessed long-term outcomes (up to three years) suggested that it is possible that survival may be prolonged.

In summary, due to the small number of trials, the small number of enrolled patients and the number of comparisons covered, making firm conclusions regarding the efficacy of nocturnal mechanical ventilation is difficult. The review provides a useful starting point for developing necessary future research to confirm any short and long term benefits that nocturnal mechanical ventilation may have in alleviating symptoms associated with chronic hypoventilation in patients with neuromuscular or chest wall disorders.

Request Carried Out: June 2001

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These pages are maintained by Ann Massey

Archived ARIF Request

Fish Oil Supplements
Essential Fatty Acids (*n*-3 series)
Child Behaviour

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in January 2006.

The Problem Submitted for ARIF to Advise Upon:

What is the evidence on the effectiveness of fish oil supplements on school aged children's behaviour and educational attainment?

Fish oils provide an abundant source of n-3 polyunsaturated fatty acids (PUFAs) which cannot be made by the body (i.e. are "essential"). The n-3 series PUFAs, along with essential PUFAs of the n-6 series, are needed for brain development and function. Evidence that a relative deficiency of certain PUFAs (both n-3 and n-6) may contribute to some behavioural and learning problems associated with attention-deficit/hyperactivity disorder (ADHD) has lead to the hypothesis that dietary supplements may be beneficial.

Reviews Identified

No systematic reviews were identified.

Primary Studies

- Itomura M, Hamazaki K, Sawazaki S, Kobayashi M, Terasawa K, Watanabe S, Hamazaki T.The effect of fish oil on physical aggression in schoolchildren-a randomized, double-blind, placebo-controlled trial.The Journal of Nutritional Biochemistry 2005;16:163-71
- Voigt RG, Llorente AM, Jensen CL, Fraley JK, Berretta MC, Heird WC. A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. The Journal of Pediatrics 2001;139:189-96
- Hirayama S, Hamazaki T, Terasawa K. Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder - a placebo-controlled double-blind study. European journal of clinical nutrition 2004;58:467-73
- Brue AW, Oakland TD, Evans RA. The use of a dietary supplement combination and an essential fatty acid as an alternative and complementary treatment for children with attention-deficit/hyperactivity disorder. Scientific Review of Alternative Medicine 2001;5:187-194
- Aman MG, Mitchell EA, Turbott SH.The effects of essential fatty acid supplementation by Efamol in hyperactive children. Journal of abnormal child psychology 198715:75-90
- Arnold LE, Kleykamp D, Votolato N, Gibson RA, Horrocks L. Potential link between dietary intake

of fatty acids and behavior: Pilot exploration of serum lipids in attention-deficit hyperactivity disorder. Journal of Child and Adolescent Psychopharmacology 1994;4:171-182

- Stevens L, Zhang W, Peck L, Kuczek T, Grevstad N, Mahon A, Zentall SS, Arnold LE, Burgess JR. EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. Lipids 2003;38:1007-21
- Richardson AJ, Puri BK. A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. Progress in neuro-psychopharmacology & biological psychiatry 2002;26:233-9

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Comments

No systematic reviews were located. However, there were seven randomised controlled trials (RCTs) and one double-blind, double-crossover study that assessed the effectiveness of different combinations of essential fatty acid (EFA) supplements.

Most research in this area (seven of the eight trials) focussed on children with ADHD and assessed the effectiveness of supplements on the behavioural symptoms associated with ADHD such as inattention, impulsivity and over-activity. The results reported to-date are somewhat equivocal and insufficient to either fully support or refute the effectiveness of EFA supplements on behaviour or educational attainment for children with ADHD. However, given the growing number of trials on this topic we feel a full systematic review of all the available evidence is required.

To-date the effectiveness of EFA supplements on 'normal' school aged children's behaviour and educational attainment does not appear to have been adequately explored. Only one trial, the results of which were inconclusive, was identified. We therefore feel there is a need for more primary research in this area, ideally a further well conducted RCT.

Request Carried Out: January 2006

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These pages are maintained by Ann Massey

DermaSilk therapeutic clothing for children with dermatitis

Synopsis

Question:	What is the clinical effectiveness of DermaSilk therapeutic clothing for children with severe dermatitis?
Evidence Identified:	No systematic reviews or health technology assessments were identified. Alongside the search one randomised controlled trial and two controlled clinical trials were identified. They were appraised together with other two controlled clinical trials indicated by the requester.
Comments:	Evidence on the clinical effectiveness of DermaSilk therapeutic clothing for children with dermatitis is currently sparse and weak. Very limited data suggests that this therapy can be beneficial for patients with atopic dermatitis, however, the usefulness of the results is greatly limited due to paucity and poor quality of the data. There is a need for large, good quality primary studies to determine the effectiveness of DemaSilk therapeutic clothing in this population.
Date Completed:	March 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

DermaSilk clothing for children with dermatitis

Request completed: March 2010

Question

What is the clinical effectiveness of DermaSilk therapeutic clothing for children with acute exacerbations of severe dermatitis?

Question clarification

DermaSilk therapeutic clothing, i.e. DermaSilk®, is a sericin-free silk fabric treated with AEGIS AEM5772/5 which has antibacterial properties. It is made into garments e.g. a T-shirt or an arm tube for dressing.

Method

Systematic reviews and health technology assessments (HTAs) were sought using the ARIF search protocol http://www.arif.bham.ac.uk/strategy.shtml. Text and index terms were used to represent the population and the intervention. Sources were searched from their inception to March 2010. No language restriction was applied to the searches. The search strategy can be found in Appendix A. The following inclusion criteria were used for search and study selection:

Population	Children with acute exacerbations of severe dermatitis referred into secondary care dermatology
Intervention	DermaSilk therapeutic clothing treatment
Comparator	Treatments recommended in NICE clinical guideline 57[1] (http://www.nice.org.uk/nicemedia/pdf/CG057NICEguideline.pdf): • emollients • topical corticosteroids • topical calcineurin inhibitor • bandages • phototherapy • systemic therapy
Outcome	Patient-oriented outcomes (e.g. skin lesion and symptoms, etc)
Study design	Systematic reviews and health technology assessments

Results

No systematic reviews or health technology assessments were identified. Alongside the search for systematic reviews and HTAs, one randomised controlled trial (RCT)[2] and two controlled clinical trials[3-4] were identified that were relevant to the question (full search results can be found in Appendix B). Two controlled clinical trials indicated by the requester were also relevant to the question.[5-6] All the trials were published between 2004 and 2008.

Of the five trials, only one controlled trial[5] compared DermaSilk with a topical corticosteroid in the treatment of atopic dermatitis (AD); none of the others compared DermaSilk with a standard therapy that was listed in the NICE guideline.[1] The RCT[2] and one controlled trial[6] compared DermaSilk with the same fabric without the AEGIS AEM 5772/5 antimicrobial; of the remaining two, one[4] compared DermaSilk with cotton clothes and the other[3] with simple silk followed by cotton clothes.

The RCT[2] included both adults and children, however, the results were not reported separately for the children. In the RCT and in one controlled trial[6] the patients had AD with eczematous lesions, the severity of the condition was not described but baseline Scoring Atopic Dermatitis index (SCORAD)* was reported for both the DermaSilk and the control arms. In the remaining trials the children were either a mixture of mild, moderate and severe,[4] or mild-to-moderate,[3] or moderate AD only.[5] Table 1 below outlined the characteristics of the trials.

Sample sizes were all small, ranging from 12 to 46 patients and giving 125 patients in total. Methodological quality was reasonable in the RCT, with randomisation, concealment, double blinding and washout phase approaches etc. being applied, but was limited in the controlled trials. Study duration in two trials[4,6] was only 7 days; in one of these[4] further information on the treatments being received before the study and whether a washout phase was given was not reported, thus it was unclear whether there could be any carry-over effect on the results. Also, in this study[4] eight children were excluded (26%) because they did not follow the instructions correctly, but there was no intention to treat analysis.

Results from the trials all showed that DermaSilk therapeutic clothing can be beneficial for patients with atopic dermatitis (see Table 2 below for details). However, small sample size and weak study design limited the reliability and the usefulness of the results.

* SCORAD index: index of SCORing atopic dermatitis; it is a clinical tool for assessing the severity (extent, intensity and subjective symptoms) of atopic dermatitis. Low value indicates less severe. (Reference: Oranje AP, Glazenburg EJ, Wolkerstorefer A, de Waard-van der Spek FB. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. British journal of Dermatology. 2007;157:645-648)

Conclusions

In conclusion, evidence on the clinical effectiveness of DermaSilk therapeutic clothing for children with dermatitis is currently sparse and weak. Very limited data suggests that this therapy can be beneficial for patients with atopic dermatitis, however, the usefulness of the results is greatly limited due to paucity and poor quality of the data. Large studies with improved methodology would fill the gap in evidence informing the use of the therapy for this patient population.

Table 1. Study characteristics

	Senti et al. 2006[5]	Stinco et al. 2008[2]	Koller et al. 2007[3]	Ricci et al. 2006[6]	Ricci et al. 2004[4]
Study design	Controlled clinical trial	Randomised controlled trial with double blinding	Controlled clinical trial	Controlled clinical trial	Controlled clinical trial
Population	Children diagnosed with moderate AD; N = 15 (one withdrew and one lost to follow-up and were excluded from the analysis)	Patients with AD with eczematous lesions located on the arms; N = 30 (of these 11 were aged > 14 years; four withdrew)	Children affected by mild-to-moderate AD with acute lesions; N=22	Children with AD with eczematous lesions located on the arms; N = 12 (four healthy children were also included as normal control to the children with AD)	Children affected by AD in an exacerbation; N = 46 (mild 4%; moderate 39%; severe 57%
Intervention	DermaSilk (in the left side arm and leg)	DermaSilk (in one arm)	DermaSilk (in one arm)	DermaSilk (in one arm)	DermaSilk (n =31; of these 8 children were excluded because they did not follow the instructions correctly)*
Control	Topical corticosteroid (with cotton clothes in the right side arm and leg)	Identical to DermaSilk but without antibacterial (in the other arm)	Simple silk for the first 2 weeks and then cotton throughout the rest of the study (in the other arm)	Identical to DermaSilk but without antibacterial (in the other arm)	Cotton clothes (n=15)*
Concurrent treatment	Topical non-medicated emollient ; wash-out phases for current treatments were given before the beginning of the study treatment	Only moisturizing therapy with emollient cream was permitted; wash-out phases for current treatments were given before the beginning of the study treatment	Systemic antihistamines and emollients. No systemic antibiotics and anti-inflammatory agents were allowed	Only moisturizing therapy with Cetafil® was permitted; wash-out phases for current treatments were given	Topical emollients. No pharmacological treatment with steroids and/or antibiotics was permitted
Follow-up duration	21 days (treatment duration 7 days)	28 days	3 months	7 days	7 days
Outcomes	EASI (modified eczema area and severity index; the lower score the better); pruritus (VAS of 10cm); patient/parent assessment of overall improvement; physician's global assessment	Photographic assessment; local modified SCORAD index; visual analogue scale of pruitius	Modified SCORAD index	Microbiological measurement (at baseline, 1hour and 7 day follow-up); local SCORAD index; local side effects	SCORAD index; local score of DermaSilk covered lesion and lesion uncovered by DermaSilk in the same child

* The authors stated that the two groups assigned were homogenous in age and clinical picture

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Table 2. Results

	Senti et al. 2006[5]	**Stinco et al. 2008[2]**	**Koller et al. 2007[3]**	**Ricci et al. 2006[6]**	**Ricci et al. 2004[4]**
Results	On both comparison sides the EASI significantly increased from baseline at day 7 and significantly decreased from baseline at day 21 but no difference observed between the comparisons. EASI of non-treated areas also decreased significantly at day 21 from baseline. Both sides had no significant decrease in pruritus between baseline and day 21. Global evaluation of efficacy by either physicians or patients/parents showed significant improvement between day 7 and day 21 on both comparison sides but no significant difference between the comparisons. One patient developed general exacerbation of eczema in treated and non-treated areas within 4 days of beginning study treatment	The intervention had significantly more total reduction from baseline at day 28 than the control in mean local SCORSD score (10.05±9.22, p<0.0001) and in mean values of the pruritus (1.88±1.7, p<0.0001), although the differences between the comparisons were not significant in mean local SCORSD score during the first 2 weeks and in mean values of pruritus during the first week	Both intensity score and subjective score at week 4, 8 and 12 were significantly lower in the DermaSilk-coved arm than the control arm	After 7 days in AD children: a significant reduction in mean SCORAD score was observed in both the intervention and control arms (from 7.3 to 4.4; p =0.019, and from 7.1 to 5; p = 0.02, respectively); the reduction in the mean number of colony forming units/cm^2 was similar in both arms; no local side effects owing to the textile	The decrease from baseline at day 7 in mean SCORAD was significant in the intervention (from 43 to 30; p=0.003) but non-significant in the control group; the improvement in the mean local score of the DermaSilk covered area was significant (from 32 to 18.6; p= 0.001) but not significant in the uncovered area (from 31 to 26; p=0.112)
Conclusion	"*DermaSilk showed potential to become and effective treatment of AD*"	"*The study demonstrates the importance of including the AEM 5772/5 finish to the specially knitted silk for a long-term improvement of atopic eczema symptoms*"	"*The use of DermaSilk has a significant beneficial effect in atopic dermatitis because of the non-irritation properties of silk as well as the antibacterial capacity of AEGIS AEM 5772/5*"	"*Although this special silk fabric seems to be able to improve skin lesions in AD, we were unable to demonstrate that such silk fabrics coated with AEGIS AEM 5572/5 have an antibacterial activity in vivo, as shown in vitro*"	"*The use of special silk clothes may be useful in the management of AD in children*"
ARIF comments	-	The results were not reported separately for children. Baseline SCORAD index: DermaSilk 47.35; control 46.68	The authors stated that "*the patients were randomised by age group and by disease severity*"; however, one arm of each child was assigned to the intervention and the other arm to the control. It was unclear	-	The authors stated that the improvement in the mean local score of the DermaSilk covered area was significantly greater than that of the uncovered area. This is incorrect as no

			how the arms were assigned and how randomising the patients by age group and by disease severity could impact on the assignment		analysis was carried out comparing the improvement between the two areas

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References

1. National Institute for Health and Clinical Excellence. Atopic eczema in children. Management of atopic eczema in children from birth up to the age of 12 years. NICE clinical guideline 57. London: National Institute for Health and Clinical Excellence (NICE); 2007. Available from http://www.nice.org.uk/nicemedia/pdf/CG057NICEguideline.pdf [Accessed on 10-03-2010]

2. Stinco G, Piccirillo F, Valent F. A randomized double-blind study to investigate the clinical efficacy of adding a non-migrating antimicrobial to a special silk fabric in the treatment of atopic dermatitis. Dermatology. 2008;217(3):191-5.

3. Koller DY, Halmerbauer G, Böck A, Engstler G. Action of a silk fabric treated with AEGISTM in children with atopic dermatitis: A 3-month trial. Pediatric Allergy and Immunology. 2007;18(4):335-338.

4. Ricci G, Patrizi A, Bendandi B, Menna G, Varotti E, Masi M. Clinical effectiveness of a silk fabric in the treatment of atopic dermatitis. British Journal of Dermatology. 2004;150(1):127-31.

5. Senti G, Steinmann L S, Fischer B, Kurmann R, Storni T, Johansen P, Schmid-Grendelmeier P, Wüthrich B, Kündig T M. Antimicrobial silk clothing in the treatment of atopic dermatitis proves comparable to topical corticosteroid treatment. Dermatology 2006;213:228-233

6. Ricci G, Patrizi A, Mandrioli P, Specchia F, Medri M, Menna G, Masi M. Evaluation of the antibacterial activity of a special silk textile in the treatment of atopic dermatitis. Dermatology 2006;213:224-227

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 dermasilk.mp.
2 (silk or clothes or clothing or textile$).tw.
3 silk/
4 Clothing/
5 Textiles/
6 fabric$.tw.
7 or/1-6
8 exp Dermatitis/
9 7 and 8
10 limit 9 to "reviews (specificity)"
11 limit 9 to "therapy (optimized)"

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Appendix B – Literature search results

Systematic Reviews

No systematic reviews identified

Primary studies

Source – Cochrane Library 2010 Issue 2 (CENTRAL)

Stinco G, Piccirillo F, Valent F. A randomized double-blind study to investigate the clinical efficacy of adding a non-migrating antimicrobial to a special silk fabric in the treatment of atopic dermatitis. Dermatology (Basel, Switzerland) 2008;217(3):191-5

Koller DY, Halmerbauer G, Böck A, Engstler G. Action of a silk fabric treated with AEGIS in children with atopic dermatitis: a 3-month trial. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology 2007;18 (4):335-8

Ricci G, Patrizi A, Bendandi B, Menna G, Varotti E, Masi M. Clinical effectiveness of a silk fabric in the treatment of atopic dermatitis. The British journal of dermatology 2004;150(1):127-31

Kanehara S, Ohtani T, Uede K, Furukawa F. Clinical effects of undershirts coated with borage oil on children with atopic dermatitis: a double-blind, placebo-controlled clinical trial. The Journal of dermatology 2007;34(12):811-5

Ramsing DW, Agner T. Effect of glove occlusion on human skin. (I). short-term experimental exposure. Contact dermatitis 1996;34(1):1-5

Ramsing DW, Agner T. Effect of glove occlusion on human skin (II). Long-term experimental exposure. Contact dermatitis 1996;34(4):258-62

Piérard GE, Arrese JE, Rodríguez C, Daskaleros PA. Effects of softened and unsoftened fabrics on sensitive skin. Contact dermatitis 1994;30(5):286-91

Gauger A, Fischer S, Mempel M, Schaefer T, Foelster-Holst R, Abeck D. Efficacy and functionality of silver-coated textiles in patients with atopic eczema. Journal of the European Academy of Dermatology and Venereology: JEADV 2006;20(5):534-41

Juenger M, Ladwig A, Staecker S, Arnold A, Kramer A, Daeschlein G. Efficacy and safety of silver textile in the treatment of atopic dermatitis (AD). Current medical research and opinion 2006;22 (4):739-50

Love WE, Nedorost ST. Fabric preferences of atopic dermatitis patients. SO: Dermatitis: contact, atopic, occupational, drug: official journal of the American Contact Dermatitis Society, North American Contact Dermatitis Group 2009;20:29-33

Bauer A, Kelterer D, Bartsch R, Stadeler M, Elsner P. Skin protection in the food industry. Current problems in dermatology 2007;34:138-50

Baack BR, Holguin TA, Holmes HS, Prawer SE, Scheman AJ. Use of a semipermeable glove during treatment of hand dermatitis. Cutis; cutaneous medicine for the practitioner 1996;58 (6):423-4

Source – MEDLINE (Ovid) 1950 – Week 3, 2010

Stinco G, Piccirillo F, Valent F. A randomized double-blind study to investigate the clinical efficacy of adding a non-migrating antimicrobial to a special silk fabric in the treatment of atopic dermatitis. Dermatology 2008;217(3):191-5

Kanehara S, Ohtani T, Uede K, Furukawa F. Clinical effects of undershirts coated with borage oil on children with atopic dermatitis: a double-blind, placebo-controlled clinical trial. Journal of Dermatology 2007;34(12):811-5

Koller DY, Halmerbauer G, Bock A, Engstler G. Action of a silk fabric treated with AEGIS in children with atopic dermatitis: a 3-month trial. Pediatric Allergy & Immunology. 2007;18(4):335-8

Gauger A, Fischer S, Mempel M, Schaefer T, Foelster-Holst R, Abeck D, Ring J. Efficacy and functionality of silver-coated textiles in patients with atopic eczema.[Erratum appears in J Eur Acad Dermatol Venereol 2006 Jul;20(6):771] Journal of the European Academy of Dermatology & Venereology 2006;20(5):534-41.

Juenger M, Ladwig A, Staecker S, Arnold A, Kramer A, Daeschlein G, Panzig E, Haase H, Heising S. Efficacy and safety of silver textile in the treatment of atopic dermatitis (AD). Current Medical Research & Opinion 2006;22(4):739-50

Source – Relevant studies provided by requester

Senti G, Steinmann LS, Fischer B, Kurmann R, Storni T, Johansen P et al. Antimicrobial silk clothing in the treatment of atopic dermatitis proves comparable to topical corticosteroid treatment. Dermatology 2006;213:228-233

Ricci G, Patrizi A, Mandrioli P, Specchia F, Medri M, Menna G et al. Evaluation of the antibacterial activity of a special silk textile in the treatment of atopic dermatitis. Dermatology 2006;213:224-227

Background information

Source – Provided by requestor

National Institute for Health and Clinical Excellence. Atopic eczema in children. Management of atopic eczema in children from birth up to the age of 12 years. London: NICE; 2007. NICE Clinical Guideline 57. Available from http://www.nice.org.uk/nicemedia/pdf/CG057NICEguideline.pdf

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Archived ARIF Request

Parent Education Programmes
Children with Conduct Disorders
Conduct Disorders

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in November 2002.

The Problem Submitted for ARIF to Advise Upon:

The effect of parent education programmes on the behaviour and mental health of children with conduct disorders and their parents.

The question focused on the effect of education or training programmes aimed solely at parents on the behaviour and mental health of both parents and children. The programmes could be individual or group-based with any underlying theoretical basis. Children of any ages with behavioural, social or conduct disorders, but not diagnosed psychiatric disorders were included.

Reviews Identified

- Barlow J. Systematic Review of the Effectiveness of parent-training programmes in improving behaviour problems in children aged 3-10 years (Second edition). Health Services Research Unit, Department of Public Health, University of Oxford 1999
- Barlow J, Coren E. Parent-training programmes for improving maternal psychosocial health (Cochrane Review). In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software
- Barlow J, Parsons J. Group-based parent-training programmes for improving emotional and behavioural adjustment in 0-3 year old children (Cochrane Review). In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software
- Coren E, Barlow J. Individual and group-based parenting programmes for improving psychosocial outcomes for teenage parents and their children (Cochrane Review). In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software
- Dimond C, Hyde C. Parent education programmes for children's behaviour problems. Medium to long term effectiveness. West Midlands Development and Evaluation Service Report 1999; 19

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Comments

The identified reviews were generally rigorous in their methodology and are likely to cover the majority of the best available evidence on this topic. There was a large amount of variation between the

included randomised controlled trials in terms of the type of parent programmes investigated, the outcome measures used (parental, child or both), the child characteristics (age, behavioural disorder) and the length of follow-up.

A consistent trend was observed across the majority of studies towards a positive effect of parent programmes on both parent and children. Due to the methodological limitation of some of the included studies, this positive effect may in some cases have been overestimated.

It is unclear whether the results are generalisable to the UK population, as many studies were US based. There is also a lack of information regarding which subgroup(s) of parent would benefit most from this intervention, which type of programme would be the most (cost-) effective and how long any effects last.

Further good quality evidence on these issues would be informative, however, given the available evidence, it appears that there may be a beneficial effect from parenting programmes, although it is not clear how large this effect is.

Request Carried Out: November 2002

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Archived ARIF Request

Pathological Myopia
Choroidal Neovascularisation
Photodynamic Therapy

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This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in January 2003.

The Problem Submitted for ARIF to Advise Upon:

Photodynamic therapy (PDT) is a newly developed type of treatment combining

- injection of a light-sensitive dye which concentrates in areas of “abnormality”
- low power laser

The rationale is that abnormal cells can be destroyed without damage to nearby normal cells.

PDT has applications in a number of areas, particularly cancer. However, requests to ARIF have focused on the use of this technology in treatment of eye disease. In this application the only currently commercially available light sensitive dye is verteporfin.

Pathological myopia (high degree myopia/severe short-sightedness) is caused by elongation of the eye. It needs to be differentiated from lesser degrees of short-sightedness, for which many people may require spectacles.

Pathological myopia has many features but one which poses a particular threat to sight is choroidal neovascularisation (new fragile blood vessels which leak blood and fluid, which in turn cause scarring). As in age-related macular degeneration these are the targets of treatment with PDT. See related requests:

Age-related Macular Degeneration (AMD/ARMD)/Sub-foveal Predominantly Classic Choroidal Neovascularisation (CNV)/Photodynamic Therapy

Age-related Macular Degeneration (AMD/ARMD)/Sub-foveal Occult Choroidal Neovascularisation (CNV)/Photodynamic Therapy

Reviews Identified

None.

Trials Identified

- Verteporfin in Photodynamic Therapy (VIP) Study Group. Photodynamic therapy of

subfoveal choroidal neovascularisation in pathological myopia with verteporfin. Ophthalmology 2001;108:841-852.

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Comments

We have confirmed that although use of PDT for pathological myopia has been licensed, it is not covered by the forthcoming NICE guidance.

There are no systematic reviews.

There appears to be only one published RCT which was generally well conducted.

This shows that verteporfin PDT leads to stable vision, in contrast to deteriorating vision with placebo PDT. The size of effect of verteporfin PDT seems to be greater than in age-related macular degeneration. Despite this, whether benefits are worth costs may still be an issue and a definitive commissioning decision should await a formal economic evaluation. Such has not been published and should be a priority for research.

Request Carried Out: January 2003

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Archived ARIF Request

Enzyme Potentiated Desensitisation (EPD)
Multiple Chemical Sensitivity
Formaldehyde Poisoning
Chronic Fatigue Syndrome
Gulf War Syndrome

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in October 2003 and September 2005.

The Problem Submitted for ARIF to Advise Upon:

ARIF has received several requests concerning the effectiveness of EPD.

There are also related web pages on Provocation-neutralisation and Breakspear Hospital.

Reviews Identified

ARIF briefing to the Regional Evaluation Panel (REP) 2003.

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Comments

The briefing paper summarises requests received up to 2003. Searches indicate an absence of RCT evidence on the effectiveness of EPD for complex, ill-defined syndromes like multiple chemical sensitivity. The searches were re-run for a further request in 2005, again with no RCT evidence being identified.

There is RCT evidence on simpler conditions with an allergic basis i.e. allergic rhinitis, but often these RCTs have not been systematically reviewed.

There is an urgent need for rigorous primary and secondary research on all aspects of enzyme-potentiated desensitisation.

Request Carried Out: October 2003 and September 2005

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Archived ARIF Request

Cognitive Behavioural Therapy and Other Treatments Chronic Fatigue Syndrome (ME)

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in August 1997.

The Problem Submitted for ARIF to Advise Upon:

What is the evidence on the effects/effectiveness of treatments for chronic fatigue syndrome?

Reviews Identified

- Sutton G, Camilleri-Ferrante C. Chronic fatigue syndrome. Epidemiology, Aetiology and Treatment. Cambridge: ACET, July 1996. Pp 35
- Best L, Stevens A. Cognitive behavioural therapy in the treatment of chronic fatigue syndrome. Winchester: Wessex Institute of Public Health, 1996. (DEC Report No. 50)

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Comments

The first review provides a general overview of the topic and the treatments which have been suggested to be of benefit. However, any recommendations made on the effects/effectiveness of these must take into account that the way the literature has been identified and summarised is not systematic and is hence susceptible to bias. This is particularly true of comments made concerning the use of antidepressant medication.

The second review, is more systematic in approach. On this basis the conclusion that CBT is "Recommended: as Out-patient treatment for a certain group of people, but the criteria for selection of those who would gain most needs clear definition" and "Not recommended: as In-patient treatment." seems just reasonable, on the basis of the evidence presented in the review. However, readers should be aware that these conclusions are based on a small number of small trials - total number of patients exposed to treatment, c 100. Further, the results are not consistent between the four main included studies, although possible reasons for this are explored. This strongly suggests that if there is a decision to purchase CBT, it should ideally be done within the context of a rigorous evaluation.

Request Carried Out: August 1997

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Archived ARIF Request

Enzyme Potentiated Desensitisation Chronic Fatigue Syndrome

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in April 2002.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of enzyme potentiated desensitisation (EPD) for chronic fatigue syndrome (CFS)?

Reviews Identified

No systematic reviews were identified.

Primary Studies

No primary studies were identified.

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Comments

Our searches did not identify any systematic reviews specifically targeting EPD for CFS. Limited searches for primary studies did not identify any articles. Therefore, it appears that very little, if any, research has been undertaken in this area.

We have previously undertaken separate requests on EPD and CFS and we feel that our reports on these requests may also be of interest.

Request Carried Out: April 2002

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Archived ARIF Request

Spinal Cord Stimulation
Chronic Neuropathic Pain
"Failed" Back Surgery Syndrome
Complex Regional Pain Syndrome

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in September 2005.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of spinal cord stimulation for chronic neuropathic pain, particularly in “failed” back surgery syndrome and complex regional pain syndrome?

Neuropathic pain refers to that arising from damage to nerves. It is often very difficult to treat and if it persists for more than 6 months it is referred to as chronic neuropathic pain. Unrelenting pain over prolonged periods is recognised to have a major impact on health-related quality of life.

Leg and back pain after back surgery (failed back surgery syndrome) and limb pain after injury (complex regional pain syndrome) are two important causes of chronic neuropathic pain.

Spinal cord stimulation involves delivering low voltage electrical impulses directly to specific sections of the spinal cord. This blocks the pain signals emanating from damaged nerves. The person feels tingling rather than pain. The stimulator consists of: a pulse generator and battery which is implanted under the skin of the abdomen; a thin lead running under the skin from the generator to the spinal cord; and electrodes resting on the spinal cord located in the fluid filled space which surrounds the spinal cord (epidural space). Surgery is required to implant the stimulator.

Reviews Identified

- Spinal cord stimulation for the management of neuropathic pain. Ontario Ministry of Health and Long-Term Care. Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care (MAS) 2005:80
  http://www.health.gov.on.ca/english/providers/program/ohtac/tech/reviews/pdf/rev_scs_030105.pdf
- Mailis-Gagnon A, Furlan AD, Sandoval JA, Taylor R. Spinal cord stimulation for chronic pain. The Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD003783. DOI:10.1002/14651858.CD003783.pub2.
  http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003783/frame.html

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Comments

There are several well conducted reviews of effectiveness on this subject. The two listed were the most up-to-date at the time the request was conducted. Both reports indicate that there is limited randomised

controlled trial evidence (two trials) that spinal cord stimulation is effective for chronic neuropathic pain due to failed back surgery and complex pain syndrome.

The Ontario health technology assessment also assessed cost-effectiveness and the authors felt there was evidence that the costs of spinal cord stimulation were justified by the observed benefits. This may have been the reason why their conclusion was less cautious than the Cochrane review, the Ontario recommendation being for:

“Increased access to this technology (spinal cord stimulation) for the management of chronic intractable neuropathic pain within the context of a multi-disciplinary comprehensive pain management program.”

This page replaces a previous page for a request on this subject in 2000.

Request Carried Out: September 2005

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Archived ARIF Request

Pulmonary Rehabilitation (Respiratory Rehabilitation) Chronic Obstructive Airways Disease (Chronic Obstructive Pulmonary Disease)

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in December 1997.

The Problem Submitted for ARIF to Advise Upon:

What is the evidence for respiratory rehabilitation for those with chronic obstructive pulmonary/airways disease?

Reviews Identified

- Lacasse Y et al. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. Lancet 1996;348:1115-19
- Devine EC, Pearcy J. Meta-analysis of the effects of psychoeducational care in adults with chronic obstructive pulmonary disease. Patient Education and Counselling 1996;29(2):167-178
- Smith K et al. Respiratory muscle training in chronic airflow limitation meta-analysis. American Review of Respiratory Diseases 1992;145:533-539

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Comments

The Lacasse review is a well conducted review whose results can be trusted. It demonstrates a range of beneficial effects suggesting that respiratory rehabilitation should be considered as a potentially useful component of the treatment of persons with chronic obstructive pulmonary disease. However, caution needs to be exercised on the grounds that neither the importance of the effects demonstrated nor their cost-effectiveness has been examined. Further, this review provides no information on potential adverse effects.

Supplementary information is provided by the two additional reviews. The Smith review is a good systematic review which suggests that respiratory muscle training alone is of little benefit to patients with chronic airflow limitation.

The review by Devine is also a fairly good review which examines the effectiveness of the psychoeducational component of pulmonary rehabilitation concluding that this has a beneficial effect on the functional ability and well-being of patients with COAD. It offers a useful alternative perspective on the topic but its methodological shortcomings are such that its results should be treated with caution.

Although the three reviews are of varying validity and measure different outcomes, they do agree as to the general effectiveness of pulmonary rehabilitation. The Lacasse review addresses respiratory rehabilitation in its widest sense and, as such, takes into account the overall effect which is likely to be more than the sum of the individual components.

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Domiciliary Oxygen
Chronic Obstructive Pulmonary Disease

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This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in July 1999.

The Problem Submitted for ARIF to Advise Upon:

When is domiciliary oxygen effective?

Reviews Identified

None.

Trials Identified

- Gorecka D, Gorzelak K, Sliwinski P et al. Effect of long term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. Thorax 1997;52:674-679
- MRC Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Lancet 1981; 1(8222): 681-686

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Comments

No relevant published reviews were identified.

Both of the cited trials are small but well-designed and reliable RCTs. Our only significant criticism is that the analysis of the MRC trial appears to have been partially data driven, and places considerable emphasis on gender differences in survival which was not a pre-stated sub-group analysis.

Taken together, the results of the trials suggest that domiciliary oxygen improves survival in patients with severe hypoxaemia but not those with mild to moderate hypoxaemia. No data is available on other outcomes and adverse effects.

Request Carried Out: July 1999

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Spirometry
Chronic Obstructive Pulmonary Disease (COPD)

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of spirometry and screening for chronic obstructive pulmonary disease (COPD) in primary versus secondary care?

Question Reformulated

What is the effectiveness and diagnostic accuracy of spirometry in primary versus secondary care for the screening/diagnosis of COPD?

Reviews Identified

No systematic reviews were identified.

Trials Identified

No trials were identified.

Other Literature Identified

A limited amount of literature of peripheral relevance to the question was identified, e.g.:

- Eaton T, Withy S, Garrett JE et al. Spirometry in primary care practice. The importance of quality assurance and the impact of spirometry workshops. Chest 1999;116:416-423

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Comments

We identified no systematic reviews on spirometry in primary versus secondary care for COPD.

Widening our searches to encompass primary studies revealed no directly relevant trials. There were a very small number of studies of indirect relevance to the question. A complete list of these studies is available on request.

In summary, the lack of a systematic review and the absence of any directly relevant primary studies

gives an indication that the effectiveness of spirometry for COPD in primary care versus secondary care has not been evaluated. Given this, and the implications of the British Thoracic Society guidelines for more effective diagnosis and management of COPD in primary care, rigorous research is urgently required on this topic.

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Non-invasive Positive Pressure Ventilation Chronic Obstructive Pulmonary Disease

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of non-invasive positive pressure ventilation (NPPV) for patients with stable hypercapnic chronic obstructive pulmonary disease (COPD) in a domiciliary environment?

Reviews Identified

No directly relevant systematic reviews were identified.

Other Literature Identified

- Nicholson D, Tiep B, Jones R, Sadana G et al. Noninvasive positive-pressure ventilation in chronic obstructive pulmonary disease. Current Opinion in Pulmonary Medicine 1998;4:66-75

A list of all the reviews identified whilst undertaking this request is available on request.

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Comments

Our searches did not identify any systematic reviews on NPPV for stable COPD in a domiciliary or other environment.

Most of the systematic reviews we identified targeted patients admitted to hospital with acute respiratory failure and therefore, these were not directly relevant to the request.

The narrative review by Nicholson et al provides an overview of NPPV for all types COPD. With regard to stable hypercapnic COPD, the authors identify four RCTs that address this issue and give a brief synopsis of the findings of these studies. Unfortunately, the review cannot be classed as systematic as no detail on methods is given. As such, we are unsure whether a comprehensive ascertainment of existing evidence was undertaken and against what criteria the four RCTs were selected for inclusion in the review. The conclusions need to be treated cautiously as a consequence, but the review does provide a useful introduction to readers new to this topic.

Request Carried Out: April 2001

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Spinal Cord Stimulation
Chronic Pain

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence on the effectiveness of spinal cord stimulation in the management of chronic pain?

Reviews Identified

- Turner JA, Loeser JD, Bell KG. Spinal cord stimulation for chronic low back pain: a systematic literature analysis. Neurosurgery 1995; 37(6): 1088-1095
- Tomlinson J et al. Spinal cord stimulation in the management of chronic pain. Sheffield: Trent Institute for Health Services Research, 1997. (Guidance Notes for Purchasers: 97/08)

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Comments

Two systematic reviews were identified. The first is a good review published in 1995 on SCS in failed back surgery syndrome. At this time the only available evidence was from observational case series and the authors concluded that, although some patients experienced an improvement in their condition, there was insufficient evidence to draw firm conclusions on the effectiveness of the treatment.

The second review is a DEC report published by the Trent Institute. Although the report does not provide sufficient information on its methods to allow a judgment on the validity of its findings, we know that recent reports produced by the InterTasc group do adhere to certain quality standards. Again the review does not identify any relevant RCTs other than two small studies of limited validity. The reviewers conclude that the existing evidence is so weak that it is difficult to draw any conclusions for most indications. The best evidence suggests the treatment may be effective in the treatment of angina and peripheral vascular disease and to a lesser extent for failed back surgery syndrome.

This is an area prone to need for regular updating as new information is continually becoming available.

Additional information relevant to this request is available in the requests entitled Intraspinal Drug Delivery/Chronic Pain, Deep Brain Stimulation/Parkinson's Disease.

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Intraspinal Drug Delivery Chronic Pain

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of intraspinal drug delivery in the management of chronic pain?

Reviews Identified

- Robert G. Implantable infusion devices (IIPs) for long-term pain management. Southampton: Wessex Institute for Health Research and Development, 1996.

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Comments

A number of reviews were identified on this topic. The most systematic and up-to-date of these is the Wessex DEC report on the role of implantable infusion devices in chronic pain. Although the report does not provide sufficient information on its methods to allow a judgment on the validity of its findings, we know that it is likely to have adhered to certain quality standards set out by the InterTasc group. The review identified no relevant trials. All evidence was obtained from observational case series. The authors tentatively suggest that IDD might be a cost effective option in patients with a good life expectancy.

This is an area prone to need for regular updating as new information is continually becoming available.

Additional information relevant to this request is available in the requests entitled Spinal Cord Stimulation/Chronic Pain, Deep Brain Stimulation/Parkinson's Disease.

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Residential Pain Management Programmes
Chronic Pain
Pain

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of residential pain management programmes (PMPs) for patients with severe chronic pain that has not responded to other therapies?

Residential PMPs aim to reduce the disability and distress caused by chronic pain, rather than attempting to cure it, by teaching physical, psychological and practical techniques to improve the patient's quality of life. Therapy is provided by a multidisciplinary team that includes psychologists, physiotherapists, nurses and occupational therapists. Patients typically attend residential PMPs for 4-5 days/week over a 4 week period.

Reviews Identified

No systematic reviews were identified.

Primary Studies

- Peters JL, Large RG. A randomised control trial evaluating in- and outpatient pain management programmes. Pain. 1990; 41: 283-93
- Williams AC deC, Richardson PH, Nicholas MK, Pither CE, Harding VR, Ridout KL, Ralphs JA, Richardson IH, Justins DM, Chamberlain JH. Inpatient vs. outpatient pain management: results of a randomised controlled trial. Pain. 1996; 66: 13-22
- Gupta S, Francis JD. Porter GE. Valentine JMJ. An independent assessment of a supraregional pain management programme and comparison of patients' and general practitioners' perceptions of the effects. Anaesthesia. 2000; 55: 367-90

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Comments

Two RCTs (Peters et al, 1990; Williams et al, 1996) and one survey (Gupta et al, 2000) that evaluated the effectiveness of residential PMPs for patients with chronic pain were identified.

Both RCTs (Peters et al, 1990; Williams et al, 1996) compared inpatient PMPs with outpatient PMPs and a control group. Both reported that whereas there was little or no change amongst the control group in terms of physical performance and psychological function, significant improvements were seen amongst patients attending the inpatient and outpatient PMPs. However, whilst Peters et al (1990) indicated similar levels of improvement amongst the inpatient and outpatient groups, Williams et al (1996) reported greater gains amongst the inpatients.

The survey (Gupta et al, 2000) assessed the therapeutic response as perceived by 20 patients and their GPs to a residential PMP provided within the region. After therapy, most patients reported improvements in their quality of life and GPs noted generally beneficial effects on their patients, fewer consultations, and small reductions in the use of analgesic medications.

In summary, the studies located indicate that both residential and outpatient PMPs may provide psychological and physiological benefits and lead to a reduction in the use of healthcare services amongst patients with chronic pain. Any additional benefit of a residential as opposed to outpatient PMP is however less clear as the results of the two studies are somewhat equivocal.

Whilst the evidence located indicates residential PMPs can be beneficial it is based on three small studies (sample size ≤ 121) and should therefore be interpreted cautiously. A further problem is that our summary is not a systematic review of all potentially relevant evidence and there is the possibility that studies reporting more positive results have appeared in print whereas those adopting a less optimistic view have not (publication bias). In conclusion, the evidence to-date seems insufficient to either fully support or refute the commissioning of this type of therapy

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Early Referral
Chronic Renal Failure

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence on the effectiveness of early referral to specialist renal services for people with chronic renal failure?

Question Reformulated

Two distinct aspects to this question can be identified:

- The likely benefits of referring people with chronic renal failure to the care of a renal specialist at least 4-6 months before they require renal replacement therapy
- The likely benefits and disbenefits of early initiation of dialysis

Reviews Identified

- Obrador & Pereira. Early referral to a nephrologist and timely initiation of renal replacement therapy: a paradigm shift in the management of patients with chronic renal failure. Americal Journal of Kidney Diseases 1998;31:398-417
- Churchill DN. An evidence based approach to earlier initiation of dialysis. American Journal of Kidney Diseases 1997;30:899-906

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Comments

Neither review is a systematic review but both are good narrative summaries which give an indication of the quality and quantity of available material. The majority of the included studies are observational and no trials appear to have been undertaken at this stage.

The evidence on early referral suggests that, as well as facilitating early initiation when this is appropriate, patients under the care of a renal specialist experience other benefits which may lead to a prolonged pre-dialysis phase. The results of the included studies in both reviews indicate that late referral and late initiation of dialysis appear to be associated with increased morbidity and mortality.

Obrador & Pereira touch on the economic implications of early initiation of dialysis, suggesting that any additional costs would be outweighed by the benefits in terms of decreased hospitalization during treatment and improved quality of life. They also cite recommendations for early referral and early initiation based on renal function but these should probably be viewed with some caution as it is unclear exactly how they were derived from the primary studies.

In summary, the evidence base around early referral to specialist services and early initiation of renal replacement therapy is weak, but suggests there appears to be potential for benefits to outweigh costs in the long term, but this requires confirmation through further, more rigorous research.

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Archived ARIF Request

Chronic Sinusitis

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The Problem Submitted for ARIF to Advise Upon:

What is the most effective diagnostic test for chronic sinusitis?

Reviews Identified

- Gleeson M. Diagnosing maxillary sinusitis: often difficult. British Medical Journal 1992;305:662-663
- Evans KL. Diagnosis and management of sinusitis. British Medical Journal 1994; 309: 1415-1422

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Comments

Although both the reviews cited are not systematic, they do provide useful background in considering the problem.

Two further articles identified:

- Van Duijin NP, Brouwer HJ, Lamberts H. Use of symptoms and signs to diagnose maxillary sinusitis in general practice: comparison with ultrasonography. British Medical Journal 1992;305 684-687
- Williams JW, Simel DL. Does this patient have sinusitis? Diagnosing acute sinusitis by history and physical examination. Journal of the American Medical Association 1993; 270: 1242-1246

provide information on the sensitivities/specifications of constellations of symptoms which could be used to improve the initial clinical diagnosis of chronic sinusitis.

Request Carried Out: April 1996

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Tonsillectomy
Chronic Tonsillitis

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The Problem Submitted for ARIF to Advise Upon:

Evidence for the effectiveness of tonsillectomy for chronic tonsillitis and chronic pharyngitis in children and adults.

Reviews Identified

- Shaikh W, Vayda MD, Feldman W et al. A systematic review of the literature on evaluation studies of tonsillectomy and adenoidectomy. Paediatrics 1976;57:401-407

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Comments

The enquirer had already identified the review referenced when the request was made. ARIF was unable to identify any further reviews.

Our appraisal of the paper by Shaikh et al was that it was not sufficiently rigorous or up-to-date to constitute a reliable summary of the avaiable research evidence at this point in time. It does, however, provide a useful starting point for examining research in the area, suggesting that an evidence based purchasing decision on this topic might be possible if studies since the 1970's could be reliably identified.

One such study would be:

- Paradise JL, Bluestone CD, Bachman RZ. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. New England Journal of Medicine 1984; 310: 674-683

Request Carried Out: April 1996

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Mental Health
Clinical Psychology (Clinical Psychologists)

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The Problem Submitted for ARIF to Advise Upon:

Is there any evidence on the effectiveness of clinical psychology in general and whether clinical psychologists are more effective than other professionals, such as counsellors, in certain situations?

Question Reformulated

Although evidence was sought which might be helpful with any aspect of the question, a clear distinction was made between research on the effectiveness of:

- Psychological interventions delivered by any of a number of health professionals including doctors, nurses, counsellors, social workers, and clinical psychologists; and
- A specific staff group who deliver any of a variety of psycho-social interventions ranging from simple counselling and education, to cognitive, behavioural and psychotherapy.

Reviews Identified

- Devine EC. Effects of psychoeducational care for adult surgical patients: a meta-analysis of 191 studies. Patient Education and Counselling 1992;19:127-142
- Devine EC. The effects of psychoeducational care provided to adults with cancer: meta-analysis of 116 studies. Oncology Nursing Forum 1995;22(9):1369-1381

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Comments

No reviews were identified which looked at the effectiveness of clinical psychologists as a professional group. The reviews identified examined the effectiveness of some of the interventions that a clinical psychologist might deliver, or train other professionals to deliver.

The two reviews utilise similar methods to look at the effects of psychoeducational care in different populations with, as might be expected, the most recent review being of better methodological quality. Both conclude that psychoeducational care is beneficial.

The effect sizes calculated by the reviews should be treated with caution for a number of reasons. The most significant of these is the degree of heterogeneity that exists between the included studies. This problem is a reflection of the broad nature of the questions addressed by the reviews, as some trade-off is inevitable between the validity of the review and the tightness of the question.

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Archived ARIF Request

Cognitive Behavioural Therapy Depression

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The Problem Submitted for ARIF to Advise Upon:

The effectiveness of cognitive behavioural therapy (CBT) in treating depression in non-white communities, particularly South Asian/Pakistani women.

Cognitive behavioural therapy aims to modify beliefs and behaviours using elements derived from cognitive and behaviour therapies. It focuses on practical elements rather than understanding past experiences to resolve current problems.

Reviews Identified

- Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J. A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety. Health Technology Assessment Vol.6: No.22, 2002:100
- Schraufnagel TJ, Wagner AW, Miranda J, Roy-Byrne P. Treating minority patients with depression and anxiety: what does the evidence tell us? General Hospital Psychiatry 2006;28:27-36

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Comments

No reviews were located which systematically examined the effects of CBT in ethnic minorities for the treatment of depression. Manual searching of general reviews on CBT in depression and anxiety highlighted one trial which reported the ethnicity of its sample. However, the individual results of the various ethnic groups were not given.

We also identified a narrative review which was useful in outlining various issues relating to ethnic minority mental health. These included difficulty in access to care by ethnic minorities, and difficulties in extrapolating findings between cultures/ethnicities/races e.g. Pakistani vs British-born Pakistani. Research examining the specific effects of CBT in ethnic minorities is urgently needed.

Request Carried Out: February 2006

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Archived ARIF Request

Screening by colonoscopy in those with family history Colorectal Cancer

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence base of the proposals made for the West Midlands Familial Cancer Initiative, particularly those concerning screening of individuals with a positive family history of colorectal cancer?

Question Reformulated

What are the effects of check colonoscopy + polypectomy + other appropriate treatment in those with a family history of colorectal cancer on that cancer's incidence, severity, mortality and morbidity?

The frequency of colonoscopy varies from two to five yearly depending on the strength of the family history; the strength of family history ranges from one first degree relative developing cancer under the age of 40 years to three close relatives developing colorectal cancer.

Reviews Identified

- NHS Centre for Reviews & Dissemination. The management of colorectal cancer. Effective Health Care 1997;3(6):1-12
- Cancer Guidance Sub-Group of the Clinical Outcomes Group. Improving outcomes in colorectal cancer: The research evidence. London: NHS Executive, Department of Health, 1997. Chapter 2 d & e.

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Comments

Both reviews are systematic in approach. Although they indicate that rigorous research on the specific question of interest is not available, the summaries of research on related aspects of the management of colorectal cancer are useful.

Of particular importance is knowledge that there is growing evidence that even crude screening to detect faecal occult blood (FOB) in a population at general risk is effective in reducing deaths from colorectal cancer. It thus seems highly likely that use of other methods of screening e.g. colonoscopy, which are likely to be as sensitive and specific as FOB testing, and probably much more so, in a population at higher risk by virtue of family history, will also be effective.

Thus in ARIF's view it does seem reasonable to offer screening to those with a positive family history of colorectal cancer, with the expectation that the risk of death from this cancer is likely to be less than if screening had not occurred.

There are however two important provisos:

- Competence of the colonoscopy examinations needs to be assured, not just to reduce to a minimum the number of false positive diagnoses, but also to ensure that adverse events associated with the procedure are minimised.
- That uncertainty about the most effective and efficient means of using different screening methods (colonoscopy and/or sigmoidoscopy + barium enema and/or faecal occult blood testing) is acknowledged. Ideally screening for colorectal cancer in those with a positive family history should be rigorously evaluated in order to contribute knowledge on the best combination of screening tools. If this is not possible, the methods of screening should be kept under review to ensure that the ones used are determined by new research findings on this point as they emerge.

This is an area prone to need for regular updating as new information is continually becoming available.

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Echinacea Common Cold

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The Problem Submitted for ARIF to Advise Upon:

What treatments have been shown to be effective in the treatment of the common cold?

Question Reformulated

Due to the breadth of this question, we focused our attention on those interventions for which there was a substantial body of evidence on their effectiveness, and on those that appeared to have a positive effect. Interventions excluded because of a lack of research evidence included mast cell stabilisers, iodine, guaifenesin, glucocorticoids, interferon and other antiviral drugs. Antibiotics were also excluded as a Cochrane review provided reliable evidence of no effect.

Reviews Identified

- Melchart D, Linde K, Fischer P, Kaesmayr J. Echinacea for the prevention and treatment of the common cold (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

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Comments

This is a well-conducted systematic review, which sensibly does not attempt a meta-analysis due to the considerable heterogeneity between, and methodological limitations of, the included studies. The main limitation of the review itself is the high likelihood of publication and foreign language bias.

The authors conclude that while the majority of the included studies demonstrated positive results, the limitations of the evidence base in terms of the methodological rigour of the included studies, and the extreme heterogeneity between the individual Echinacea preparations evaluated and case definitions of the common cold, make it difficult to draw clear conclusions as to when it is likely to be effective and in what doses. It is worth noting that, on the basis of the evidence examined the risk of serious adverse effects from oral preparations appears small, but more research is clearly required.

Additional information relevant to this request is available in the other requests on the Common Cold entitled Zinc; Vitamin C; Antihistamines; Anticholinergics; "Over-the-Counter" Remedies; Alpha Agonists; NSAIDs; Steam Inhalation.

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NSAIDS
Common Cold

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The Problem Submitted for ARIF to Advise Upon:

What treatments have been shown to be effective in the treatment of the common cold?

Question Reformulated

Due to the breadth of this question, we focused our attention on those interventions for which there was a substantial body of evidence on their effectiveness, and on those that appeared to have a positive effect. Interventions excluded because of a lack of research evidence included mast cell stabilisers, iodine, guaifenesin, glucocorticoids, interferon and other antiviral drugs. Antibiotics were also excluded as a Cochrane review provided reliable evidence of no effect.

Reviews Identified

None.

Trials Identified

- Gwaltney JM Jr. Combined antiviral and antimediator treatment of rhinovirus colds. The Journal of Infectious Diseases 1992;166:776-782
- Hsia J et al. Immune modulation by aspirin during experimental rhinovirus colds. Bulletin of the New York Academy of Medicine 1989;65(1):45-56
- Graham NMH et al. Immune modulation by aspirin during experimental rhinovirus colds. Bulletin of the New York Academy of Medicine 1989; 65(1): 45-56
- Graham NMH et al. Adverse effects of aspirin, acetaminophen and ibuprofen on immune function, viral shedding and clinical status in rhinovirus infected volunteers. The Journal of Infectious Diseases 1990;162:1277-1282
- Stanley E et al. Increased viral shedding with aspirin treatment of rhinovirus infection. JAMA 1975; 231(12):1248-1251
- Sperber SJ et al. Effects of naproxen on experimental rhinovirus colds. A randomised, double-blind controlled trial. Annals of Internal Medicine 1992; 117: 37-41
- Martinez Gallardo F et al. Symptomatic treatment of the common cold in children with a new combination of naproxen sodium plus pseudoephedrine hydrochloride: a comparative trial against pseudoephedrine syrup. Proc. West. Pharmacol. Soc. 1994;37:157-158

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Comments

We looked at a number of trials on aspirin and other non-steroidal anti-inflammatory drugs. The majority of these were small with significant methodological limitations. Despite documented concern around the possibility that aspirin causes increased viral shedding and thus increased transmission of the virus, the evidence to support this claim appears to have come from one small trial (Stanley et al 1975) and the result has not been replicated in subsequent studies. Naproxen was shown in one reasonably robust trial to reduce symptoms of headache, malaise and myalgia, but not to influence other symptoms such as sore throat and runny nose, with no increased viral shedding (Sperber et al 1992). It was also shown in two trials to be effective when taken in combination with other treatments known to be of benefit for other symptoms, but these were both very small and of uncertain reliability (Gwaltney 1992 and Martinez Gallardo et al 1994).

Additional information relevant to this request is available in the other requests on the Common Cold entitled Zinc; Vitamin C; Antihistamines; Anticholinergics; "Over-the-Counter" Remedies; Alpha Agonists; Echinacea; Steam Inhalation.

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"Over the Counter" Remedies Common Cold

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The Problem Submitted for ARIF to Advise Upon:

What treatments have been shown to be effective in the treatment of the common cold?

Question Reformulated

Due to the breadth of this question, we focused our attention on those interventions for which there was a substantial body of evidence on their effectiveness, and on those that appeared to have a positive effect. Interventions excluded because of a lack of research evidence included mast cell stabilisers, iodine, guaifenesin, glucocorticoids, interferon and other antiviral drugs. Antibiotics were also excluded as a Cochrane review provided reliable evidence of no effect.

Reviews Identified

- Smith MBH and Feldman W. Over-the-counter cold medications. A critical review of clinical trials between 1950 and 1991. JAMA 1993; 269(17): 2258-2263

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Comments

This is a fairly good systematic review on what is essentially a very broad question. The breadth of the question, and the limitation of the search strategy to a Medline search and citation checking, introduces a potential for bias. However, when viewed alongside the results of other ARIF requests on the effects of specific "ingredients" on specific symptoms, it does provide a useful overview of non-prescription medications used in the common cold. The authors conclude that there is sufficient evidence to support the effectiveness of certain products in adults but not in children. They note that any benefits must be weighed against potential adverse effects and costs, particularly those that relate to accidental ingestion in children and overdose for certain ingredients in adults.

Additional information relevant to this request is available in the other requests on the Common Cold entitled Zinc; Vitamin C; Antihistamines; Anticholinergics; Alpha Agonists; Echinacea; NSAIDs; Steam Inhalation.

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Steam Inhalation Common Cold

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The Problem Submitted for ARIF to Advise Upon:

What treatments have been shown to be effective in the treatment of the common cold?

Question Reformulated

Due to the breadth of this question, we focused our attention on those interventions for which there was a substantial body of evidence on their effectiveness, and on those that appeared to have a positive effect. Interventions excluded because of a lack of research evidence included mast cell stabilisers, iodine, guaifenesin, glucocorticoids, interferon and other antiviral drugs. Antibiotics were also excluded as a Cochrane review provided reliable evidence of no effect.

Reviews Identified

None.

Trials Identified

- Saketkhoo K et al. Effects of drinking hot water, cold water and chicken soup on nasal mucus velocity and nasal airflow resistance. Chest 1978;74(4):408-410
- Cohen BM and Dressler WE. Acute aromatics inhalation modifies the airways. Effects of the common cold. Respiration 1982;43:285-293
- Ophir D and Elad Y. Effects of steam inhalation on nasal patency and nasal symptoms in patients with the common cold. American Journal of Otolaryngology 1987;8(3):149-153
- Tyrell D et al. Local hyperthermia benefits natural and experimental common colds. BMJ 1989;298: 1280-1283

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Comments

A large number of trials were examined which related to the inhalation of steam, sometimes with added aromatics. The majority of these did not demonstrate any benefits over placebo or no treatment. Those cited are those with positive results, but it is important to note that they are generally methodologically weaker. Common sense suggests that the benefits of steam inhalation will be the short term relief of

symptoms but the majority of studies did not evaluate this, investigating instead the effects of steam inhalation in the longer term on the duration and severity of the cold. Tyrell et al did attempt to measure the short term effects but only detected very small benefits over what was a very similar intervention in the control group.

Additional information relevant to this request is available in the other requests on the Common Cold entitled Zinc; Vitamin C; Antihistamines; Anticholinergics; "Over-the-Counter" Remedies; Alpha Agonists; Echinacea; NSAIDs.

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Vitamin C
Common Cold

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The Problem Submitted for ARIF to Advise Upon:

What treatments have been shown to be effective in the treatment of the common cold?

Question Reformulated

Due to the breadth of this question, we focused our attention on those interventions for which there was a substantial body of evidence on their effectiveness, and on those that appeared to have a positive effect. Interventions excluded because of a lack of research evidence included mast cell stabilisers, iodine, guaifenesin, glucocorticoids, interferon and other antiviral drugs. Antibiotics were also excluded as a Cochrane review provided reliable evidence of no effect.

Reviews Identified

- Douglas RM, Chalker EB, Treacy B. Vitamin C for the common cold (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

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Comments

This is a reasonably well-conducted review with a meta-analysis, which may not have been appropriate for certain outcomes given the small number of studies reporting them. The main weakness of the review lies within the fact that it attempts to reanalyse the results of two existing reviews and, as a result, some aspects of the methods are not sufficiently well described.

Nevertheless, the conclusions that there is no evidence to support the use of Vitamin C to prevent colds, but that it may be of some benefit in reducing the duration of cold symptoms, are probably justified. The heterogeneity around the different dosages evaluated by the included studies means that more research is required to help establish the relationship between dose and any therapeutic benefit.

Additional information relevant to this request is available in the other requests on the Common Cold entitled Zinc; Antihistamines; Anticholinergics; "Over-the-Counter" Remedies; Alpha Agonists; Echinacea; NSAIDs; Steam Inhalation.

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Zinc
Common Cold

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The Problem Submitted for ARIF to Advise Upon:

What treatments have been shown to be effective in the treatment of the common cold?

Question Reformulated

Due to the breadth of this question, we focused our attention on those interventions for which there was a substantial body of evidence on their effectiveness, and on those that appeared to have a positive effect. Interventions excluded because of a lack of research evidence included mast cell stabilisers, iodine, guaifenesin, glucocorticoids, interferon and other antiviral drugs. Antibiotics were also excluded as a Cochrane review provided reliable evidence of no effect.

Reviews Identified

- Marshall I. Zinc for the common cold (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software.

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Comments

This is a reasonably well-conducted systematic review with a meta-analysis. The statistical pooling of the results may, however, have been inappropriate due to the degree of statistical and clinical heterogeneity between the included studies, and the small number of studies that measured certain outcomes. What the review lacks in terms of its own methodological rigour is partly compensated for by the quality of the included studies, which are all randomised controlled trials which scored "medium" to "high" in the validity assessment. The author's conclusion that there is no strong evidence to support the effectiveness of zinc in the common cold, and that more research is required, is probably justified. It is also worth noting that many of the included studies report a fairly high rate of unpleasant side effects associated with the intervention.

Additional information relevant to this request is available in the other requests on the Common Cold entitled Vitamin C; Antihistamines; Anticholinergics; "Over-the-Counter" Remedies; Alpha Agonists; Echinacea; NSAIDs; Steam Inhalation.

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Screening Tools (WILSTAAR, CHAT)
Speech and Language Therapy
Communication Disorders in Pre-School Children

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The Problem Submitted for ARIF to Advise Upon:

Community Trusts are seeking an effective screening tool for communication disorder in children as part of the pre-school child health surveillance programme. The local Trust was particularly interested in WILSTAAR and CHAT. Are these tools effective?

Question Reformulated

The key components of this question are:

- Intervention: Screening for communication disorders + speech/language therapy.
- Population: Pre-school children, especially those 9 to 18 months old, attending for routine infant development checks.
- Outcomes: "Normal development" particularly with respect to speech and language; possible adverse effects, including stigmatisation; and costs. Each of these considered for: true positives; true negatives; false positives; false negatives.

In the absence of any randomised trials assessing screening programme effectiveness, two specific sub-questions were addressed:

1. What are the effects/effectiveness of speech and language therapy on those with communication disorders likely to be identified by pre-school screening (and are there any adverse effects of speech and language therapy on those who do not truly have a communication disorder?)
2. What are the test performance characteristics (sensitivity, specificity, positive and negative predictive values) of potentially useful early pre-school screening tools for communication disorders e.g. Ward Infant Language Screening Test?

Reviews Identified

Question 1:

- Nye C, Foster SH, Seaman D. Effectiveness of language intervention with the language learning disabled. Journal of Speech and Hearing Disorders; 1987:52:348-357
-

Pearson VA. Speech and language therapy: is it effective? Public Health 1995;109:143-153

- Enderby P, Emerson J. Does Speech and Language Therapy Work? A Review of the Literature. London: Whurr Publishers Limited, 1995. pp 180.

Question 2:

No Reviews identified.

Other Literature Identified

Prospective comparison of test accuracy

- Ward S. The predictive validity and accuracy of a screening test for language delay and auditory perceptual disorder. European Journal of Disorders of Communication 1992;27:55-72

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Comments

Question 1:

Taken together, the three reviews identified indicate that the main limiting factot in assessing the effects and effectiveness of speech and language therapy generally is availability of relevant and valid research. Although in many applications of speech and language therapy, the available research is tentatively positive regarding effectiveness, in communication disorders likely to be identified by positive screening at around 1 year of age there are particular problems with respect to the natural history and possible spontaneous resolution which make any statements about likely effectiveness very difficult indeed. These and other important issues concerning the assessment of the effectiveness of speech and language therapy in children with communication disorders are usefully discussed in Chapter 3 of the book by Enderby P, Emerson J.

Question 2:

Although subject to several biases the results of this study do give an early indication that this screening tool has potential. However it would need considerable further evaluation before routine application in practice.

Overall the available research suggests it would be reasonable to commission this initiative, provided this was done in the context of a rigorous research evaluation, ideally a randomised controlled trial of the screening programme. The uncontrolled introduction of such a screening programme is not supported given the considerable uncertainty about likely effectiveness and cost effectiveness.

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Health Promotion
Community Development Programmes

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The Problem Submitted for ARIF to Advise Upon:

Are Community Development Programmes an effective way of empowering committees?

Question Reformulated

Community development programmes were defined as health promotion initiatives which were developed by local communities for those communities, in which the health professional plays the role of supporter or facilitator. The desired outcomes of these programmes are complex, and may not be known at the outset, but typically include increased self-reliance, and decision making powers resulting from the process of community development.

Reviews Identified

- Ploeg J, Dobbins M, Hayward S, Ciliska D, Thomas H and Underwood J. Effectiveness of Community Development Projects: systematic overview. Ontario Health Care Evaluation Network/Public Health Effectiveness Inventory Project/Hamilton Teaching Health Unit. 1996.

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Comments

One systematic review was identified which summarises the descriptive accounts of a number of community development projects. Despite the lack of any truly experimental primary research, on what is potentially a very elusive topic, the review achieves a high degree of systematicity in its approach. The only area of possible concern is that of the comprehensiveness of the search strategy. For example, the studies included in the review display a degree of bias towards the North American literature.

Nevertheless, the findings and results of the review are helpful. The reviewers take an innovative approach towards the appraisal and synthesis of an extremely heterogeneous group of case studies. They conclude that community development projects can have a positive effect on a wide range of outcomes, including building the capacity of communities and individuals to identify and address their own issues of concern. However, because of the difficulties inherent in the evaluation of such projects, which extend beyond those of the evaluation of health promotion in general, a high degree of uncertainty persists.

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Elderly Physically Frail People Community Health Teams

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The Problem Submitted for ARIF to Advise Upon:

Is there any evidence that the provision of a community health team for older people with physical health problems and frailty would benefit service users?

Question Reformulated

A community health team for the elderly was defined as: A group composed of a consultant physician, secretarial support, a health visitor, an occupational therapist and physiotherapists as core members whose purpose is to provide specialist care for the elderly in a way where there is much greater integration with primary care and social services. The group has responsibility for care of the elderly in a specific area.

There were no systematic reviews or trials relating to the effects of such a team, thus a search for reviews of interventions which might be applied by such a team was conducted. One systematic review seemed particularly relevant.

Reviews Identified

- Stuck AE, Siu AL, Wieland D et al. Comprehensive geriatric assessment: a meta-analysis of controlled trials. Lancet 1993;342:1032-36

RCTs Identified

In addition to the 28 trials identifiable through the meta-analysis by Stuck et al.

- Weinberger M et al. Does increased access to primary care reduce hospital re-admissions? New England Journal of Medicine 1996;334:1441-7
- Bula CJ et al. Community physicians' cooperation with a program of in-home comprehensive geriatric assessment. Journal of the American Geriatric Society 1995;43:1016-20
- Stuck AE et al. A trial of annual in-home comprehensive geriatric assessments for elderly people living in the community. New England Journal Medicine 1995;333:1184-9
- Martin F et al. A randomized controlled trial of a high support hospital discharge team for elderly people. Age & Ageing 1994; 23:228-234
- Hansen FR et al. Geriatric follow-up by home visits after discharge from hospital: a randomized

controlled trial. Age & Ageing 1992;21:445-450

- Townsend J et al. Reduction in hospital readmission stay of elderly patients by a community based hospital discharge scheme: a randomised controlled trial. British Medical Journal 1988;297:544-7

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Comments

Stuck AE et al is particularly useful, indicating at least one set of activities, comprehensive geriatric assessment, which might be a prominent and effective feature of a CHTE's work (or indeed any other multidisciplinary group with responsibility for care of the elderly). Although the review is systematic in approach, it does require careful interpretation, particularly the credence which should be given to the sub-group analyses made. Further, it is increasingly in need of up-dating to take into account new research published since 1992/3.

The principle value of the list of RCTs is to indicate other aspects of the care of the elderly which have been rigorously evaluated. It is tempting to try and read a lot into the results of individual studies, for instance the recent publication by Weinberger et al, but we would warn against this. The variation in results from one study to the next is likely to be particularly pronounced in this area because the interventions are complex - that is they are difficult to standardise. This taken together with random variation which can occur in any area of research, mean that the most reliable conclusions can only be drawn by observing the pattern of results from many studies examining related interventions, and this requires a systematic review. Only in this situation is it possible to begin to understand whether inconsistency in results from one study to the next is what one would expect due to the play of chance or due to the way that the study has been conducted or due to subtle differences in the nature of the intervention itself or due to the general characteristics of the population to which the intervention has been applied.

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Community Hospitals

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The Problem Submitted for ARIF to Advise Upon:

Is there any evidence on the effectiveness of community hospitals within the UK for the delivery of services such as rehabilitation, GP beds, and nurse run clinics for chronic conditions such as diabetes and epilepsy?

Reviews Identified

- Chappel D. Purchasing Community Hospitals in Buckinghamshire. Part II Thesis, Faculty of Public Health Medicine 1994

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Comments

This was the only review identified which was directly relevant, but there were many other reviews contributing indirectly. It is generally systematic in approach, particularly with respect to the ascertainment of original research. Thus this review provides strong support for the paucity of research in this area. It further demonstrates that the research which is available is highly prone to bias and that the degree to which the research is generalisable to the concept of community hospitals today needs to be carefully considered.

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Continuous Hyperfractionated Accelerated Radiotherapy (CHART) Lung Cancer (Non-Small Cell Lung Cancer - NSCLC)

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of Continuous Hyperfractionated Accelerated Radiotherapy (CHART)?

Question Reformulated

Given that CHART has been suggested as a treatment for a number of malignancies, we focused on ascertaining the effectiveness of CHART versus conventional radiotherapy in the treatment of lung cancer.

Reviews Identified

- NHS Centre for Reviews and Dissemination. Management of lung cancer. Effective Health Care 1998;4(3):1-12
- Clinical Outcomes Group. Guidance on commissioning cancer services. Improving outcomes in lung cancer. The research evidence. Leeds: NHS Executive, 1998

Trials Identified

- Saunders M, Dische S, Barrett A et al. Randomised multicentre trials of CHART vs conventional radiotherapy in head and neck and non-small-cell lung cancer: an interim report. British Journal of Cancer 1996;73:1455-62
- Saunders M, Dische S, Barrett A, Harvey A, Gibson D, Parmar M. Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial. CHART Steering Committee [see comments]. Lancet 1997;350:161-5
- Saunders M, Dische S, Barrett A et al. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering Committee. Radiotherapy & Oncology 1999;52(2): 137-48

Other Literature Identified

- Saunders MI, Rojas A, Lyn BE, Pigott K, Powell M, Goodchild K, Hoskin PJ, Phillips H, Verma N. Experience with dose escalation using CHARTWEL (continuous hyperfractionated accelerated

radiotherapy weekend less) in non-small cell lung cancer. British Journal of Cancer 1998; 78(10): 1323-8

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Comments

We identified an Effective Health Care Bulletin (EHCB, 1998) on the management of lung cancer, which was based on a series of interlinked systematic reviews undertaken for the Department of Health (NHS Executive, 1998). One of the reviews was on CHART for non-small cell lung cancer (NSCLC). It was obvious from this review and our own searches that only one RCT of CHART versus conventional radiotherapy for lung cancer has been undertaken (Saunders et al 1996 & 1997). The trial was multicentred and involved 563 patients with inoperable NSCLC confined to the thorax who were followed for a period of up to two years. The methodology employed in the trial appears to have been robust.

The findings were that CHART significantly reduces mortality compared to conventional radiotherapy. Acute adverse effects were similar between treatments, although early adverse events developed more rapidly and were more severe with CHART, but did resolve relatively quickly. Although it is more expensive than conventional therapy, due to the need for both access to treatment outside normal working hours and (near) hospital accommodation, a cost effectiveness evaluation reported in the EHCB suggests that CHART can be highly cost effective.

In the course of our reading around this topic we came across a new protocol based on CHART, called CHARTWEL (CHARTWeekEndLess) (Saunders et al 1998). This protocol gives a similar dose and a similar number of fractions to CHART except that radiotherapy is not given over the weekend. We have identified no studies that directly compare CHARTWEL with CHART or conventional radiotherapy, and as such this protocol has yet to be evaluated. However, should CHARTWEL prove to have similar efficacy to CHART, then it is likely that it may be more cost effective, given that access to radiotherapy treatment will not be required at the weekend.

In summary, CHART for lung cancer has only been evaluated in one well conducted RCT. From this study it does appear to be a promising treatment which is more effective than conventional radiotherapy in reducing mortality in patients with inoperable NSCLC.

This is an area prone to need for regular updating as new information is continually becoming available.

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Continuous Positive Airways Pressure (CPAP) Sleep Apnoea

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of continuous positive airways pressure for obstructive sleep apnoea?

Reviews Identified

- Wright J, White J. Continuous positive airways pressure for obstructive sleep apnoea (Cochrane Review). In: The Cochrane Library, Issue 3, 2000. Oxford: Update Software

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Comments

In general the identified review, which was last updated March 1998, is a well-conducted systematic review, the conclusions of which can be relied upon. The review found that despite limitations in the methodology of included trials and the small numbers of patients studied, continuous positive airways pressure (CPAP) appears to be more effective than placebo in improving some quality of life measures for people with sleep apnoea. CPAP also appears more effective than oral appliances at improving respiratory disturbance. Patients also seem to prefer CPAP treatment to placebo but prefer treatment with oral appliances to CPAP.

It should be noted that the conclusions of this version of the review are considerably more optimistic about the benefits of CPAP on comparison with earlier versions, such as that published in the BMJ (Wright J et al, BMJ 1997; 314: 851-860).

A number of reviews and health technology assessments are currently in progress on this topic, including a further update of the Cochrane review.

This is an area prone to need for regular updating as new information becomes available.

Additional information relevant to this request is available in the requests entitled Surgery/Sleep Aonoea.

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Osteo-odonto-keratoprosthesis Corneal Disease

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of osteo-odonto-keratoprosthesis in the management of severe corneal disease?

Reviews Identified

- Marchi V et al. Osteo-odonto-keratoprosthesis. Description of surgical technique with results in 85 patients. Cornea 1994;13(2):125-130

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Comments

There were no reviews identified. The single relevant paper appraised describes a case-series. In order to accept the results of this as valid the natural history must be sufficiently clear that there is no necessity for a control group. This did not seem unreasonable. Having accepted that a case-series would give a reasonable measure of the effects of a procedure in this situation, our appraisal was as follows:

1. As in studying any cohort, all those entering the case-series should do so at a similar stage in the course of their disease. In this article we had little information beyond the range of conditions for which the procedures were undertaken. We were left to assume that the patients at entry had no functional sight.
2. Further, all those entering a case-series should be included in the final analysis. In this article we had no information by which to make a judgement on whether this was the case. Although 85 patients were accounted for in the analysis at 10 years, we did not know whether there were truly 85 at the outset. There is always a natural tendency to ignore those who are lost to follow-up when considering a case-series retrospectively.
3. It is always important to ensure that the outcome is assessed as objectively as possible, ideally independently of those undertaking the procedure. Again we had little detail about the method of assessing visual acuity, standardisation of which might have been very important where the observations had taken place over a very long period. However, one could reasonably assume that testing visual acuity was likely to be objective, which gives some assurance that any change in outcome observed is not entirely due to a placebo effect.

Thus this study was open to bias and the possibility exists that the reported outcomes overestimate the true effect.

Bearing the above in mind, the key points arising from this article are:

- That this procedure is one of last resort, where other procedures such as corneal grafting cannot be employed. Table 1 in the article provides useful information on some of the conditions where this may apply.
- The procedure seems to be effective in restoring useful sight (assuming the patients in the series started off with no sight), but this deteriorates with time. It would be useful to know whether changes in visual acuity were translated into improved quality of life and daily activities.
- That complications related to the procedure, such as secondary glaucoma, are not uncommon.

In conclusion, this article gives some reassurance that there is a reasonable chance of improvement with this operation, provided the operation described is the same as that being proposed and provided and patients satisfy the sort of criteria suggested in this article. In addition it gives some useful background on the nature of the procedure and an indication in the references to some old case-series of British patients. (Choyce DP. Results of keratoprosthetics in Britain. Ophthalmic Surgery 1973;4:23-32.)

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Archived ARIF Request

Mental Health Counselling

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in September 1997

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of counselling services in general and in the primary care setting in particular?

Reviews Identified

- Wessex Institute of Public Health Medicine. Counsellors in Primary Care. Winchester: Wessex Institute of Public Health Medicine, 1995 (DEC Report No.40)

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Comments

No reviews were identified on the effectiveness of counselling services in general.

The review recommended is not a systematic review and its results should be treated with caution. Nevertheless, it represents a well-structured review of the key literature on the role of counsellors in primary care, which clearly sets out all the important issues.

At the time the report was produced there was a paucity of robust research in this area and as a result the Committee came to a "not proven" verdict. The report does, however, suggest that counselling services in primary care are potentially cost-effective, particularly when the counsellors are well-trained and experienced, and the primary care team exhibits good multi-disciplinary working.

Although it is not directly relevant readers may also wish to look at the Effective Health Care Bulletin on The Treatment of Depression in Primary Care (March 1993, Number 5).

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This is an area prone to need for regular updating as new information is continually becoming available. Readers may wish to note that some primary research on this topic has been commissioned as part of the national HTA programme.

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Counselling
Domestic Violence

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of counselling for the victims of domestic violence?

ARIF has undertaken two related requests on domestic violence:
What is the effectiveness of brief interventions including alcohol counselling services in reducing the frequency and severity of domestic violence?
How effective is routine screening for domestic violence by healthcare professionals?

Reviews Identified

- Klevens J, Sadowski L. Domestic violence towards women. Clinical Evidence 2005;13:1-3 http://www.clinicalevidence.com/ceweb/conditions/who/1013/1013.jsp
- Wathen CN, MacMillan HL. Interventions for violence against women: scientific review. JAMA 2003;298(5):589-600

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Comments

These are both well conducted systematic reviews. The chapter from Clinical Evidence (Klevens and Sadowski) is useful because it is up-to-date (search date December 2004) and it allows counselling to be considered in the context of other interventions targeted at female victims. It defines these clearly, which is helpful as the distinction between counselling in its various formats and advocacy is potentially important. Two minor problems are that it does not cover interventions targeting males and the links between the included studies and recommendations are sometimes unclear. The JAMA paper (Wathen and MacMillan) deals better with each of these issues, but the search date is December 2002.

Both systematic reviews indicate that limited amounts of rigorously conducted effectiveness research are the main barrier to drawing firm conclusions. Caution must thus be exercised in defining any intervention in this area as definitely ineffective as we are dealing with absence of evidence. What does seem clearer is that counselling combined with other interventions, for instance mentoring, is probably more effective than counselling alone. Further, careful account needs to be taken as to the nature of counselling, as some types apparently offer greater benefits than others. Cost-effectiveness is

inevitably raised as an ancillary question.

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Street Lighting Crime

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of improved street lighting on reduction in crime?

As part of the West Midlands Crime GRIP initiative, ARIF was asked to appraise the best available systematic review on this topic.

Reviews Identified

- Farrington DP, Welsh BC. Effects of improved street lighting on crime: a systematic review. Home Office Research Study 251. London: Home Office Research, Development and Statistics Directorate, August 2002.

  A Campbell Collaboration review updating this review is planned.

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Comments

The review by Farrington and Welsh is an extremely valuable summary of research (mainly controlled-before after studies, rather than randomised controlled trials) on this topic.

A detailed appraisal of the review is available from ARIF on request. There are some shortcomings with the review method, the most important of which were:

- No detailed assessment of included study quality
- Limited exploration of the reasons for the marked variation in the results of one included study to the next (heterogeneity)

In consequence, some care needs to be exercised in interpreting and applying the stated conclusions of the review, particularly those based on the numerical outputs of the meta-analysis.

Despite this, the review does present convincing evidence that qualitatively street lighting reduces crime, although the results probably only apply to areas where the risk of crime is high.

However, with respect to implementation there are further issues which commissioners would probably need to explore:

- What is the precise nature of the improvements in street lighting needed to bring about reduction in crime (the review provides little information on this)?
- Does the nature of the improvement determine how much crime is reduced by?
- Is reduction in crime the only possible beneficial or disbeneficial effect which needs to be taken into account?
- Are the net benefits of improved street-lighting worth the costs?

Further research, including up-dating of the review, is required and may improve the quantity and quality of information on which to make decisions on this topic in the future.

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Restorative Justice Crime

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of face-to-face restorative justice on repeat offending and victim satisfaction?

Restorative Justice (RJ) encompasses a range of informal justice practices which emphasise offenders taking responsibility for their actions and trying to repair harm to victims affected by their crime. It requires the direct participation of offenders and their victims in decisions about how best to repair the harm caused by the crime. The face-to face form of RJ involves a conference where the offender and the victim are present and all participants deliberate about what actions the offender could take to repair the harm.

As part of the West Midlands Crime GRIP initiative, ARIF was asked to appraise the systematic review below on this topic.

Reviews Identified

- Strang H, Sherman LW. Effects of face-to-face restorative justice on repeat offending and victim satisfaction. A systematic review for the Campbell Collaboration (May 16 2003).

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Comments

The review represents an important piece of work and is a valuable resource for those examining strategies to reduce re-offending and the impact of crime.

The review is a work in progress and provides a good starting point for understanding the evidence base for restorative justice. In general the review appears to have been conducted systematically, although some methodological detail is under-reported and there are some methodological limitations.

Due to heterogeneity at several levels, it is difficult to arrive at any conclusions on the effectiveness of restorative justice conferences in reducing re-offending. There appears to be some benefit for victims, however, maintenance of satisfaction or benefit in reducing other consequences of crime i.e. anxiety or post traumatic stress are unknown. It is clear that restorative justice may be difficult to implement because of non-compliance by offenders and victims. Additional robust primary research examining the effectiveness of restorative justice interventions on a variety of offences and offenders is required

and some is already underway in the UK.

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SYSTEMATIC REVIEW OF EFFECTIVENESS OF TEACHING CRITICAL APPRAISAL

AUGUST 2000

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EXECUTIVE SUMMARY

Background

Critical appraisal is the process of assessing and interpreting evidence by systematically considering its validity, results and relevance to an individual's work. Due to the increasing volume of biomedical publications and the variable quality of research, the importance of critical appraisal skills has been emphasised for all those involved in the process of transferring research findings into practice, including doctors and other health care professionals, health care managers and health care consumers. Within the last decade critical appraisal has been added as a topic to many medical school and Royal College curricula, and several CPD ventures have been funded to provide further training.

Objective

To assess whether teaching critical appraisal has beneficial effects on health care workers and patients, considering outcomes of patient health, professional behaviour that is up-to-date, decision-making behaviour, critical appraisal skills, knowledge and attitudes, and increased satisfaction.

Methods

A systematic review was undertaken of studies comparing outcomes after critical appraisal training with outcomes before training, or with those of another group not receiving training. Studies of all designs from which these comparisons could be derived were considered. Only studies recruiting healthcare related students, professionals and consumers were included, where the training intervention was fitted a pre-stated definition confirming that it was (a) an educational intervention, and (b) that the material delivered was critical appraisal.

Data sources

Ten electronic databases and the world-wide-web were searched, major medical education centres were contacted, experts were contacted through mailing lists, and references of retrieved papers and articles were scanned.

Study selection, data extraction and validity assessment

Studies were independently assessed by 3 reviewers for eligibility. Data extraction and validity assessment were undertaken by 1 reviewer and double-checked. It was noted where data were

ambiguous or unclear. The validity of each study was considered at the level of each outcome for each study. Major threats to validity were noted arising through design, execution and analysis.

Data synthesis

A qualitative approach to data synthesis was used for most outcomes, due to the diversity of outcome measures, interventions, and inadequate reporting. The conclusions were driven by evidence of consistency of effect, size of effect and statistical significance. Studies thought to have a major threat to their validity were excluded in a sensitivity analysis.

Results

Of 4004 articles located, 137 were thought to be potentially relevant. Sixteen of these met the inclusion criteria, 12 from peer reviewed journals, and 4 available only in an unpublished form. One study was an RCT, 8 were non-randomised between group studies, and 7 were before-and-after studies. None of the studies assessed patient health or satisfaction outcomes.

The impact of critical appraisal teaching on clinicians' behaviour (principally reading behaviour) was mixed. Of the eight comparisons for this outcome six had major threats to validity. Most, but not all, of the comparisons showed benefit of critical appraisal teaching, two acting in the opposite direction.

Critical appraisal teaching was seen to consistently increase skills: fourteen of the sixteen comparisons for this outcome showed a positive effect. The strength of the effect remained when self-assessed comparisons were removed. Five comparisons were thought not to be subject to major flaws: four of these indicated a benefit of critical appraisal teaching.

The strongest and most consistent impact of critical appraisal teaching was seen on knowledge outcomes: 7 of the 12 studies showed a statistically significant positive effect. However consideration of the size of the benefit revealed heterogeneity.

There were four comparisons of the impact on attitudes- all were positive, but it was not possible to separate out real effects from a tendency for participants to respond in a "desired" manner.

There were inadequate data to assess whether there was variation in outcome according to the mode of delivery of the educational intervention. Also, there was no convincing evidence that the effectiveness of the intervention varied according to the participants' background.

Conclusions

There is evidence that critical appraisal teaching has positive effects on participants attitudes, knowledge and skills, but there are gaps in the evidence as to whether it impacts on decision making or patient health, or on satisfaction. It is also unclear whether the size of benefit seen is large enough to be of practical significance, nor whether it varies according to participant background nor teaching method.

The evidence supporting all outcomes is weakened by poorly designed, executed and reported studies.

There was no usable evidence on the impact of teaching critical appraisal to health care consumers or lay audiences.

Implications for policy

This review provides reassurance to those who have invested in critical appraisal teaching activities that they are likely to have a positive impact. The evidence is not, however, sufficient to encourage further expansion of critical appraisal activities, due to limitations on its validity and significance in practice, and the total absence of results for important outcomes.

Recommendations for research

Further studies should be undertaken in partnership between adult educationalists and healthcare researchers to ensure studies are properly designed and valid outcomes are used.

It is of importance to assess the size of benefit of critical appraisal training to postgraduates/CPD, as this is where greatest investment is made. Such an evaluation should be large, randomised and assess outcomes and changes which are of significance in practice.

ABBREVIATIONS USED IN TEXT AND TABLES

Ä	Change	**Int**	Interns
95% CI	95% confidence interval	**ITS**	Interrupted time-series design
A	After	**m**	Months
B	Before	**MCQ**	Multiple choice question
BA	Before-after design	**MedSt**	Medical students
BG	Between groups	**Mult**	Multidisciplinary
CA	Critical appraisal	**MW**	Midwives
CASP	Critical Appraisal Skills Programme	**N/S**	Not stated
CAT	Critical appraisal teaching	**NHS**	National health service
CBA	Controlled before-after design	**NS**	not significant
CCT	Controlled clinical trial	**NTRAG**	North Thames Research Appraisal Group
CON	Controls	**QALY**	Quality adjusted life years
CPD	Continuing professional development	**R&D**	Research and Development
CT	Clinical trial	**RCT**	Randomised controlled trial
d	Day	**Re**	Residents
E/A	Externally assessed	**S/A**	Self-assessed
EB	Evidence based	**w**	Weeks
EBM	Evidence-based medicine	**WG**	Within groups
EPOC	Effective Practice and Organisation of Care	**WMD**	Weighted mean difference
GPs	General practitioners	**y**	Years
h	Hours		

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APPENDICES

1 Background information

1.1 What do we mean by critical appraisal

Although precise wording varies, there is broad agreement on the definition of critical appraisal being:

"The process of assessing and interpreting evidence *(usually published research)* by systematically considering its validity *(closeness to the truth)*, results and relevance to the individual's work. "

This is the definition we have used in this systematic review. However, before proceeding with our report, by way of introduction we briefly consider the history and development of the premise that identifying the strengths and weaknesses of a piece of research is a valuable activity, and teaching individuals how to do this is similarly worthwhile.

1.2 The relationship of "critical appraisal" to other associated terms

There are a number of terms which are so closely associated with critical appraisal that is important to consider whether they are synonymous or represent overlapping entities.

Critical reading. This term appears to be used interchangeably with critical appraisal. Authors referring to this concept sometimes emphasise that choosing material to be read, and identifying the reasons for reading it, are as important skills as determining what the strengths and weaknesses of any individual piece of material are. However, critical appraisal also usually emphasises the need to formulate a clear question and choose a piece of information most likely to provide an accurate answer to a given question, so differences in practice are likely to be minimal.

Journal clubs. These are meetings whose original purpose was to encourage reading of published research and stimulate related clinical discussion [1]. Subsequently it was recognised that such regular meetings could be harnessed to teach or reinforce critical appraisal skills. However, this purpose is not sufficiently exclusive or universal that journal clubs could be considered synonymous with teaching critical appraisal.

Epidemiology and statistics. These are the basic sciences which the teaching of critical appraisal is often said to draw on, epidemiology being, "The study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems" [2], and statistics being, " A blend of mathematics, logic and judgement" [3]. Although in both cases

there is emphasis on understanding limitations of studies of particular designs there is clearly much more to both these subjects than critical appraisal. Thus although providing useful background, a general course in epidemiology and statistics is unlikely to provide in depth skills in critical appraisal. Further, the emphasis in epidemiology and statistics is generally on doing research, rather than using it as in critical appraisal.

Clinical epidemiology and biostatistics / medical statistics. A very close link between these two disciplines and critical appraisal is also claimed. Although debated, in broad terms they can both be described as the application of the sciences of epidemiology and statistics to clinical activities. The same comments about there being more to clinical epidemiology and biostatistics / medical statistics than critical appraisal apply, but for clinical epidemiology in particular, the ethos of critically appraising any information is so central, that courses in clinical epidemiology are also very likely to cover critical appraisal skills development.

Evidence-based medicine (EBM). This is, "The conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients." [4] Although this has it origins in clinical epidemiology, its components are much more specific. Five elements of key importance are identified, the third being the critical appraisal of evidence, " for its validity (closeness to the truth) and usefulness (clinical applicability)." Thus teaching EBM usually implies teaching of critical appraisal, albeit alongside other skills, especially question identification and literature retrieval.

Evidence-based clinical practice, healthcare and patient choice. These are the application of the skills in the same key areas originally developed in EBM, to other important groups involved in health care decision making [5]. Although care needs to be taken that the original principles of EBM are being adhered to, the prefix EB in the context of teaching will usually imply teaching of critical appraisal too.

1.3 The history of critical appraisal and its further development

Although it is easy to falsely interpret the existence of very early examples of rigorous research as indicating the origins of advocacy and facilitation of greater research use, it is true that critical appraisal and related phenomena have a long history. However, importantly, it is also clear from general surveillance of the literature, that critical appraisal has been subject to development, starting from the point where Sir William Osler and others used journal clubs, "for the purpose and distribution of periodicals to which he could ill afford to subscribe as an individual" in the 19th century [1]. Key stages, the earliest of which would not constitute critical appraisal as we have defined it, include:

- Identification of the need to facilitate access to and consideration of research.

- Recognition of the variable quality of research and the need to be able to identify shortcomings, leading in turn to critical appraisal being regarded as the science of trashing research [6, 7].
- Development of checklists to make the process of appraisal more structured, explicit and straight-forward [8].
- Emphasis on application of research findings. In particular changing the main aim from identifying as many things as possible wrong with a piece of research to making a balanced assessment of the strengths as well as the weaknesses of the research and applying it within these limits, in the context of a particular patient or group [9].
- Firmly embedding critical appraisal in a wider package of skills eg question identification and literature retrieval which together help the use of research, rather than the expectation that critical appraisal alone will achieve this [4].
- Recognition that the approach is of value to, and can be adapted for use by, all those potentially involved in making health care decisions including: nurses; professions allied to medicine; social workers; healthcare managers; and patients [10, 11].

The important role played in these developments by McMaster University in Canada should be highlighted.

Although not directly part of the development of critical appraisal, the rise of systematic reviews and meta-analysis has undoubtedly also had an important influence by:

- Increasing the prevalence of a type of research that had previously been rare, so requiring de novo development of a specific checklist for this type of research.
- Focusing attention on the importance of examining individual studies in the context of others.
- Emphasising that the process by which research is selected for appraisal and collected can introduce as much if not more bias than was present in the original studies.
- Providing some solutions to the problem of how an individual faced with an exponentially increasing volume of biomedical research literature and limited time can identify all relevant literature on a particular subject.

This account of the development of critical appraisal is not complete by any means, but should be sufficient to emphasise that critical appraisal is not a static entity. Indeed the development continues in many areas, such as extending the approach to other types of evidence e.g. qualitative research and exploring means to improve the structured integration of different streams of information into a final decision. An unfortunate corollary of this continuing evolution is that precision is required in defining the term “critical appraisal” in particular. At any point in time it is clear that the term may be being used in different ways by different authors and commentators.

1.4 The rationale for critical appraisal

Getting the "right" answer more often. The inputs used to inform decisions in health care come from many different sources. For instance, medical decision making involves an amalgam of information arising from the history, examination and investigation of patients, basic clinical sciences (anatomy, biochemistry, physiology, pathology and social sciences), clinical experience (the practitioner's own and that of colleagues), information from textbooks and lastly empirical research findings [4]. As far as external information, not specific to a given patient with a given problem, is concerned, there has long been a concern that empirical research (careful observation of what has actually happened to groups of patients, communicated in published reports) has been underused and overlooked. Although long suggested [12], it is only recently that the ramifications of failure to systematically incorporate the findings of empirical research into practice have emerged clearly. The best publicised example is the delay in widespread implementation of the use of thrombolysis in acute myocardial infarction [13].

One key rationale for critical appraisal has thus been to increase the use of existing empirical research to improve the accuracy of health care decisions. However, just as the literature shows that the term "critical appraisal" has different meanings, so it makes clear that the rationale for critical appraisal (and implicitly the outcomes most greatly valued) are also very varied. Depending particularly on the person or group undertaking or supporting critical appraisal teaching, they vary as follows:

- *Making epidemiology and statistics valued.* In response to apparent lack of interest in these subjects by medical undergraduates, critical appraisal in relation to actual research articles has sometimes been introduced specifically as a means to improve the effectiveness with which epidemiology and statistics are taught [14].
- *Contributing to more effective and efficient means of keeping up-to-date.* This is particularly emphasised by EBM to help overcome the problems, already alluded to, that many sources of information relied on by clinicians, theories from basic sciences, advice from colleagues and text-books are out-of-date [4]. Critical appraisal is one skill allowing continuing self-directed learning throughout a career in health care.
- *Changing the hierarchical nature of medical practice*. Enabling individuals, often "juniors", to more independently identify the "best" course of action, will inevitably destabilise any system based on patronage [15]. Thus, the important objectives of teaching critical appraisal to non-clinicians (especially health care managers and patients) may include empowering and challenging orthodoxy, even if they are not explicitly stated.
- *Raising awareness of the importance of critical appraisal.* An important rationale may not be to turn all participants into skilled appraisers of research, but to increase the appreciation of the importance and need for high levels of such skills in those "professionals" directly involved in making health care decisions [10].

- *Encouraging wider involvement in doing research*. Irrelevance of research is often referred to as a barrier to its use. This in turn may be connected with a perception by many practitioners that research is remote and something over which they have no influence [16]. Thus, an important rationale for teaching critical appraisal skills might not only be to improve research uptake, but by breaking down any mystique, stimulate direct involvement in research activity, so creating wider ownership of the research which practitioners are expected to act upon.
- *Improving the efficiency of health services*. A spectre which has often been raised is that the rationale of critical appraisal and associated activities such as EBM, particularly when promulgated by central authorities, is to control costs [17]. There are probably few politicians or policy-makers who actually believe this. However, a more widely held rationale for encouraging critical appraisal not just by practitioners but healthcare managers too, is as a way of supporting shifts of investment from areas of activity which are ineffective, to ones which are effective [5]. With the increasing realisation that health care activities rarely fall clearly into effective and ineffective categorisation, this rationale has been further refined to preferentially pursue activities which generate most health gain for a given amount of investment [18]. In the UK, central support of improved critical appraisal skills as part of wider programmes has been manifest throughout the 1990's through initiatives such as, "Promoting clinical effectiveness" [19]. Commitment to the use of sound evidence in patient care has been maintained in a recent government health White paper and its sequelae [20]. However, the need to marry this with quality assurance (including monitoring and maintaining professional standards) and the need for responsibility for quality of care to be taken as equally seriously by senior managers as clinicians, has also been recognised, resulting in current emphasis on "clinical governance" [21]. Greater consistency of advice on the meaning of research is also being sought via the establishment of the National Institute of Clinical Excellence.

1.5 Alternative approaches to teaching critical appraisal

The preceding paragraphs emphasise that there is variation in the content and rationale of critical appraisal. This in turn invites consideration of whether the "teaching" of critical appraisal skills has undergone its own development cycle.

Superficially it appears that this is not the case, the general focus still being on whether the subject should be taught, as a prelude to justifying the continued teaching of critical appraisal to existing and extended target audiences. However, below the surface it becomes apparent that in parallel with the evolution of ideas on what constitutes critical appraisal, there has also been gradual percolation of research on different teaching methods. The clearest contrasts are between early attempts of epidemiologists teaching clinicians critical appraisal skills through series of lectures supplemented by seminars [22], to approaches heavily influenced by adult-learning theory, emphasising problem-solving

approaches in facilitated small groups [23]. It is only recently that articles have explicitly addressed whether the particular approach adopted to teaching critical appraisal skills has any theoretical basis [10].

Given the goal of greater use of empirical research by all those involved in making decisions on the provision of health care, it should also be acknowledged that teaching as many practitioners as many relevant skills of critical appraisal as possible may not be the most efficient way to proceed. An extreme alternative, is to concentrate on ensuring that existing sources of information, such as text-books are up-to-date, truly reflecting what is known from empirical research as well as theory. Targeting critical appraisal teaching on those most likely to influence other practitioners during training is a further variant on this theme. EBM acknowledges that practical constraints dictate that it may be necessary to "apply evidence-based summaries generated by others" [4].

1.6 How much critical appraisal and teaching of critical appraisal goes on already?

Although the sentiment running through the literature on critical appraisal and EBM is that too little critical appraisal is carried out by too few, there is little or no objective evidence quantifying this, particularly outside primary care. There has probably been increasing exposure to critical appraisal in examinations, but even this does not appear to have been clearly documented. Further, whether this translates into continued use once qualifications have been achieved remains doubtful, although the issue has been raised that formal critical appraisal may not be appropriate in all reading situations [24].

The work by McColl et al was the best attempt we identified quantifying the prevalence of appraisal skills [25]. In a 25% random sample of general practitioners in the former Wessex region of England, of whom 67% responded to the circulated questionnaire, consistently less than 1/3 claimed that they "understood and could explain to others" terms which are intimately associated with an ability to critically appraise research on effectiveness, such as relative risk, absolute risk and confidence interval. Although an imperfect measure of actual critical appraisal skills, even the most optimistic interpretation of these findings suggests that there are large numbers of GPs who do not possess critical appraisal skills. However, whether the appropriate response to achieve greater use of research evidence is to correct this deficit by offering teaching is challenged by the authors.

Beyond information from this survey, there is some indirect evidence suggesting critical appraisal skills are neither highly developed nor widely dispersed. One study in GPs in Italy [26] and another in executive and non-executive members of health authorities in the former Anglia & Oxford region of England [27] show an inability to spot that results presented in different formats (relative risk reduction,

absolute risk reduction, proportion of event free patients and numbers needed to treat) were equivalent, and indeed derived from the same raw data. The way in which the data were presented would have heavily biased participants against coming to this conclusion, but even so low levels of critical appraisal skills must partly explain why only 0 out of 148, and 3 out of 140 individuals respectively noted equivalence.

As regards the amount of teaching of critical appraisal skills, quantification is again virtually impossible. In England and Wales, a survey of health authorities and NHS trusts in 1996/7 gave a broad indication that "many health authorities and trusts were providing critical appraisal skills training" [28]. However, the denominator for this comment is unclear, and the response rate to the questionnaire was low to moderate (71 of 105 health authorities [68%] and 192 of 460 NHS trusts [42%]). Anecdotally it is clear that the activities of CASP based in Oxford, NTRAG based in London, the Centre for Evidence-based Medicine in Oxford and its sister organisations providing support to other clinical specialties for courses on doing and teaching critical appraisal, have made a considerable impact. However, it is impossible to estimate the coverage of teaching to any particular level in any particular target audiences, beyond observing that demand for such training is high and frequently outstrips supply.

1.7 Previous attempts to address this problem by reviewing research

In order to ensure that our systematic review built on the strengths and weaknesses of existing work, we carefully considered the evidence of four previous reviews of this topic: two previously published reviews [29, 30] and two unpublished [31, 32]. The review by Taylor and colleagues [32] has subsequently been published in full [33], but for the purposes of planning our review we were restricted to information provided in the initial abstract. Each of the four reviews available to us at the outset was appraised in detail using criteria based on those developed by Oxman and colleagues [34]. An English translation of the article by Audet was used. All met minimal criteria for being systematic, with clear statements of review method and inclusion criteria. Further detail on each of the reviews is provided in the Table 1.

On the basis of our analysis of existing systematic reviews the key strengths we wanted to emulate were:

- Inclusiveness with respect to target groups for appraisal teaching, outcomes and study designs examined, as per the review by Burls [31].
- Comprehensiveness of the search strategy again exemplified in the review by Burls [31]. Beyond this we identified the need to up-date searches done in previous reviews, and to be as rigorous as possible in our attempts to uncover unpublished material.

- Rigorous assessment of the quality of included studies, building on the methods used by Audet et al [29] particularly by being more explicit about what impact variation in included study quality could have on overall conclusions.

Table 1. Details of previous systematic reviews of the effectiveness of teaching critical appraisal skills.

	Audet et al [29]	**Norman & Shannon [30]**	**Burls [31]**	**Taylor et al [32]**
Question addressed	Effectiveness of teaching critical appraisal of the literature to *medical students*. Emphasis on assessment of quality of studies.	Effectiveness of instruction in critical appraisal (evidence-based medicine) to *undergraduate medical students and residents*.	Effectiveness of critical appraisal skills teaching to *any person making healthcare decisions*.	Effectiveness of teaching critical appraisal skills to *healthcare professionals*.
Outcomes of interest	Knowledge, reading habits and ability to critically appraise.	Knowledge, skill and use of literature in clinical decision-making.	Knowledge, skills, attitudes and behaviour.	Any objective measurement.
Study designs included	≥ 10 participants.	Some form of control group – not single group, before-after designs.	No restrictions stated.	Included a comparison (control) group.
Main elements of search	MEDLINE & FAMLI (1980-1990).	MEDLINE (1966-1995); personal collections; discussion with experts.	MEDLINE (1966-Sept 1996): Embase, Cinahl, HealthSTAR, DHSS Data, ERIC, LISA (1991-Sept 1996); forward tracking using Science Citation Index; discussion with experts.	MEDLINE, Cinahl (1966-1995).
Quality assess-ment	17 point checklist; each point scored 0-2 – max score 34. Triplicate assessment; reasonable level of agreement achieved.	As for Audet. Whether quality assessed by one or more assessors not stated.	General comments on strengths and weaknesses only.	None stated.
Data summary	Qualitative. Limited attempt to integrate observations on quality with assessment of effectiveness.	Qualitative and quantitative – simple mean effect for included studies calculated. Sub-group analysis employed (undergraduates vs residents); no evidence that this was pre-stated.	Qualitative.	Qualitative. Results categorised as positive, negative or inconclusive.

The one general weakness of all previous reviews we wanted to overcome was:

- Providing more detailed and informative summaries of the characteristics and results of included studies.

We also wanted to closely scrutinise the sub-group analysis in the review by Norman & Shannon [30], according to whether the target groups for critical appraisal teaching were undergraduate medical students or residents.

2 Review aims and objectives

2.1 Questions addressed

This review aimed to investigate the effect of teaching critical appraisal to health care professionals (both practising and in training) and consumers on a variety of outcomes related to their practice of health care and use of health care facilities and interventions. This has been achieved by reviewing existing empirical evidence, both published and unpublished. For the purpose of the review critical appraisal has been defined as:

"The process of assessing and interpreting evidence by systematically considering its validity, results and relevance to the individuals' own work."

and teaching to be:

"Any co-ordinated educational intervention, by any medium of any duration in any format."

This review primarily attempts to deal with the fundamental question of whether the teaching of critical appraisal has beneficial effects on health care worker behaviour or patient related outcomes. A secondary goal is to investigate whether there is any evidence to suggest that effectiveness is dependent on the detailed nature of the critical appraisal and the method by which it was taught. We structured the review around a hierarchy of seven questions, all relevant to gauging the success of the intervention, but with decreasing relevance to patient's health:

1. Does teaching critical appraisal produce beneficial effects on *patient health*, which are not outweighed by negative effects?
2. Does teaching critical appraisal result in *behaviour* that is more up to date in relation to current good practice?
3. Does teaching critical appraisal change clinical, decision making or health seeking *behaviour*?
4. Does teaching critical appraisal result in change of *skills* of the learner?
5. Does teaching critical appraisal result in a change in *knowledge* of the learner?
6. Does teaching critical appraisal result in a change of *attitudes* of the learner?
7. Does teaching critical appraisal skills leads to increased *satisfaction* in the teacher and learner?

In addition we considered whether the available empirical evidence could answer an eighth question:

8. Is there an optimum method for teaching critical appraisal?

3 Review Methods

3.1 General

Detailed methods are outlined below, based on the structure proposed in the NHS Centre for Reviews and Dissemination Guidelines [35]. The review was undertaken according to a pre-specified protocol (see Appendix 1). Modification and amplification of the original methods, clearly indicated in the following, was required in certain respects in response to particular problems encountered during the course of the review. It should be noted that the protocol for the associated Cochrane Review [36] differs because of the narrower focus required by the EPOC editorial group.

3.2 Literature search strategy and study retrieval

The aim of the literature search was to provide a comprehensive list of primary studies of relevance to the review. It was anticipated that the literature would be spread across the medical and health care literature, psychology and education, so sources in all areas were considered in the search. Search strategies and sources were developed with assistance from medical librarians at the Cairns Library, John Radcliffe Hospital, Oxford and the Institute of Health Sciences, Oxford. Certain databases in the original protocol were not interrogated as a result of this consultation e.g. FAMLI, NTIS and DISSABS. Also in departure from our original intention, no hand-searching of journals was conducted.

The following general sources were thus interrogated:

- Electronic databases
- The World-Wide-Web
- Writing to major medical education centres in UK, Europe and USA.
- Contacting experts in the field directly and through electronic mailing lists
- Scanning the reference lists of located studies and other reviews

Electronic databases and the World-Wide-Web

We searched the following 10 databases from inception until December 1997:

1. Medline
2. Embase

3. The Cochrane Library
4. PsychLit
5. LISA
6. ERIC
7. CINAHL
8. SIGLE
9. Social Science Citation Index
10. Science Citation Index

The search terms used are detailed in Appendix 2, as are details of the World-Wide-Web search.

Direct contacts

Individuals and centres with expertise in teaching critical appraisal were identified through published literature, abstracts of meetings, course advertisements, personal knowledge, local contacts, and through networking at relevant meetings (the evidence based educators meetings (funded by the Department of Health) at The Kings Fund Centre London-1996/1997 and the annual Cochrane meeting in Amsterdam 1997). Individuals (listed in Appendix 2) and centres were contacted requesting details of published and unpublished studies, as well as ongoing work. Replies were received from 25 of the 37 centres we contacted. General requests for details of completed and ongoing studies were requested through email discussion lists. Ten replies were received.

Checking of reference lists

In addition to electronic searching and direct contact, the bibliographies of all included studies and past reviews were checked for further potentially relevant studies.

3.3 Inclusion criteria

The results of all searches were initially screened by one reviewer (JP), who excluded articles clearly of no relevance to the study. Copies of all other articles were retrieved and reviewed by three independent assessors (JP, JD, CH) who judged whether they were eligible for inclusion in the review. Judgements were made according to the explicit inclusion criteria detailed below, which are based upon the questions outlined in Chapter 2. The proforma reproduced in Appendix 3 was used to aid this process. Where there was disagreement that could not be resolved by discussion, a fourth opinion was sought. The degree of agreement between the assessors in their initial ratings was assessed by calculation of kappa statistics for the overall decision. Abstracts were only included if a full article (published or unpublished) could be obtained. Letters and editorials were excluded, as

were review articles unless they contained original data in addition to summaries of previously published research.

Types of participants and setting

Participants in any clinical setting, including health care students, professionals, managers, purchasers, and health care users.

Type of intervention

Educational interventions (defined as a co-ordinated educational activity, of any medium, duration or format) teaching critical appraisal (defined as the process of assessing and interpreting evidence by systematically considering its validity, results and relevance to ones' own work). The critical appraisal educational intervention could either be a single intervention or one of a package of interventions as long as data was separately extractable. Studies which simply taught biostatistics and/or epidemiology were judged as not fulfilling these criteria.

Types of outcomes

Studies had to include at least one of the following outcomes:

Patient outcomes:

- Health outcomes (mortality and morbidity)
- Quality of life
- Satisfaction

Learner outcomes;

- Behaviour, including process of care
- Critical appraisal skills
- Knowledge
- Attitudes
- Satisfaction

Teacher outcomes;

- Satisfaction

Types of studies

Any comparative study design, including randomised controlled trials, non randomised controlled trials, controlled before and after studies, interrupted time series and simple before-after designs. Inclusion of this last group was an amplification from our original protocol. The minimal requirement in consequence was that there had to be a comparison with no training in critical appraisal either in a separate group or in the same group before teaching was undertaken.

Further discussion on admissible study designs

Cook and colleagues [37] have proposed a clear hierarchy of study designs for the evaluation of evidence concerning the effectiveness of clinical interventions, based on the gold standard of the randomised controlled trial. However, there are specific issues that make randomised controlled trials (RCT) difficult to undertake for educational interventions. These include problems in acquiring adequate subject numbers to undertake cluster randomised designs (the interventions generally being delivered at a group rather than individual level), and problems in preventing contamination occurring between randomised groups. Also, it may be difficult to obtain both institutional approval and students' agreement to be randomised to experimental interventions within accredited training programmes. The infrastructure required to undertake a randomised controlled trial often requires funding, which has not always been easily available for studies of educational interventions, and may be a reason why few have been attempted in these fields.

Alternative study designs have been recognised as potentially providing adequate evaluations of the effects of professional interventions by the Cochrane Collaboration's Effective Practice and Organisation of Care (EPOC) review group [38] and others. These include controlled trials (CT), controlled before-and-after studies (CBA), and interrupted time series (ITS). The EPOC definition of a controlled trial requires individuals to be allocated either to receive the experimental or control interventions by the researcher according to a quasi-random mechanism. Quasi-randomisation includes methods such as alternate alternation and allocation by birth-date, which are not concealed and are more susceptible to bias. Whilst the benefit of true concealed random allocation is that it guarantees in the long-run that experimental and control groups are comparable in all respects other than the intervention that they receive, quasi-randomisation may also achieve reasonably comparable groups. However, it is important that such studies demonstrate that the groups are comparable on prognostic factors. There appear to be few practical advantages in undertaking quasi-randomisation over proper randomisation, although historically such study designs have often been performed.

CBA studies are similar in design to trials in that they include contemporaneous control and experimental groups. However, in addition they measure outcome both before the intervention and after it. Their use is thus restricted to outcomes where this is possible. If the groups are shown to be similar at the outset of the study, concern about differences in the control and experimental groups being responsible for differences in final outcomes is reduced. They can often be undertaken as observational studies in situations where the researcher cannot influence which group individuals belong to. For assessments of educational interventions typically they require participants in intervention and control groups to complete assessment tools (such as

short tests) before and after the intervention period. The drawback of these studies is that the assessing outcomes twice introduces the possibility that differences are due to an assessment learning effect rather than the intervention, although such an effect should be equal in both control and intervention groups.

ITS may provide less convincing evidence, but are very easy to undertake as they are based on assessments of a single group, measuring the outcomes at several points in time before and after the intervention. They are therefore very suitable for evaluating the change in knowledge of a group on a teaching programme. The inference from an ITS relies on the assumption that all differences in the outcome before and after the intervention are caused by the intervention, although having sufficient data points to construct a background trend assists. As for CBA studies using repeated measures of the same outcome can be problematic.

As initial searches indicated that there were few empirical studies available for this review, the range of acceptable included studies was extended still further to include purely within-group comparisons where only a single assessment of outcome was compared with a single outcome after the intervention (before-after (BA) or pre-post studies). Clearly in such BA designs the problems of inference for ITS are compounded by an absence of any background trend, as well as all the other problems of interpretation noted above for CBA studies.

Thus all comparative studies which compared individuals who had received critical appraisal teaching with individuals who had not (whether they were the same group or a different group), were initially included. This greatly extended the range of admissible study designs beyond those traditionally considered in systematic reviews. In anticipation of the problems that this was likely to generate in terms of the openness to bias encountered in the review, particular attention was paid to quality assessment. During the analysis the studies were categorised according to their design and threats to validity, and conclusions derived taking clear account of the potential biases identified.

In the review we frequently use the terms between-group and within-group to highlight fundamental differences in the way impact on an outcome has been evaluated in a particular study. A between-group comparison refers to a situation where an outcome measure (or change in an outcome measure) in a treatment group is compared to that in a control group. Such comparisons would typically be found in an RCT or CT. A within-group comparison refers to a situation where an outcome measure is compared before and after the intervention in the same group. Such comparisons would typically be found in a BA study. A corollary of the above, and

one reason why the terms between-group and within-group comparisons have been employed, is that CBA studies contain both types of comparison. As the openness to bias of the two may differ dramatically, it is important to distinguish between them.

3.4 Assessment of study quality

General approach

Although adhering to the principles outlined in the initial protocol, the precise means of assessing study quality underwent considerable evolution during the project. A particular challenge was to convey the strengths and weaknesses of studies using different designs in a way that allowed reasonable relative assessment of their overall openness to bias. The main purposes of the quality assessment were in order of priority: to explicitly describe the strengths and weaknesses of the included studies; to identify a sub-set of studies for the purposes of sensitivity analysis which were self-evidently less open to bias; and to rank all studies according to their openness to bias. In the final event the last of these was not attempted. Use of scoring systems as a way of quantifying the quality of included studies, such as employed in previous systematic reviews on this subject [29] were rejected at the outset of the project.

A feature of this review worth emphasising was to consider openness to bias at the level of each outcome addressed in a particular study, rather than at study level alone. This is in contrast to the approach to quality assessment used in most other systematic reviews. In this way we attempted to differentiate outcomes which would be greatly affected by openness to bias arising from the design and conduct of a specific study, from those which would be relatively immune.

The detailed approach employed to assess quality initially involved stratifying by whether a particular outcome had been assessed by a between-group comparison such as provided by RCT, CT and CBA studies, or a within-group comparison such as provided by ITS and BA studies. In the case of between-group comparisons careful note was also made of whether the assessment of impact involved comparing a before-after *change* or just comparison of single values of the outcome at or after the *end* of the periods of critical appraisal teaching/no teaching. By definition within-group comparisons must assess a before-after change.

The execution of studies was then critiqued according to the particular features of quality given below. These were based generally on the framework suggested by the Cochrane Collaboration

considering bias arising from selection, performance, detection and attrition [39]. This was amplified by items from specific appraisal checklists for particular study designs [38, 40]. In presenting the results of the validity assessment selection and performance bias were considered together as "openness to confounding". Similarly detection and attrition bias were presented together as "threats to validity arising from methods of outcome assessment," to which was added issues arising from the methods of statistical analysis employed in the studies. The assessment of validity by the above method was performed by one reviewer (CH). This was done independently of extracting data on study results. A 10% sample of cells in the final tables on validity were checked for accuracy by a second reviewer (RM), part of a wider check described in the next section on data extraction. Independently of this, the accuracy of all judgements on the appropriateness of statistical analyses were double-checked by an experienced statistician (JD).

Features of quality for outcomes measured using *between-group* comparisons

- Was there randomisation and if so was there concealment of allocation?
- If not randomised with concealed allocation, were the groups compared similar with respect to time, location, experience and measured baseline characteristics (number of measured characteristics being noted)? Did differences noted appear to be of major or minor importance? Was there any adjustment for differences, particularly use of before-after change as the outcome measure?
- Was critical appraisal training the only intervention operating to explain any difference in outcomes observed? Was contamination of the control group with critical appraisal teaching targeted at the experimental group possible?
- Was the same measurement tool for a particular outcome used in both groups (and before and after where change was used as the outcome in each of the groups)? If not was the risk of bias high or low?
- Had the validity of a particular outcome measure been assessed? Was this partial or complete (defined as two or more reported validation exercises)?
- Was the particular outcome measure assessed independently and double blind? If no or unstated, was the risk of bias high or low? If the outcome was self-assessed, was the study objective apparent to participants; if the outcome was externally-assessed, were there clear criteria?
- What was the overall loss to follow-up? Was there differential loss to follow-up between groups?
- Was the statistical analysis appropriate? In particular, was there a power calculation, were confidence intervals or p values given and were the correct statistical tests used?

- Were other sources of bias excluded? In particular, was the possibility of a background trend taken into account particularly for outcomes assessed more than 6 months after the start of the critical appraisal teaching and was a learning effect for repeated use of the same outcome measure considered?

Features of quality for outcomes measured using *within-group* comparisons

- Were the groups compared similar? Were only paired responses analysed?
- Was critical appraisal training the only intervention operating to explain any difference in outcomes observed? Was the time between before and after measurements so short as to preclude other interventions? If delayed was the possibility of other "interventions" which might cause any before-after change excluded?
- Was the same measurement tool for a particular outcome used before and after? If not was the risk of bias high or low?
- Had the validity of a particular outcome measure been assessed? Was this partial or complete (defined as two or more reported validation exercises)?
- Was the particular outcome measure assessed independently and double blind? If no or unstated, was the risk of bias high or low? If the outcome was self-assessed, was the study objective apparent to participants; if the outcome was externally-assessed, were there clear criteria?
- What was the loss to follow-up?
- Was the statistical analysis appropriate? In particular, was there a power calculation, were confidence intervals or p values given and were the correct statistical tests used?
- Were other sources of bias excluded? In particular, was the possibility of a background trend taken into account particularly for outcomes assessed more than 6 months after the start of the critical appraisal teaching and was a learning effect for repeated use of the same outcome measure considered?

Making an overall assessment of openness to bias

The purpose of the features above was primarily to provide a structured framework for systematically reporting the strengths and weaknesses of included studies. It also formed the basis of the attempt to gauge the severity of the implications of openness to bias arising from deficiencies in design and conduct. In this respect, although specific criteria were used to some extent (e.g. for loss to follow-up >20% was classified as a major threat to validity), in other cases categorisation of whether the weakness constituted a minor or a major threat to validity or generated a low or high risk of bias was more subjective. Sensitive to this we attempted to be explicit about the information that led to any judgement, so that others could assess whether they agreed that a particular feature denoted openness to bias. Further we highlighted those

assessments where we were uncertain about whether a weakness observed constituted a major threat to validity.

Studies were categorised according to whether any major threat to validity was judged to be present in any of the quality features examined. If they were, the study/outcome was removed in the sensitivity analysis focusing on just those studies least subject to bias (see below). Despite the element of subjectivity in the assessment of the degree of openness to bias, we believe that the categorisation achieved for this purpose was robust. However, it should also be emphasised that absence of perceived major threats to validity in no way equates to being bias free.

3.5 Data extraction

Descriptions of the participants, content and delivery of the educational interventions and methods of outcome assessments were extracted from all studies, in addition to details of the study design, execution, analysis and results. Contact with lead authors of all included trials was made to request further relevant data not included in the published reports, and full reports of evaluations that had only been published in abstract form. Nine out 16 lead authors responded.

One researcher (JP) initially extracted the necessary data using a structured data-extraction form. Problems with this process, particularly resulting from poor reporting of studies, required the whole of the data extraction process to be repeated by a second researcher (CH). Having achieved consensus by this means on all abstracted data items, a 10% random sample of cells from all the data tables was then checked for a third time (RM). This confirmed the general accuracy of the extracted data following the second round. The checking by the third reviewer (RM) revealed 8 potential errors in 364 table cells checked. Of these, in four cases the originally recorded details were confirmed as being correct. In the case of the other four, the problems were traced to irresolvable ambiguity in the original reports. As for information on study quality, in presenting the abstracted data, items about which there was considerable uncertainty or ambiguity were highlighted.

3.6 Study synthesis and drawing conclusions

The main strategy used was structured tabulation of the characteristics, threats to validity and results (separated into the different general outcome areas), followed by drawing conclusions on the basis of the pattern of results revealed. In relation to results for each general outcome group, direction of effects, size of effects and clinical importance of effects were separately considered. Each of the above areas was considered in isolation before attempts to inter-relate characteristics and quality with results were made. To inter-relate study quality and results a crude sensitivity

analysis was used in which the overall patterns of results were first considered in relation to all available data from the included studies, and then in relation to just those studies judged to be at least risk of bias. In each target area for conclusions the key points were first generated by one researcher (CH), and then independently corroborated or challenged by two other reviewers (RM & JD).

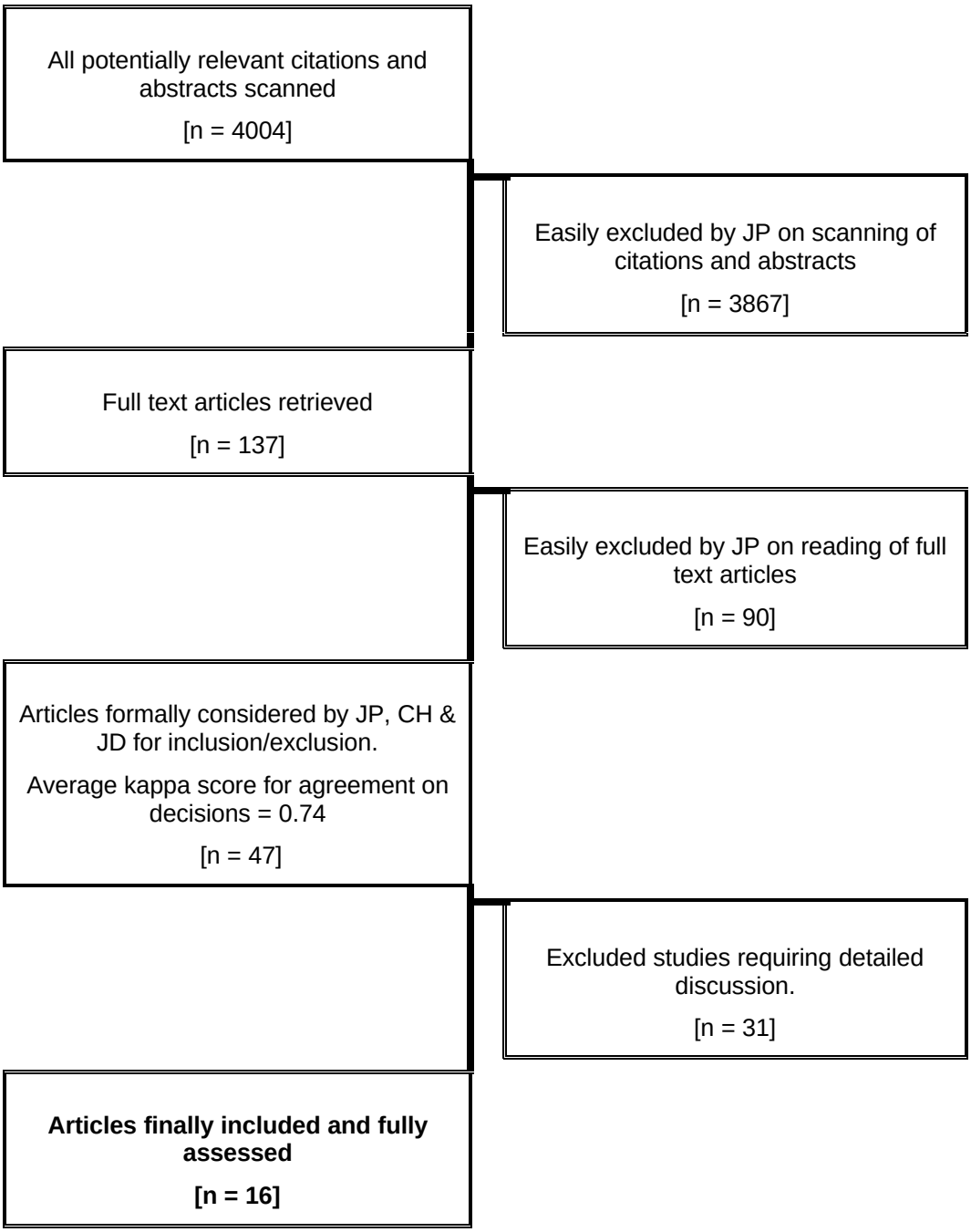
Quantitative synthesis can generally only be applied to systematic reviews where the interventions, participants, outcomes and study designs are similar enough to suggest that results can be pooled. A priori in this review we anticipated little consistency in these characteristics and quantitative pooling was not envisaged. In the event, however, specific application of meta-analysis was used to clarify and amplify particular conclusions initially generated by the qualitative method described in the preceding paragraph. In this Meta-View 3.1 software was used. As a general rule, random effects models were employed in preference to fixed effects models because of the greater intrinsic variability of critical appraisal teaching as an intervention.

4 Results

4.1 Results of searches and study selection

These are summarised in Figure 1.

Figure 1. Search results



The searches initially identified a total of 4004 potentially relevant articles. Most of these were rejected on basis of relevance from scanning of titles and abstracts. 137 articles could not be immediately excluded and the full text was retrieved. Using this information many more of these could again be quickly excluded. The main reasons were that the article was a review article, a letter, an editorial, or that it was solely concerned with the process of teaching critical appraisal or with the methodology involved with critical appraisal of the literature. Descriptive accounts of studies of teaching critical appraisal were also excluded if they did not include formal evaluations of their impact.

47 articles retrieved in full appeared to report or allude to evaluation studies. Three independent reviewers formally assessed these. The level of initial agreement on inclusion between the reviewers was good, indicating that the inclusion criteria could be reliably applied. The average kappa score for inclusion was 0.74 (individual kappa's were JD /JP 0. 76, CH /JP 0. 68, JD/ CH 0. 79). All disagreements were resolved by discussion without resort to a fourth opinion.

Thirty-one of the articles were excluded. Full reasons for exclusion are given in Appendix 4. The majority of the articles (19) were excluded on the criterion that there was not a comparison with no critical appraisal teaching. Of these 19, 4 (studies 6,17, 25 and 27 in Appendix 4) made comparisons between different methods of teaching critical appraisal. Potentially this pool of studies could be of value, but analysing them in detail was beyond the scope of this review. The other 12 studies were excluded because the participants were not taught critical appraisal (11) and because of duplication of an included study (1). In four of the studies (studies 5,9,22,23 in Appendix 4) excluded on the criterion of "not being taught critical appraisal" the problem was that the teaching of critical appraisal formed only a small part of much more extensive courses on epidemiology &/or public health.

During the course of the review several studies looking at the effectiveness of critical appraisal teaching in progress or planned were identified. These are detailed in Appendix 5.

4.2 Problems relating to quality of reporting of included studies

A general observation was the poor reporting of included studies. This accounts for the unusually rigorous checking of abstracted data employed in the review involving three separate rounds of data abstraction – see section 3.5. Although consensus was eventually achieved in the vast majority of abstracted items, considerable uncertainty remained on a number owing to the ambiguity of the reporting. These items are indicated in the relevant tables of abstracted data by shaded cells (where

the cell in question contains multiple pieces of information, the particular detail in question is underlined).

4.3 General characteristics of included studies

16 studies were included [41-56]. Analysis of 12 of these was based on articles published in peer reviewed journals (Journal of Medical Education (3); Journal of General Internal Medicine (3); Journal of the American Medical Association (2); Journal of Biocommunication (1); Bulletin of the Medical Library Association (1); Southern Medical Journal (1); Midwifery (1)). Analysis of the remaining 4 was from unpublished full manuscripts, although two of these were initially identified via published abstracts of presentations made at annual meetings of the Southern Region, Society of General Internal Medicine, USA. For one article [54], ancillary information was available from an early published report of the same study [57].

The general characteristics of the included studies are given in Table 2. Important issues arising from considering these were as follows.

Publication dates

Studies were evenly spread over the 1980's and 1990's, the earliest of which was undertaken in 1978/9.

Location

All but four of the studies were undertaken in US medical schools, one coming from McMaster University in Canada, and three from the UK. However, taking into account the number of individuals studied (see below) it is in the UK setting that the most subjects (approximately 2000) have been assessed.

Design

Only one of the studies [52] was an RCT, this also providing BA information. 8 were CTs where the main comparison was between groups; 5 of these also provided simultaneous within-group comparison i.e. were CBA studies. The remaining 7 studies relied solely on within-group comparisons ie were BA studies. None of the BA studies had sufficient points of data collection before and/or after the intervention to be categorised as an interrupted time-series study. The consequences of the different designs are further considered in the section on validity of included studies.

Table 2. Included studies; general characteristics

1st author [ref]	Year published	Year/s Conducted	Location	Design [i]	Participants	Size [ii]	CA teaching intervention [iii]	Outcomes assessed [iv]
Bennett [41]	1987	Not stated	Ontario, Canada	CT + BA	Medical students	92	Tutorials (16 h)	Skills
Burls [42]	Unpublished Manuscript dated 1997	1993-96	England & Wales, UK	BA	Multi-disciplinary	Circa 1,880	Workshop (minimum of 2.7 h)	Knowledge Attitudes
Caudill [43] + author's manuscript	Unpublished Abstract date 1993	Not stated	Kentucky USA	BA	Doctors – residents	70	Lectures and seminars (estimated 11 h)	Behaviour Skills Knowledge Attitudes
Cuddy [44]	1984	Not stated	Missouri-Kansas, USA	BA	Medical students	18	Lecture (1 h) **or** slide/tape programme (0.33 h)	Knowledge
Frasca [45]	1992	Not stated	Illinois, USA	CT	Medical students	92	Seminars (15 h)	Skills
Gehlbach [46]	1980	1978-79	N Carolina, USA	CT	Doctors – residents	35	Seminars (8 h)	Skills
Hicks [47]	1994	Not stated	England, UK	BA	Midwives	19	Study day (7 h)	Behaviour Skills
Hillson [48] + author's manuscript	Unpublished Abstract date 1993	1992	Minnesota, USA	BA	Doctors residents	29	Lectures + journal clubs (minimum of 7 h)	Skills
Ibbotson [49]	Unpublished Manuscript dated 1997	Not stated	Scotland, UK	BA	Multi-disciplinary	115	Workshop (minimum of 2.7 h)	Knowledge
Kitchens [50]	1989	1987	Kentucky, USA	Phase I CT Phase II CT + BA	Doctors-residents	83	Seminars (minimum of 8.5 h [Phase I], or 4h [Phase II])	Knowledge
Landry [51]	1994	Not stated	Maryland, USA	CT + BA	Medical students	146	Seminars – large group (3 h)	Behaviour Knowledge Attitudes
Linzer [52]	1988	Not stated	N Carolina, USA	RCT + BA	Doctors-interns	44	Journal clubs (min of 3 h [actually attended])	Behaviour Skills Knowledge
Radack [53]	1986	1984-85	Ohio, USA	CT + BA	Medical students	34	Seminars (4.2 h)	Skills
Reigelman [54] See also [57]	1986	1981-85	Washington DC, USA	CT + BA	Medical students	296	Lectures + seminars (16 h)	Behaviour Skills Knowledge
Seelig [55, 56]	1991	Not stated	N Carolina, USA	BA	Doctors-residents	14	Seminar + journal clubs (8 h)	Behaviour Skills Knowledge Attitudes
Seelig [56]	1993	Not stated	N Carolina, USA	CT + BA	Doctors-interns	30	Seminar (1 h)	Behaviour Skills Knowledge Attitudes

NOTES: Shaded cells indicate data items on which there was ambiguity. Where cells contain several items of information the ambiguous item is underlined.

i) RCT, randomised controlled trial; CT, controlled trial; BA, before-after study; + BA indicates that either a RCT or a CT assessed before-after changes as well as comparing outcomes with a control group.

ii) Total number of participants exposed to intervention, and where appropriate control conditions.

iii) Gives the format used to teach critical appraisal and the *planned* total duration of the CAT intervention in hours. Where this varied, the minimum that all participants would have been exposed to is given.

iv) General outcomes assessed. Only those outcomes where a between-group or a within-group comparison could be made are included.

Participants and size

Further detail on this is provided in Appendix 6. Most studies were on doctors, either in training (6 studies; 678 individuals) or within 10 years of their initial registration (7 studies; 305 individuals). This analysis requires some understanding of the general pattern of medical training in the USA. In essence this involves 4 years as a medical student, followed by 3 years as a resident. The first year of residency is referred to as the intern year. The remainder were multidisciplinary (2 studies; approximately 2000 individuals) or on midwives (1 study; 19 individuals). Thus the multidisciplinary group predominates overall by virtue of the much greater size of the study by Burls [42]. Reference to Appendix 6 indicates that the main groups in the multidisciplinary studies were qualified doctors, managers and researchers.

Nature of intervention

Further detail on this is provided in Appendix 7. There was particular ambiguity concerning reporting of this indicated by the high proportion of shaded cells in Table 2. Despite this it seems certain that there was marked heterogeneity between studies, particularly in terms of the duration of the critical appraisal teaching intervention. The variation is clear in Table 2, ranging from extremely brief (1 hour or less in the case of the studies by Cuddy [44] and Seelig (1993) [56], to prolonged courses of over 10 hours (Bennett [41], Caudill [43], Frasca [45] & Reigelman [54, 57]). Where there was variation in duration within a study, because the intervention was repeated a number of times to different groups, the minimum level that could have been received by all participants is given. An important difference in the nature of the duration given should be noted for the study by Linzer [52]. In this study the figure denotes actual attendance (mean of 5 hours, range 3 to 6 hours) rather than the duration of the whole course, reported for all other included studies, but not by Linzer. There was also heterogeneity in terms of the teaching formats used. The descriptions applied in Table 2 generally report the term used by the original authors. In this there is particular ambiguity between use of the terms seminars, tutorials and journal clubs. In general these all seem to refer to small group formats, with the exception of Landry [51] where the seminars in question seem to much more akin to lectures with a likely student to teacher ratio of over 50, which is the reason why “large group” has been added. Although categorisation of the interventions is again complicated by incomplete reporting, they seem to broadly fall into four types:

- Courses with predominantly small group formats in the studies by Bennett [41], Frasca [45], Gehlbach [46], Hillson [48], Kitchens [50], Linzer [52], Radack [53] and Seelig 1991 [55,56]
- Courses with predominantly large group formats ie lectures in the studies by Caudill [43], Landry [51] and Reigelman [54,57]. (The categorisation of Caudill is problematic. It describes a combination of 4 one hour of lectures and a critical appraisal seminar series. Unfortunately the

number and student to tutor ratio in the latter are not defined, making it difficult to decide whether large group or small group formats dominated.)

- One-off workshops and study days by Burls [42], Ibbotson [49] and Hicks [47]. In the former two cases a mixture of large group formats and small group sessions is used; the latter employs a format with an intermediate student to tutor ratio of approximately 20.
- Other one-off interventions. Seelig 1993 [56] employed a single one hour seminar with an intermediate student to tutor ratio of 18. Cuddy [44] employed two interventions. One involved a one hour lecture (although this would have apparently only been delivered to nine students) and the other a slide-tape program in which no tutor would have been directly involved.

Reference to Appendix 7 indicates that there were also probably important differences in the nature of the critical appraisal teaching intervention beyond duration and teaching format including:

- The extent to which educational principles were considered in devising the content of the intervention.
- The actual attendance achieved. At least two studies, Caudill [43] and Radack [53], suffered considerable non-attendance indicating that the actual quantum of intervention received by participants was considerably lower than described. Given this, it is of considerable concern that many included studies, which were not one-off, Bennett [41], Frasca [43], Gehlbach [46], Hillson [48], Kitchens [50], Landry [51], Reigelman [54,57] and Seelig [55,56] gave no clear information on this at all. The fact that all these studies involved captive audiences, which were not volunteers, adds further to this concern.
- Whether the intervention included an innovative teaching component above and beyond the attempt to teach critical appraisal skills. Again in the majority of studies it was clear, or seemed likely, that the intervention whose effect was being tested consisted not only of teaching critical appraisal skills but also enhanced or novel teaching methods. The latter, particularly where there was no parallel control group, was judged relative to the norm for medical education being lectures.

With respect to these other features of the intervention, the original intention had been to attempt to rank, independently of knowledge of the actual results achieved, the quality of the educational intervention offered. Unfortunately although there are some indications suggesting important differences, poor and inconsistent reporting of studies made this impossible to achieve in a reliable manner. It is however important to indicate that some of the included studies with interventions of greatest duration ie Caudill [43] and Riegelman [54, 57] are also those with features likely to reduce impact (ie have no innovative teaching component). Even for the two other included studies with >10 hours duration (Bennett [41] and Frasca [45]), where there is evidence of attempts to deliver

teaching on critical appraisal in an engaging manner, information on actual attendance as opposed to the intended intervention described is not presented.

Finally, in contrast to additional features of the interventions presented in Appendix 7 indicating potentially important sources of heterogeneity, it should also be noted that eleven of the sixteen included studies appear to be based in some measure on the model of critical appraisal developed by McMaster. This was indicated directly or by reference to articles in the Canadian Medical Association Journal series on how to read clinical journals.

Outcomes assessed

Table 2 shows that the included studies provided no usable information on patient outcomes or satisfaction. A number of the included studies without parallel control groups measured participant satisfaction, but only after the intervention. Hence the means by which this information on patient satisfaction was obtained did not conform to our inclusion criteria. All studies assessed skills and/or knowledge, to which information on behaviour and attitudes was added to varying degrees. The exact means by which behaviour, skills, knowledge and attitudes were measured in each study differed and the implications of this are discussed further in subsequent sections reporting results on each general outcome. It is however, worth noting at this stage that there were occasional problems in deciding whether a particular measure provided information on knowledge or skills, in particular in the studies by Cuddy [44] and Landry [51].

Further information on the outcomes assessed is provided in Table 3 and Appendix 8. Table 3 shows that the 16 included studies contained information on at least 58 different relevant comparisons. The greater of number of comparisons relative to the studies is contributed to by:

- Studies presenting outcome information on two interventions e.g. Cuddy (lecture or slide-tape program arms) or the same on two groups e.g. Kitchens (Phases I & II).
- Studies addressing several outcomes
- Studies providing information on the impact on a given outcome through both between- and within-group comparisons.

Table 3. Included studies; outcome information available

General outcome assessed	Nature of comparison	Number of comparisons	Studies contributing
Patient health	Any	0	None
Behaviour	Between-group	3	Landry 94; Linzer 88; Reigelman 86
	Within-group (duplicating between-group)	3	Landry 94; Linzer 88; Reigelman 86
	Within-group	5	Caudill 93; Hicks 94 (2); Seelig 91; Seelig 93
Skills	Between-group	9	Bennett 87 (2); Frasca 92 (2); Gehlbach 80; Linzer 88 (2); Radack 86; Reigelman 86
	Within-group, (duplicating between-group)	6	Bennett 87 (2); Linzer 88 (2); Radack 86; Reigelman 86
	Within-group	7	Caudill 93; Hicks 94 (2); Hillson 92 (2); Seelig 91; Seelig 93
Knowledge	Between-group	6	Kitchens 89 (Phase I); Kitchens 89 (Phase II); Landry 94; Linzer 88; Reigelman 86; Seelig 93
	Within-group, (duplicating between-group)	5	Kitchens 89 (Phase II); Landry 94; Linzer 88; Reigelman 86; Seelig 93
	Within-group	7	Burls 97 (2); Caudill 93; Cuddy 84 (2); Ibbotson 97; Seelig 91
Attitudes	Between-group	1	Landry 94
	Within-group, (duplicating between-group)	1	Landry 94
	Within-group	5	Burls 97 (2); Caudill 93; Seelig 91; Seelig 93
Satisfaction	Any	0	None
TOTAL (crude)		58	
TOTAL (excluding within-group duplicating between-group)		43	

With respect to the last of these points a decision was made that the impact assessed in any between-group comparisons should take precedence in order to avoid "double-counting" in the context of the review. Thus in subsequent sections we report only the information available from 43 of the available 58 comparisons. However, it was also thought important to note where impact had been simultaneously assessed in between- and within-group comparisons as it might give important indications of the relative validity of studies relying on within-group comparisons alone. Further results are presented sub-grouped according to the general outcome they contribute to. Although this generates some duplication, it does facilitate easier of assessment of how issues relating to study quality and validity, in particular, might affect the overall conclusions on each set of outcomes.

4.4 Quality and validity of comparisons reported in included studies

Issues relating to study design

Table 4 summarises the main threats to validity arising from the study design employed, using the features described in detail in 3.4. Further explanation of why any noted threats arise is given in Appendix 9. The key points arising from Table 4 for each of the general outcomes are:

Behaviour: Important threats to validity were identified for the data contributed by Riegelman [54,57]. This arises from the nature of the comparison in which year 4 students in the Class of 1981 were compared with year 4 students from the Class of 1984. Although three sets of baseline characteristics (mean grade, prior research experience and specialty choice) were compared for those completing the questionnaire in each intake and said to show no differences, this did not provide adequate reassurance that there was no confounding given the great potential for differences. Beyond this, the studies by Caudill [43], Hicks [47] and Seelig 1993 [56] were also considered slightly susceptible because the times between before and after assessments in these within-group comparisons were thought just long enough that changes other than the CAT intervention could possibly explain any changes in behaviour. However, as indicated by the shaded cells these judgements were debatable. In the case of the Caudill study although not explicitly stated it seems likely that the before and after measurements were separated by six months, the likely length of the CAT program being four months; in the case of the Hicks study the intervening period was 2 months, the intervention being a study day; and in the case of the Seelig 1993 the intervening period was four months, the intervention again being a one-off seminar. This contrasts with the situation in Seelig 1991, which was not felt to be vulnerable to bias in the same way, where the CAT programme was four months in duration and the post intervention measure of behaviour made at four months.

Even so, again as indicated by the shaded cell, the judgement that this meant that CAT was the only intervention operating is debatable.

Table 4. Included comparisons; threats to validity arising from study design

Study (Year)	Comparison type (Between- or within-group) Design	Openness to confounding?			Sample size
		Was allocation Concealed?	Were the groups Compared similar? Major or minor differences noted? Adjusted for?	Was CAT the only "intervention" possibly operating to explain any change in outcome observed?	
BEHAVIOUR – Between-group comparisons					
Landry (1994)	Between-group CT	N/A	No – minor – but adjusted for	Yes	146
Linzer (1988)	Between-group RCT	Unknown	No – minor – but adjusted for	Yes	44
Reigelman (1986)	Between-group CT	N/A	No – potentially major – **not** adjusted for	Yes	296
BEHAVIOUR – Within-group comparisons					
Caudill (1993)	Within-group BA	N/A	Yes.	Unknown	70
Hicks (1994)	Within-group BA	N/A	Yes	No	19
Seelig (1991)	Within-group BA	N/A	Yes	Yes	14
Seelig (1993)	Within-group BA	N/A	Yes	No	18
SKILLS – Between-group comparisons					
Bennett (1987)	Between-group CT	N/A	No – minor – but adjusted for	Yes	92
Frasca (1992)	Between-group CT	N/A	No – minor – **not** adjusted for	Yes	92
Gehlbach (1980)	Between-group CT	N/A	No – major – **not** adjusted for	No	35
Linzer (1988)	Between-group RCT	Unknown	No – minor – but adjusted for	Yes	44
Radack (1986)	Between-group CT	N/A	No – minor – but adjusted for	Yes	34
Reigelman (1986)	Between-group CT	N/A	No – potentially major - **not** adjusted for	Yes	296
SKILLS – Within-group comparisons					
Caudill (1993)	Within-group BA	N/A	Yes	Unknown.	70
Hicks (1994)	Within-group BA	N/A	Yes	For "Concordance with expert appraisal" – Yes For "Confidence in appraisal skills" – No	19
Hillson (1994)	Within-group BA	N/A	Yes	Yes	29
Seelig (1991)	Within-group BA	N/A	Yes	Yes	14
Seelig (1993)	Within-group BA	N/A	Yes	No	18

Shaded cells indicate data items on which there was ambiguity or where there was uncertainty about the degree to which the feature constituted a threat to validity.

Cells outlined in bold indicate those features considered to constitute a major threat to validity.

Table 4 (continued)

Study (Year)	Comparison type (Between- or within-group) Design	Openess to confounding?			Sample size
		Was allocation Concealed?	Were the groups Compared similar? Major or minor differences noted? Adjusted for?	Was CAT the only "intervention" possibly operating to explain any change in outcome observed?	
KNOWLEDGE – Between-group comparisons					
Kitchens (1989) (Phase I)	Between-group CT	N/A	No – minor – **not** adjusted for	Yes	83 CAT = 51 Con = 32
Kitchens (1989) (Phase II)	Between-group CT	N/A	No – minor – but adjusted for	Yes	83 CAT = 32 Con = 51
Landry (1994)	Between-group CT	N/A	No – minor – but adjusted for	Yes	146
Linzer (1988)	Between-group RCT	Unknown	No – minor – but adjusted for	Yes	44
Reigelman (1986)	Between-group CT	N/A	No – potentially major - **not** adjusted for	Yes	296
Seelig (1993)	Between-group CT	N/A	No – minor – but adjusted for	Yes	30
KNOWLEDGE – Within-group comparisons					
Burls (1997)	Within-group BA	N/A	Yes	Yes	Approx 1880
Caudill (1993)	Within-group BA	N/A	Yes	Unknown	70
Cuddy (1984) (Lecture)	Within-group BA	N/A	Yes	Unknown	9
Cuddy (1984) (Slide-tape)	Within-group BA	N/A	Yes	Unknown	9
Ibbotson (1997)	Within-group BA	N/A	Yes	Yes	115
Seelig (1991)	Within-group BA	N/A	Yes	Yes	14
ATTITUDES – Between-group comparisons					
Landry (1994)	Between-group CT	N/A	No – minor – but adjusted for	Yes	146
ATTITUDES – Within-group comparisons					
Burls (1997)	Within-group BA	N/A	Yes	Yes	Approx 1880
Caudill (1993)	Within-group BA	N/A	Yes	Unknown	70
Seelig (1991)	Within-group BA	N/A	Yes	Yes	14
Seelig (1993)	Within-group BA	N/A	Yes	No	18

Shaded cells indicate data items on which there was ambiguity or where there was uncertainty about the degree to which the feature constituted a threat to validity.

Cells outlined in bold indicate those features considered to constitute a major threat to validity.

Skills: Among the between-group comparisons contributing to this outcome, concerns about validity were noted for the studies by Frasca [45], Gehlbach [46] and Reigelman [54,57]. In the case of Frasca the concern arose from the fact that one of the four measured base-line characteristics (age) showed a statistically significant difference in age (25.8 years [CAT] vs 24.7 years [control]). Debatably, it was felt that not only might the one year difference in age reflect an important difference in experience in the medical students concerned, but might also be a general indicator of other important unmeasured differences between the CAT and control groups. In the case of Gehlbach the threats to bias were even more severe as not only were years 2 and 3 students [CAT] compared to year 1 students without any attempt to assess equivalence, but there was also no attempt to clearly exclude the possibility that other elements of training in years 2 and 3 might have brought about any changes in behaviour observed. The threat to validity arising in Reigelman is for the same reason given under behaviour.

Among the within-group comparisons contributing information on impact on skills the studies by Caudill [43], Hicks [47] and Seelig 1993 [56] were again considered slightly susceptible to bias in the same way as described under behaviour. The concern about the Hicks study applied only to the measure of skills involving self-perceived confidence in appraisal skills; the other involving concordance with expert appraisal was measured immediately after the study day.

Knowledge: Two between-group comparisons assessing impact on knowledge were identified as potentially susceptible to bias with respect to the study design employed. The potential for major differences in the two groups compared, as noted for behaviour, was again a concern about the study by Reigelman [54,57]. Imbalance in one of the two measured baseline characteristics was the source of concern in the study by Kitchens [50], although the impact of this is debatable. In the group receiving CAT in the first phase there was a slightly greater proportion of participants in the third post-graduate year, at the expense of those in their first. The impact of this in the second phase of the Kitchens study was however reduced by using before-after change as the outcome measure, which provides some measure of adjustment for any imbalance in baseline characteristics with an influence on the outcome in question.

Concerns about validity were identified in two studies employing within-group comparisons. There were minor concerns about the study by Caudill [43] for the same reasons cited for the impact on behaviour. The concerns were similar for the two comparisons provided by Cuddy [44]. In this study the timing of the assessment of knowledge after the one-off CAT interventions was completely unknown, being stated as when was convenient for the students participating. Although it was likely that the timing was soon after the interventions for 9 students studied for each intervention, the

possibility that events other than the interventions in question might have been responsible for any changes in outcome observed cannot be completely disregarded.

Attitudes: There were no concerns about the validity of the single between-group comparison contributing information on impact on attitudes. There were concerns about two within-group comparisons provided by Caudill [43] and Seelig 1993 [56]. In both the reasons were the same as those given in the sections above on behaviour.

Issues relating to method of outcome assessment and data analysis

Table 5 summarises the main threats to validity arising from the methods of outcome assessment and data analysis. Further explanation of why any noted threats arise is given in Appendix 10.

Table 5. Included comparisons; threats to validity arising from methods of outcome assessment and data analysis

Study (Year)	What was assessed? Changes over study period assessed *[Change]* or States at end of study compared *[End]* ?	Timing of assessment/s (In reference to start of period of CAT = time 0)		[i] S/A Or E/A?	[ii] Same tool? Risk of bias, if not?	Valida-Tion of tool? Partial/ Comp-lete?	[iii] Indepen-dent & Blind? Risk of bias, if not?	Loss to follow-up? (%)	Appro-priate statistical analysis?	Other sources Of bias excl-uded?
		Before	After							
BEHAVIOUR – Between-group comparisons										
Landry (1994)	Use of medical literature in patient write-ups. *Change.*	-1w	5w	E/A	Yes	Not stated	Yes	0	No	Yes
Linzer (1988)	Reading behaviour. *Change.*	0	Ave of 9.5m	S/A	Yes	Yes - Partial	No - low	7	Yes	Yes
R'lman (1986)	Reading behaviour. *End.*	N/A	Approx. 3y	S/A	Yes	Not stated	N/S - high	42	No	No
BEHAVIOUR – Within-group comparisons										
Caudill (1993)	Reading behaviour. *Change.*	N/S (<0)	N/S (>6m)	S/A	Yes	N/S	No - high	69	Yes	No
Hicks (1994)	Reading behaviour [RB] & frequency of review of current practice prompt-ed by articles read [PR]. *Change.*	0	2m	S/A	Yes	N/S	No - high	RB 11 PR 47	No	Yes
Seelig (1991)	Reading behaviour. *Change.*	N/S (<0)	4m	S/A	Yes	N/S	No - high	N/S	Yes	Yes
Seelig (1993)	Reading behaviour. *Change.*	N/S (<0)	4m	S/A	Yes	N/S	No - low	N/S	Yes	Yes

Shaded cells indicate data items on which there was ambiguity or where there was uncertainty about the degree to which the feature constituted a threat to validity. Cells outlined in bold indicate features considered to constitute a major threat to validity.

i) Was measurement instrument primarily dependent on assessment by the participant themselves (S/A) or on assessment by the investigator or a third party (E/A)?

ii) Was the same tool used in CAT & control and/or before & after? If no, was risk of bias thought, high or low?

Iii) Was assessment a) independent and b) double blind (participants & investigators) of whether the participant was in CAT/ control group or was being assessed before/after the intervention? If no, was risk of bias thought, high or low?

Abbreviations: N/S – not stated (no information in article)
N/A – not applicable ie entry for "before" in timing of assessment where b-a change was not measured

Table 5 (continued)

Study (Year)	What was assessed? Changes over study period assessed *[Change]* or States at end of study compared *[End]* ?	Timing of assessment/s (In reference to start of period of CAT = time 0)		[i] S/A Or E/A?	[ii] Same tool? Risk of bias, if not?	Valida-Tion of tool? Partial/ Comp-lete?	[iii] Indepen-dent & Blind? Risk of bias, if not?	Loss to follow-up? (%)	Appro-Priate Statistical analysis?	Other sources Of bias excl-uded?
		Before	After							
SKILLS – Between-group comparisons										
Benn't (1987)	Critical appraisal: exercises on therapy & diagnosis. *Change.*	N/S (<0)	N/S (>8w)	E/A	No - Low	Yes - comp	Yes	14	Yes	Yes
Frasca (1992)	Critical appraisal and library skills: MCQ. *End.*	N/A	3m	E/A	Yes	N/S	N/S - low	0	Yes	Yes
G'bach (1980)	Critical appraisal: MCQ test. *End.*	N/A	N/S (2m-1y)	E/A	Yes	N/S	N/S - low	0	No	Yes
Linzer (1988)	Critical appraisal: test article. *Change.*	0	Ave of 9.5m	E/A	Yes	Yes - comp	Yes	7	Yes	Yes
Linzer (1988)	Critical appraisal: perception of own skill. *Change.*	0	Ave of 9.5m	S/A	Yes	Yes - partial	No - low	7	Yes	Yes
Radack (1986)	Critical appraisal: Exercise on diagnosis. *Change.*	0	2m	E/A	Yes	N/S	N/S - high	38	No	Yes
Reigel'n (1986)	Critical appraisal: perception of own skill. *End.*	N/A	Approx 3y	S/A	Yes	N/S	N/S - high	42	No	No
SKILLS – Within-group comparisons										
Caudill (1993)	Critical appraisal: perception of own skill. *Change.*	N/S (<0)	N/S (>6m)	S/A	Yes	N/S	No - high	69	Yes	No
Hicks (1994)	Critical appraisal: of test article. *Change.*	0	1d	E/A	Yes	Yes - partial	No - low	0	No	No
Hicks (1994)	Critical appraisal: perception of own skill. *Change.*	0	2m	S/A	Yes	N/S	No - high	32	No	Yes
Hillson (1992)	Critical appraisal: of test article. *Change.*	0	2m	E/A	No - Low	Yes - partial	No - low	21	Yes	Yes
Hillson (1992)	Critical appraisal: Perception of own skill. *Change.*	0	2m	S/A	Yes	N/S	No - high	21	Yes	Yes
Seelig (1991)	Critical appraisal: perception of own skill. *Change.*	N/S (<0)	4m	S/A	Yes	N/S	No - high	N/S	Yes	Yes
Seelig (1993)	Critical appraisal: perception of own skill. *Change.*	N/S (<0)	4m	S/A	Yes	N/S	No - low	N/S	Yes	Yes
	[NB Uncertainty about eligibility of data on this outcome from this study.]									

Shaded cells indicate data items on which there was ambiguity or where there was uncertainty about the degree to which the feature constituted a threat to validity. Cells outlined in bold indicate features considered to constitute a major threat to validity.

i) Was measurement instrument primarily dependent on assessment by the participant themselves (S/A) or on assessment by the investigator or a third party (E/A)?
ii) Was the same tool used in CAT & control and/or before & after? If no, was risk of bias thought, high or low?
iii) Was assessment a) independent and b) double blind (participants & investigators) of whether the participant was in CAT/ control group or was being assessed before/after the intervention? If no, was risk of bias thought, high or low?

Abbreviations: N/S – not stated (no information in article)
N/A – not applicable ie entry for "before" in timing of assessment where b-a change was not measured

Table 5 (continued)

Study (Year)	What was assessed? Changes over study period assessed *[Change]* or States at end of study compared *[End]* ?	Timing of assessment/s (In reference to start of period of CAT = time 0)		[i] S/A Or E/A?	[ii] Same tool? Risk of bias, if not?	Valida-Tion of tool? Partial/ Comp-lete?	[iii] Indendent & Blind? Risk of bias, if not?	Loss to follow-up? (%)	Appro-Priate Statistical analysis?	Other sources Of bias excl-uded?
		Before	After							
KNOWLEDGE – Between-group comparisons										
K'hens (1989) (Ph I)	Clinical epidemiology principles: T/F & MCQ test. *End.*	N/A	21w	E/A	Yes	N/S	N/S - low	5	Yes	Yes
K'hens (1989) (Ph II)	Clinical epidemiology principles: T/F & MCQ test. *Change.*	N/S (<0)	12w	E/A	Yes	N/S	N/S - low	16	Yes	Yes
Landry (1994)	Basic research design: T/F test. *Change.*	-6w	5w	E/A	Yes	Yes - partial	No - low	0	No	Yes
Linzer (1988)	Epi and bio-statistics: test questions. *Change.*	0	Ave of 9.5m	E/A	Yes	Yes - partial	No - low	7	Yes	Yes
R'lman (1986)	Study design and stats: T/F questions. *End.*	N/A	Approx 3y	E/A	Yes	N/S	N/S - low	42	Yes	No
Seelig (1993)	Basic principles of critical appraisal: test questions. *Change.*	N/S (<0)	4m	E/A	Yes	N/S	N/S - low	N/S	Yes	Yes
KNOWLEDGE – Within-group comparisons										
Burls (1997)	Understanding of key terms used in systematic reviews: perception of own knowledge (crude score). *Change.*	-2w	1d	S/A	Yes	Yes - partial	No - high	30	Yes	Yes
Burls (1997)	Understanding of key terms used in systematic reviews: perception of own knowledge (overall impact score). *Change.*	-2w	1d	S/A	Yes	Yes - partial	No - low	30	Yes	Yes
Caudill (1993)	Epi and bio-statistics - test questions. *Change.*	N/S (<0)	N/S (>6m)	E/A	Yes	Yes - partial	No - low	69	Yes	No
Cuddy (1984) (Lect & s-tape)	Basic concepts of literature evaluation: MCQ test. *Change.*	N/S (<0)	N/S (>1h or > 21min)	E/A	Yes	N/S	No - low	0	Yes	No
Ibbot-son (1997)	Understanding of key terms used in systematic reviews: perception of own knowledge (crude score). *Change.*	-2w	1d	S/A	Yes	Yes - partial	No - high	25	Yes	Yes
Seelig (1991)	Basic principles of critical appraisal: test questions. *Change.*	N/S (<0)	4m	E/A	Yes	N/S	No - low	N/S	Yes	No

Shaded cells indicate data items on which there was ambiguity or where there was uncertainty about the degree to which the feature constituted a threat to validity. Cells outlined in bold indicate features considered to constitute a major threat to validity.

i) Was measurement instrument primarily dependent on assessment by the participant themselves (S/A) or on assessment by the investigator or a third party (E/A)?
ii) Was the same tool used in CAT & control and/or before & after? If no, was risk of bias thought, high or low?
iii) Was assessment a) independent and b) double blind (participants & investigators) of whether the participant was in CAT/ control group or was being assessed before/after the intervention? If no, was risk of bias thought, high or low?

Abbreviations: N/S – not stated (no information in article)
N/A – not applicable ie entry for "before" in timing of assessment where b-a change was not measured

Table 5 (continued)

Study (Year)	What was assessed? Changes over study period assessed *[Change]* or States at end of study compared *[End]* ?	Timing of assessment/s (In reference to start of period of CAT = time 0) Before	Timing of assessment/s (In reference to start of period of CAT = time 0) After	[i] S/A Or E/A?	[ii] Same tool? Risk of bias, if not?	Validation of tool? Partial/ Complete?	[iii] Indendent & Blind? Risk of bias, if not?	Loss to follow-up? (%)	Appro-Priate Statistical analysis?	Other sources Of bias excluded?
ATTITUDES – Between-group comparisons										
Landry (1994)	Value of research: agreement with statements. *Change.*	-6w	5w	S/A	Yes	N/S	No - low	0	No	Yes
ATTITUDES – Within-group comparisons										
Burls (1997)	Need to use research: degree of agreement with statements (crude score). *Change.*	-2w	1d	S/A	Yes	Yes - partial	No - high	28	Yes	Yes
Burls (1997)	Need to use research: degree of agreement with statements (overall impact score). *Change.*	-2w	1d	S/A	Yes	Yes - partial	No - low	28	Yes	Yes
Caudill (1993)	Limits to use of research literature: degree of agreement with statements. *Change.*	N/S (<0)	N/S (>6m)	S/A	Yes	N/S	No - high	69	Yes	No
Seelig (1991)	Importance and purpose of reading journal articles: degree of agreement with statements. *Change.*	N/S (<0)	4m	S/A	Yes	N/S	No - high	N/S	Yes	Yes
Seelig (1993)	Importance and purpose of reading journal articles: degree of agreement with statements. *Change.*	N/S (<0)	4m	S/A	Yes	N/S	No - low	N/S	Yes	Yes

Shaded cells indicate data items on which there was ambiguity or where there was uncertainty about the degree to which the feature constituted a threat to validity. Cells outlined in bold indicate features considered to constitute a major threat to validity.

i) Was measurement instrument primarily dependent on assessment by the participant themselves (S/A) or on assessment by the investigator or a third party (E/A)?
ii) Was the same tool used in CAT & control and/or before & after? If no, was risk of bias thought, high or low?
iii) Was assessment a) independent and b) double blind (participants & investigators) of whether the participant was in CAT/ control group or was being assessed before/after the intervention? If no, was risk of bias thought, high or low?

Abbreviations: N/S – not stated (no information in article)
N/A – not applicable ie entry for "before" in timing of assessment where b-a change was not measured

The key issues arising from Table 5 for each of the groups of outcomes are:

Behaviour: Of the three studies contributing information on impact on behaviour from between-group comparisons, there was very major concern about the validity relating to assessment of outcome and analysis for the study by Reigelman [54,57]. The main sources of this were very high loss to follow-up, reinforced by lack of independent and blind assessment of a participant-assessed outcome, possible errors in the statistical analysis, and failure to consider the possibility of a background trend or a differential learning effect from repeated use of the same measurement instruments.

For all four studies contributing information from within-group comparisons there were major concerns. Most open to bias was the study by Caudill [43] with extremely high loss to follow-up and lack of independent and blind assessment of outcome. The study by Hicks [47] was similarly highly open to bias with respect to behaviour as measured by self-assessed frequency of reviewing current practice based on articles read. The measure based on reading behaviour was less open to bias as loss to follow-up was 11%. Nonetheless it was still potentially biased by lack of independent and blind assessment of outcome. Both studies by Seelig [55,56] suffered from an absence of information about loss to follow-up which were considered major threats to validity. This was compounded in Seelig 1991 by a lack of independent and blind assessment of outcome. In Seelig 1993 the presence of a control group, although not used in this comparison, may have provided some protection from detection bias, but as indicated by the shaded cell in Table 5 this is debatable.

Skills: All six studies contributing between-group comparisons to assessment of impact on skills had at least minor flaws relating to outcome measurement and analysis. For Bennett [41] there was some concern about different participants receiving different exercises. However, the chance of bias being introduced by this was thought to be low, as the exercises were allocated randomly from the pool of nine. Further concern arose, as indicated in Appendix 10, from there being differential loss to follow-up: 8% in the CAT group; 21% in the control group; 14% overall. A particularly strong feature of the study was the efforts to validate the skills measure used. The studies by Frasca [45] and Gehlbach [46] were both open to bias arising from lack of a clear indication that the outcome was measured in an independent and blind manner. However in both cases the effect of this was likely to have been minimal because of having clearly defined right or wrong answers to the MCQ questions which comprised the measure. There were also some concerns about the use of one-tailed statistical tests in the Gehlbach study. The study by Linzer [52] contributing two measures of skill was again felt to be open to little bias, particularly as far as the measure involving performance in critically appraising a test article was concerned. Like Bennett, a particular strength was the attempts to validate this measure. In the Linzer study there were however greater concerns about the validity of the measure of skills involving self-perception, although as indicated by the shaded cell there was uncertainty about the magnitude of the threat. In this instance it would be have been more difficult to assure that the assessment was independent, although the fact that participants were masked to the purpose of the study may have introduced an element of blinding. For the two remaining studies contributing between-group comparisons, Radack [53] and Riegelman [54,57], there were major threats to validity principally arising from high losses to follow-up. In both studies this was compounded by the possibility of detection bias arising from lack of clear demonstration that the

skills measures were assessed independent and blind of the group to which the participant had been allocated. There were also concerns about the statistical analysis in both studies.

All five studies contributing within-group comparisons were open to bias. In all but one case this bias was felt to have major implications. This clear exception was the measure employing critical appraisal of a test article in the study by Hicks (although this too used one-tailed tests throughout) [47]. The minimal loss to follow-up and the increased objectivity of the measure used were the main features that set it apart from the other contributions to the assessment of impact on skills from within-group comparisons. Describing the study by Hillson [48], particularly for the measure using performance on a critical appraisal test, as major, on the basis of an overall loss-to-follow up of 21%, may have been debatable.

Knowledge: Two of the five studies contributing between-group comparisons to the assessment of impact on knowledge were felt to be open to major sources of bias from the way the outcome was measured and analysed. In the study by Reigelman [54,57] the sources of this were the same as mentioned in the foregoing sections on behaviour and skills. In the study by Seelig 1993 [56] the main concern arose from an absence of information on loss to follow-up. For the other studies, Kitchens [50], Landry [51] and Linzer [52] there were minor concerns relating to lack of clear statement about whether the outcome was assessed independently and blindly. In all cases the risk of bias was felt to be low through use of measures with clearly defined correct/incorrect answers.

Only one of the studies contributing within-group comparisons to the assessment of impact of skill was felt to be relatively free of bias. This was the study by Cuddy [43]. Although no major threats to validity were isolated, there were minor concerns arising from a failure to take account of problems arising from repeated application of the same test to assess skills. There was uncertainty about the magnitude of bias likely to arise from the latter of these in particular. The remaining four studies (Burls [42], Caudill [43], Ibbotson [49] and Seelig 1991 [56]) all suffered from major concerns relating to loss to follow-up. To this were added concerns arising from lack of independent and blind assessment of outcome. The impact of this was felt to be less when using the overall impact score in the study Burls, and through use of measures with clearly defined correct/incorrect answers in the case of the studies by Caudill and Seelig.

Attitudes: Only minor concerns were recorded relating to bias arising from method of outcome assessment and analysis for the one study, by Landry [51] providing a between-group comparison. However, the scale of the concerns about detection bias arising from the difficulty of the self-assessed outcome being measured in an independent and blind manner was difficult to gauge.

Although the presence of a control would provide some protection from bias, it was felt possible that participants could relatively easily discern whether they were in the CAT arm and tailor their answers to what was perceived to be desirable.

Repeating the pattern for previous general outcomes, there were again major concerns about validity arising from high or unstated losses to follow-up in the four studies (Burls [42], Caudill [43], Seelig 1991 [55,56] and Seelig 1993 [56]) contributing within-group comparisons to assessment of impact on attitudes. These were compounded by concerns arising from the possibility of detection bias, reduced in the case when the overall impact score as opposed to crude score was used by Burls and in the case of Seelig 1993 by virtue of a control group being part of the study design.

General issues: As well as specific observations concerning the validity of the included studies arising from consideration of the means by which outcomes were measured and analysed, there are a number of general issues.

The first is a justification of the assessment of validity at the level of each outcome considered in each included study, in contrast to considering the study as a whole. This is because loss to follow-up may be suffered to different degrees by different outcomes within the same study. A clear example of this in the included studies is found in Hicks [47] where depending on the outcome considered loss to follow-up ranged from 0% to 47%. Similarly, openness to detection bias may also vary with the nature of the outcome under consideration. For instance in the study by Landry [51] it was relatively easy to accept that behaviour change assessed by consideration of patient write-ups with reference to defined criteria was likely to be assessed in an independent and blind manner. In contrast, it was much more debatable as to whether assessing attitudes measured by self-assessed agreement with various statements about the value of research would be. Again, for the assessment of impact on knowledge by Burls [42], it was much easier to make a judgement that detection bias would be unlikely in an overall impact score where the impact on test questions had been down-graded to take account of changes in control questions which had not been addressed by the critical appraisal teaching, than in the crude score.

The second general issue, was the demonstration that study design makes a considerable contribution to helping assure that an outcome has been assessed independently and blindly. Without a control group it is very difficult to envisage how a participant or investigator would not be aware that they were part of an experimental study, and that they would in turn modify their responses to take account of this. This would be particularly true for self-assessed outcomes, such as frequently encountered in this review in attempting to measure impact on behaviour and attitudes. This raises

the question of whether any outcome which is not highly objective can be accurately measured in a within-group comparison. The only innovative approach identified in a within-group comparison, to make a the impact of a self-assessed outcome more convincing, was the attempt in the study by Burls [42] to adjust improvement in test questions for smaller improvements observed in control questions which had not been addressed by the critical appraisal workshops in question.

Summary of quality and validity

The findings relating to validity are summarised in Table 6. This indicates whether there were no threats, minor threats or major threats to validity following directly from the assessments reported in the two foregoing sections. In the case of major threats the number of these is indicated. As for previous tables, shading indicates where there was uncertainty, particularly about whether problems in study design and conduct constituted major or minor threats to validity. In the last column, showing whether a study was excluded in the sensitivity analysis because one or more major threats to validity were noted, the shading reflects whether any uncertainty identified could have made a difference to whether a study was included or excluded, particularly where a study included could have been excluded if a harsher assessment of threat to validity had been made.

The key point from Table 6 is that considering bias from both study design issues and issues relating to measurement of outcomes and their analysis reveals that 12 of the 16 included studies have major threats to all or some of the outcomes assessed. The studies by Bennett [41], Cuddy [44], Landry [51] and Linzer [52] alone seem to be relatively free of bias. Unfortunately Landry did not statistically test the differences between the groups (and provided inadequate data for a reader to perform the tests), hence the results are difficult to interpret. Beyond these, measurement of skills by Hicks [47] and knowledge by phase II of the study by Kitchens [50] also seems to be relatively bias free. On this basis a crude sensitivity analysis was undertaken on the overall pattern of results considering whether this pattern would change depending on whether just those studies least susceptible to bias were considered. However, it should be further noted that considering those studies/outcomes where uncertainty was identified, indicates that harsher assessment of some of the weaknesses classified as minor would have led to exclusion in the sensitivity analysis of all but 5 of the 43 included comparisons: Landry's assessments of behaviour and knowledge; Linzer's assessments of skills (using test appraisal) and knowledge; and phase II of the study by Kitchens assessing knowledge. This emphasises that the evidence-base for the effectiveness of teaching critical appraisal skills is open to bias and needs to be interpreted with extreme caution.

Table 6. Included comparisons; summary of threats to validity

Study and comparison	Concerns from study design [See Table 3 & Appendix 9]	Concerns from outcome assessment and analysis [See Tab 4 & Appx 10]	Remove in sensitivity analysis?
BEHAVIOUR – Between-group comparisons			
Landry	None	Minor	No
Linzer	None	Minor	No
Riegelman	Major	Major (x3)	Yes
BEHAVIOUR – Within-group comparisons			
Caudill	Minor	Major (x2)	Yes
Hicks; reading behaviour	Minor	Major	Yes
Hicks; change in practice	Minor	Major (x2)	Yes
Seelig 1991	None	Major (x2)	Yes
Seelig 1993	Minor	Major	Yes
SKILLS – Between-group comparisons			
Bennett; therapy & diagnosis exercises	None	Minor	No
Frasca; critical appraisal & library skills	Major	Minor	Yes
Gehlbach	Major (x2)	Minor	Yes
Linzer; test article	None	None	No
Linzer; self-perceived skill	None	Minor	No
Radack	None	Major (x2)	Yes
Reigelman	Major	Major (x3)	Yes
SKILLS – Within-group comparisons			
Caudill	Minor	Major (x2)	Yes
Hicks; test article	None	Minor	No
Hicks; self-perceived skill	Minor	Major (x2)	Yes
Hillson; test article	None	Major	Yes
Hillson; self-perceived skill	None	Major (x2)	Yes
Seelig 1991	None	Major (x2)	Yes
Seelig 1993	Minor	Major	Yes
KNOWLEDGE – Between-group comparisons			
Kitchens; phase I	Major	Minor	Yes
Kitchens; phase II	None	Minor	No
Landry	None	Minor	No
Linzer	None	Minor	No
Reigelman	Major	Major (x2)	Yes
Seelig 1993	None	Major	Yes
KNOWLEDGE – Within-group comparisons			
Burls; crude score	None	Major (x2)	Yes
Burls; overall impact score	None	Major	Yes
Caudill	Minor	Major (x2)	Yes
Cuddy; lecture & slide-tape program	Minor	Minor	No
Ibbotson	None	Major (x2)	Yes
Seelig 1991	None	Major	Yes
ATTITUDES – Between-group comparisons			
Landry	None	Minor	No
ATTITUDES – Within-group comparisons			
Burls; crude score	None	Major (x2)	Yes
Burls; overall impact score	None	Major	Yes
Caudill	Minor	Major (x2)	Yes
Seelig 1991	None	Major (x2)	Yes
Seelig 1993	Minor	Major	Yes

Table shows whether minor or major threats to validity were identified when assessing the specified features of quality of the included comparisons. Where more than one major threat was identified the number is indicated in brackets.
Shaded cells in columns 2 & 3 indicate where there was uncertainty about whether shortcomings identified constituted major or minor threats to validity.
Shaded cells in column 4 indicate where this uncertainty could have altered whether a comparison was included or excluded in the sensitivity analysis, focusing particularly on where a study included would have been excluded if judgements on threats to validity had been harsher.

That all but one of the least biased studies employed between-group comparisons might have been predicted by some, or even be seen as a manifestation of the reviewers' bias against other experimental designs. However, in this respect it is worth noting that the reason why within-group comparisons generally faired poorly in the assessment of validity had nothing directly to do with study design. Indeed the analysis of validity clarifies that provided outcomes are assessed and reported immediately before the intervention and immediately after (with the timing being clearly reported) and provided the outcomes can be objectified, before-after designs could have provided valid outcome information in the context of this systematic review. The main reason why they did not was high levels of loss to follow-up. Further it was not clear to us that the implications of high losses were any different in before-after designs than they were in between-group comparisons, or indeed why achieving complete follow-up would be more difficult in within-group comparisons.

4.5 Results by outcome category of comparisons provided by included studies

Patient outcomes

No information was found about patient outcomes.

Behaviour

Seven of the included studies provided information on this general outcome. All but one assessed self-perceived reading behaviour, including measures such as number of articles read per unit time, number of hours reading per week, or reported regular reading of research. The remaining study by Landry [51] used an objective assessment of use of literature in patient write-ups assessed against four defined criteria. Hicks [47] also provided information from a self-assessed measure of change in behaviour on the frequency of reviewing practice based on the results of research articles read. The majority assessed behaviour change between 1 and 10 months. The results of these eight comparisons are presented in Table 7.

It should be immediately noted that there is an implicit assumption in most of the comparisons that more reading is always better. Although we accepted this assumption, it is worth noting that reductions in the number of articles read for instance, could also be argued as being beneficial, particularly if it was accompanied by greater focus, spending more time on a smaller number research papers.

Table 7. Included comparisons; results for behaviour

i **Study (Year)**	Ii **Outcome**	iii **Time**	iv **Pop**	v **Int & dur**	vi **Results (direction & stat signif)**	vii **Results (numerical)**
Measures of behaviour, other than reading beahviour						
Hicks (1994)	Frequency of review of current practice prompted by articles read. *WG; change.*	2m	MW	Study day (7 h)	*Mean rating of influence these articles had in reviewing aspects of clinical practice.* **Greater after CAT.** Statistically significant.	CAT (10/19) B: 1.3 A: 1.7 Δ: +0.4 P<0.025
Landry (1994)*	Use of medical literature in patient write-ups. *BG; change.*	5w	Med St	Sem-inars – large group (3 h)	*4 criteria to assess use of literature in medical write-ups (E/A):* 1. % citing lit in write-ups ↑ CAT; ↑↑ control. Favours control. 2. No articles cited → CAT; ↓ control. Favours CAT. 3. % referring directly to article in body of write-ups ↓ CAT; ↓↓ control. Favours CAT. 4. % mentioning quality of article ↑ CAT; ↓ control. Favours CAT. Statistical significance of between-group differences not stated. Overall: **Favours CAT.**	CAT (65/65) Con (81/81) Criterion 1. CAT B: 51% A: 53% Δ: +2% P=NS Con B: 48% A: 53% Δ: +5% P=NS BG Δ: -3% P N/S Criterion 2. CAT B: 2.5 A: 2.5 Δ: 0 P=NS Con B: 3.5 A: 3.0 Δ: -0.5 P=NS BG Δ: +0.5 P N/S Criterion 3. CAT B: 16% A: 14% Δ: -2% P=NS Con B: 20% A: 13% Δ: -7% P=NS BG Δ: +5% P N/S Criterion 4. CAT B: 0% A: 3% Δ: +3% P=NS Con B: 6% A: 0% Δ: -6% P=NS BG Δ: +9% P N/S

GENERAL NOTES:
Shaded cells indicate data items about which there was ambiguity. Where there is more than one data item in the cell, the one underlined is that where there was uncertainty.
CAT= critical appraisal teaching group. Con= control group (no CAT).
More positive values always indicate more of the specific behaviour indicated.

SPECIFIC HEADING NOTES & ABBREVIATIONS:
i) * indicates one of least biased studies considered in the sensitivity analysis.
ii) BG = between-group comparison; WG = within-group comparison; *change* indicates that before-after differences were used as the outcomes; *end* (only relevant for BG comparisons) indicates that the outcome at the end of the observation period was compared in the CAT and control groups.
iii) Indicates the time after the start of CAT when the outcomes were measured. d=days; w=weeks; m= months; y=years.
iv) Mult=multi-disciplinary (see Appx 6 for details) ; MW=midwives; Med St=medical students; Int=interns; Re=residents.
v) Gives the format used to teach critical appraisal and the planned total duration of the CAT intervention in hours. Where this varied, the minimum that all participants would have been exposed to is given.
vi) Gives the direction of effect stated in words and whether this was said to be statistically significant in the original paper [p<0.05 unless stated; if studies did not state, p<0.05 was assumed]. Where several measures contributed to the outcome eg specific items from a questionnaire, these are listed. In this case the overall direction of effect, taking into account the directions of effect in the specific measures are given in bold. For BG; *change* comparisons only: → indicates no change from before to after; ↑ indicates increase from before to after; ↓ indicates decrease from before to after; ↓↓ indicates the size of decrease was over twice as great as that in the other group. E/A=externally assessed outcome.
vii) Gives the numerical information, as presented in the original papers, used to support the statements made in column 6. First line(s) generally indicate the number of participants providing information on the measure/outcome and the total numbers originally exposed to CAT or no CAT. B=value before; A=value after; Δ=(A-B); BGΔ=(Δ CAT)-(Δ control). The exact p values are given where available. NS=non-significant, as stated in article, assumed to be p>0.05. N/S=not stated.

Table 7 (continued)

i **Study (Year)**	Ii **Outcome**	iii **Time**	Iv **Pop**	v **Int & dur**	vi **Results (direction & stat signif)**	vii **Results (numerical)**
Reading behaviour (self-perceived) – assumes more reading better						
Caudill (1993)	Reading behaviour. *WG; change.*	>6m	Drs (R)	Lect-ures and sem-inars (estim-ated 11 h)	4 measures used: 1. Subscriptions (total): Greater after CAT. 2. Articles read / week: Lower after CAT. 3. Articles critically appraised / week: Greater after CAT. 4. Articles discussed / week: No change. 0/4 statistically significant. Overall: **Favours CAT.**	CAT (22/70) Measure 1. B: N/S A: 2.4 Δ: +0.2 P=NS Measure 2. B: N/S A: 1.6 Δ: -0.2 P=NS Measure 3. B: N/S A: 1.3 Δ: +0.1 P=NS Measure 4. B: N/S A: 1.6 Δ: 0 P=NS Inconsistencies noted in presented results.
Hicks (1994)	Reading behaviour. *WG; change.*	2m	Mid Wi	Study day (7 h)	*Mean rating of frequency of reading research articles routinely:* **Greater after CAT.** Statistically significant.	CAT (17/19) B: 2.0 A: 3.0 Δ: +1.0 P<0.005
Linzer (1988)*	Reading behaviour. *BG; change.*	Ave of 9.5m	Drs (Int)	Journal clubs (min 3h [actual attend-ance])	*3 measures used:* 1. Articles per month: ↓ CAT; ↓ control. Favours control. 2. Journal subscriptions: ↑ CAT; ↑ control. Favours control. 3. Complete reading: → CAT; → control. Favours neither. 0/3 statistically significant Overall: **Favours control.**	CAT (22/22) Con (20 or 19/22) Measure 1. CAT B:13.4 A:11.1 Δ: -2.3 Con B:9.3 A:7.3 Δ: -2.0 BG Δ: -0.3 P=0.59 Measure 2. CAT B:3.0 A: 3.5 Δ: +0.5 Con B:2.2 A:2.8 Δ: +0.6 BG Δ: -0.1 P=0.89 Measure 3. CAT B:47% A: 47% Δ: 0 Con B:47% A: 47% Δ: 0 BG Δ: 0 P=0.91
R'lman (1986)	Reading behaviour. *BG; end.*	About 3y	Med St	Lect-ures + sem-inars (16 h)	*% reading research journals regularly:* Lower in CAT. **Favours control.**	CAT (91/150) A: 83% Con (82/146) A: 84% BG Δ: -1% P N/S
Seelig (1991)	Reading behaviour. *WG; change.*	4m	Drs (Re)	Sem-inar + journal clubs (8 h)	*No of hours reading per week:* **Greater after CAT.** Not statistically significant.	CAT (?/14) ie numerator N/S B: 3.8 A: 4.5 Δ: +0.7 P=0.17
Seelig (1993)	Reading behaviour. *WG; change.*	4m	Drs (Int)	Sem-inar (1 h)	No of hours reading per week: **"No change"** Statistical significance not stated.	CAT (?/18) ie numerator N/S Numerical results not given

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CAT= critical appraisal teaching group. Con= control group (no CAT).
More positive values always indicate more of the specific behaviour indicated.
See previous page for heading notes and abbreviations.

The overall pattern of results was mixed, both between studies and within studies where a number of criteria had been used to assess reading behaviour change. Of the eight comparisons, two favoured the control, five favoured CAT and one neither. The actual assessment of written patient write-ups by Landry, probably the most relevant behaviour measure used, was amongst the five comparisons favouring CAT. Two changes were statistically significant, both occurring in comparisons favouring CAT, and both provided by the study by Hicks. Giving due caution to the fact that this analysis constitutes a crude form of vote counting, giving equal weight to the included comparisons, the above provides very tentative support that CAT can bring about behaviour change. However, this needs to be tempered by the further observation that even in the studies with the most favourable results, the absolute size of any effects is small and of arguable significance in practice. Thus the highly statistically significant result on reading behaviour in the study by Hicks, referred to a change on a five-point Likert scale from 2 on average before the intervention, to 3 after (1 being infrequent). Similarly in the assessment of actual use of literature by Landry, the favourable change noted in number of articles cited in each write-up represented on average 0.5 of an additional article in the CAT intervention group. Further, this addition was not caused by increased use in the CAT group, but a fall in use in the control group.

Behaviour – sensitivity analysis

Considering only the studies least open to bias, Landry [51] and Linzer [52], further reinforces the need for caution in concluding that critical appraisal teaching has a demonstrable impact on behaviour. The study by Landry, assessing actual use of literature in patient write-ups against four criteria, narrowly favours CAT and the study by Linzer, assessing three aspects of self-perceived reading behaviour slightly favours control. None of the changes either in favour of CAT or control is statistically significant.

Table 8. Included comparisons; results for skills

i **Study (Year)**	Ii **Outcome**	iii **Time**	iv **Pop**	v **Int & dur**	vi **Results (direction & stat signif)**	Vii **Results (numerical)**
Critical appraisal exercises						
Ben-nett (1987)*	Crit appr: exercises on diagnosis. *BG; change.*	>8w	Med St	Tut-orials (16 h)	*Mean score on diagnosis exercises:* ↑ CAT; ↓ control. **Favours CAT.** Difference statistically significant.	CAT (45/49) B: 21% A: 58% Δ: +37 Con (34/43) B: 32% A: 27% Δ: -5 BG Δ: +42% (95% CI 24-60) P<0.001
Ben-nett (1987)*	Crit appr: exercises on therapy. *BG; change..*	>8w	Med St	Tut-orials (16 h)	*Mean score on therapy exercises:* ↑ CAT; ↓ control. **Favours CAT.** Difference statistically significant.	CAT (45/49) B: 27% A: 35% Δ: +8 Con (34/43) B: 28% A: 23% Δ: -5 BG Δ: +13% (95% CI 4-22) P<0.01
Hicks (1994)*	Crit appr: of test article. *WG; change.*	1d	MW	Study day (7 h)	*Concordance with expert appraisal on 8 criteria:* **Greater after CAT.** Statistically significant.	CAT (19/19) Pearson Product Moment Correlation Coefficient B: + 0.56 df 6 P=NS A: +0.69 df 6 P<0.05
Hillson (1992)	Crit appr: of test article. *WG; change.*	2m	Drs (Re)	Lect-ures + journal clubs (min of 7 h)	*Concordance with expert appraisal on 15 criteria:* Greater after CAT for 7 criteria. 1/7 statistically significant. Worse after CAT for 4. 0/4 statistically significant No change for 4. Overall: **Favours CAT.** † NB: Sign of change altered so that + denotes difference indicating improvement in skill.	CAT (23/29) Mean absolute difference from expert score - eg Hypothesis is clear: B: 1.0 A: 0.9 Δ: +0.1† P=NS Study appears biased: B: 1.4 A: 0.9 Δ: +0.5 † P=0.04 Subjects are well defined: B: 0.7 A: 1.0 Δ: -0.3 † P=NS The authors appropriately discuss study limitations: B: 1.1 A: 1.1 Δ: 0 † P=NS
Linzer (1988)*	Crit appr: test article. *BG; change.*	Ave of 9.5m	Drs (Int)	Journal clubs (min 3h [actual attend-ance])	*Mean score (max 18):* ↑ CAT; ↑↑ control. **Favours control.** Difference not statistically significant.	CAT (22/22) B: 5.9 A: 6.4 Δ: +0.5 Con (20/22) B: 4.3 A: 6.0 Δ: +1.7 BG Δ: -1.2 P=0.09
Rad-ack (1986)	Crit appr: exercise on diagnosis *BG; change.*	2m	Med St	Sem-inars (4.2 h)	*% showing significant improvement in score:* ↑ CAT; ↑ control. **Favours CAT.** Difference not statistically significant.	CAT (13/22) (B – A) > N/S: 77% Con (8/12) (B – A) > N/S: 75% BG: +2% P=NS Cut-off for significance not stated.

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CAT= critical appraisal teaching group. Con= control group (no CAT).
More positive values generally indicate greater skills. NB Hillson (1992) does not conform to this.
See following page for detailed heading notes and abbreviations.

Table 8 (continued)

i **Study (Year)**	Ii **Outcome**	iii **Time**	iv **Pop**	v **Int & dur**	vi **Results (direction & stat signif)**	vii **Results (numerical)**
MCQs on application of critical appraisal & library skills						
Frasca (1992)	Crit appr skills: MCQ test. *BG; end.*	3m	Med St	Sem-inars (15 h)	*Mean no correct (max 13):* **Favours CAT.** Statistically significant.	CAT (48/48) A: 7.4 Con (44/44) A: 4.6 BG Δ: +2.8 P<0.001
Frasca (1992)	Library skills: MCQ test. *BG; end.*	3m	Med St	Sem-inars (15 h)	*Mean no correct* (*max* 7)*:* **Favours CAT.** Statistically significant.	CAT (48/48) A: 2.5 Con (44/44) A: 1.1 BG Δ: +1.4 P<0.001
G'bach (1980)	Crit appr: MCQ test. *BG; end.*	2m-1y	Drs (Re)	Sem-inars (8 h)	*Mean score (max 7):* **Favours CAT.** Statistically significant.	CAT (23/23) A: 74% Con (44/44) A: 64% BG Δ: +10% P<0.05

GENERAL NOTES:
Shaded cells indicate data items about which there was ambiguity. Where there is more than one data item in the cell, the one underlined is that where there was uncertainty.
CAT= critical appraisal teaching group. Con= control group (no CAT).
More positive values generally indicate greater skills.

SPECIFIC HEADING NOTES & ABBREVIATIONS:
i) * indicates one of least biased studies considered in the sensitivity analysis.
ii) BG = between-group comparison; WG = within-group comparison; *change* indicates that before-after differences were used as the outcomes; *end* (only relevant for BG comparisons) indicates that the outcome at the end of the observation period was compared in the CAT and control groups.
iii) Indicates the time after the start of CAT when the outcomes were measured. d=days; w=weeks; m= months; y=years.
iv) Mult=multi-disciplinary (see Appx 6 for details) ; MW=midwives; Med St=medical students; Int=interns; Re=residents.
v) Gives the format used to teach critical appraisal and the planned total duration of the CAT intervention in hours. Where this varied, the minimum that all participants would have been exposed to is given.
vi) Gives the direction of effect stated in words and whether this was said to be statistically significant in the original paper [p<0.05 unless stated; if studies did not state, p<0.05 was assumed]. Where several measures contributed to the outcome eg specific items from a questionnaire, these are listed. In this case the overall direction of effect, taking into account the directions of effect in the specific measures are given in bold. For BG; *change* comparisons only: → indicates no change from before to after; ↑ indicates increase from before to after; ↓ indicates decrease from before to after; ↓↓ indicates the size of decrease was over twice as great as that in the other group. E/A=externally assessed outcome.
vii) Gives the numerical information, as presented in the original papers, used to support the statements made in column 6. First line(s) generally indicate the number of participants providing information on the measure/outcome and the total numbers originally exposed to CAT or no CAT. B=value before; A=value after; Δ=(A-B); BGΔ=(Δ CAT)-(Δ control). The exact p values are given where available. NS=non-significant, as stated in article, assumed to be p>0.05. N/S=not stated.

Table 8 (continued)

i **Study (Year)**	Ii **Outcome**	iii **Time**	iv **Pop**	v **Int & dur**	vi **Results (direction & stat signif)**	vii **Results (numerical)**
Self-perceived skills						
Caudill (1993)	Crit appr: perception of own skill. *WG; change.*	>6m	Drs (Re)	Lect-ures and sem-inars (estim-ated 11 h)	*Mean rating of confidence on four aspects of skill:* 1. Research design 2. Identification of study population 3. Statistics 4. Generalisation All 4 greater after CAT. 1/4 statistically significant. Overall: **Favours CAT.**	CAT (22/70) Aspect 1. B: 1.6 A: 1.8 Δ: +0.2 P=NS Aspect 2. B: 1.7 A: 2.5 Δ: +0.4 P<0.05 Aspect 3. B: 1.4 A: 1.6 Δ: +0.2 P=NS Aspect 4. B: 1.8 A: 2.2 Δ: +0.4 P=NS Inconsistencies noted in presented results.
Hicks (1994)	Crit appr: perception of own skill. *WG; change.*	2m	MW	Study day (7 h)	*Mean rating of confidence in evaluating articles:* **Greater after CAT.** Statistically significant.	CAT (13/19) B: 1.6 A: 2.5 Δ: +0.9 P<0.005
Hillson (1992)	Crit appr: perception of own skill. *WG; change.*	2m	Drs (Re)	Lect-ures + journal clubs (min of 7 h)	*Mean rating of confidence on seven aspects of skill:* 1. Study design 2. Measurements used 3. Statistics used 4. Sources of bias 5. Interpreting results 6. Clinical significance 7. How to use in practice All 7 greater after CAT. 7/7 statistically significant. Overall: **Favours CAT.**	CAT (23/29) Aspect 1. B: 3.0 A: 4.0 Δ:+1.0 P<0.001 Aspect 2. B: 3.0 A: 4.0 Δ:+1.0 P=0.001 Aspect 3. B: 2.0 A: 2.9 Δ:+0.9 P<0.001 Aspect 4. B: 2.9 A: 3.9 Δ: +1.0 P=0.001 Aspect 5. B: 3.2 A: 4.0 Δ:+0.8 P<0.001 Aspect 6. B: 3.2 A: 4.0 Δ:+0.8 P=0.006 Aspect 7. B: 3.2 A: 3.9 Δ:+0.7 P=0.002
Linzer (1988)*	Perception of own skill. *BG; change.*	Ave of 9.5m	Drs (Int)	J clubs (min 3h)	*Exact measure not stated:* **"Marked improvement in CAT group."**	Data not given.

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CAT= critical appraisal teaching group. Con= control group (no CAT).
More positive values generally indicate greater skills.

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iii) Indicates the time after the start of CAT when the outcomes were measured. d=days; w=weeks; m= months; y=years.
iv) Mult=multi-disciplinary (see Appx 6 for details) ; MW=midwives; Med St=medical students; Int=interns; Re=residents.
v) Gives the format used to teach critical appraisal and the planned total duration of the CAT intervention in hours. Where this varied, the minimum that all participants would have been exposed to is given.
vi) Gives the direction of effect stated in words and whether this was said to be statistically significant in the original paper [p<0.05 unless stated; if studies did not state, p<0.05 was assumed]. Where several measures contributed to the outcome eg specific items from a questionnaire, these are listed. In this case the overall direction of effect, taking into account the directions of effect in the specific measures are given in bold. For BG; *change* comparisons only: → indicates no change from before to after; ↑ indicates increase from before to after; ↓ indicates decrease from before to after; ↓↓ indicates the size of decrease was over twice as great as that in the other group. E/A=externally assessed outcome.
vii) Gives the numerical information, as presented in the original papers, used to support the statements made in column 6. First line(s) generally indicate the number of participants providing information on the measure/outcome and the total numbers originally exposed to CAT or no CAT. B=value before; A=value after; Δ=(A-B); BGΔ=(Δ CAT)-(Δ control). The exact p values are given where available. NS=non-significant, as stated in article, assumed to be p>0.05. N/S=not stated.

Table 8 (continued)

i **Study (Year)**	Ii **Outcome**	iii **Time**	iv **Pop**	v **Int & dur**	vi **Results (direction & stat signif)**	vii **Results (numerical)**
Self-perceived skills (continued)						
Reigel-man (1986)	Crit appr: perception of own skill. *BG; end.*	About 3y	Med St	Lect-ures + sem-inars (16 h)	*Mean rating of confidence on five aspects of skill:* 1. Study design 2. Assignment 3. Study outcomes 4. Interpreting results 5. Extrapolation All 5 favour CAT. 1/5 statistically significant. Overall: **Favours CAT.** † NB: As higher score on scale used indicates less confidence, sign of change altered so that + denotes improved confidence in skill.	CAT (91/150) Con (82/146) Aspect 1. CAT A: 3.1 Con A: 3.5 BG Δ: +0.4 † P=NS Aspect 2. CAT A: 2.6 Con A: 3.2 BG Δ: +0.6 † P<0.05 Aspect 3. CAT A: 3.0 Con A: 3.3 BG Δ: +0.3 † P=NS Aspect 4. CAT A: 2.6 Con A: 2.7 BG Δ: +0.1 † P=NS Aspect 5. CAT A: 3.0 Con A: 3.1 BG Δ: +0.1 † P=NS
Seelig (1991)	Crit appr: perception of own skill. *WG; change.*	4m	Drs (Re)	Sem-inar + journal clubs (8 h)	*Mean rating of confidence evaluating 3 article types:* 1. Original res articles 2. Other types of articles 3. Med journals (in gen) All 3 greater after CAT. 1/2 statistically significant. Overall: **Favours CAT.**	CAT (?/14) ie numerator N/S Type 1. B: 3.3 A: 4.1 Δ: +0.8 P=0.01 Type 2. B: 4.0 A: 4.1 Δ: +0.1 P>0.05 Type 3. B: 3.9 A: 4.4 Δ: +0.5 P>0.05
Seelig (1993)	Perception of own skill. *WG; change.*	4m	Drs (Int)	Sem-inar (1 h)	*Mean rating of confidence evaluating 3 articles types:* **"Little or no effect".**	CAT (?/18) ie numerator N/S Numerical results not given

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iii) Indicates the time after the start of CAT when the outcomes were measured. d=days; w=weeks; m= months; y=years.
iv) Mult=multi-disciplinary (see Appx 6 for details) ; MW=midwives; Med St=medical students; Int=interns; Re=residents.
v) Gives the format used to teach critical appraisal and the planned total duration of the CAT intervention in hours. Where this varied, the minimum that all participants would have been exposed to is given.
vi) Gives the direction of effect stated in words and whether this was said to be statistically significant in the original paper [p<0.05 unless stated; if studies did not state, p<0.05 was assumed]. Where several measures contributed to the outcome eg specific items from a questionnaire, these are listed. In this case the overall direction of effect, taking into account the directions of effect in the specific measures are given in bold. For BG; *change* comparisons only: → indicates no change from before to after; ↑ indicates increase from before to after; ↓ indicates decrease from before to after; ↓↓ indicates the size of decrease was over twice as great as that in the other group. E/A=externally assessed outcome.
vii) Gives the numerical information, as presented in the original papers, used to support the statements made in column 6. First line(s) generally indicate the number of participants providing information on the measure/outcome and the total numbers originally exposed to CAT or no CAT. B=value before; A=value after; Δ=(A-B); BGΔ=(Δ CAT)-(Δ control). The exact p values are given where available. NS=non-significant, as stated in article, assumed to be p>0.05. N/S=not stated.

Skills

Eleven studies, providing information from 16 comparisons contributed to assessment of the impact on skills. Six comparisons assessed skill using responses to test articles or critical appraisal problems; two used MCQs requiring application of critical appraisal skills or interpretation of an article; one used MCQs requiring application of library skills; and seven comparisons assessed self-perceived skills. Although there was a considerable amount of ambiguity on the timing of assessments for a number of studies, as for behaviour, the majority assessed skills change between 1 and 10 months after the start of the critical appraisal teaching interventions. The results, grouped according to the means by which skills were assessed, are presented in Table 8.

The overall pattern with respect to direction of effect consistently favours critical appraisal teaching. 14 of the 16 comparisons favoured CAT; 1 from the study by Seelig 1993 [56] showed “little or no effect”; and 1 from the study by Linzer [52] favoured the control group. 12 of the 14 favourable comparisons were wholly or in part (where several criteria were used) statistically significant.

This pattern remains considering just those comparisons that might be judged to give the most objective measures of impact on skills. Where a critical appraisal exercise was used, 5 of the six comparisons favoured CAT. In four of these, the differences were of statistical significance. In the fifth comparison favouring CAT in the study by Hillson [48], 15 criteria were used of which one was statistically significant. Given the large number of outcomes compared (and the absence of any adjustment for multiple comparisons) the true significance of this result is debatable. Similarly where MCQs were used all three comparisons favoured CAT, and all in an unequivocally statistically significant manner.

It thus seems reasonable to assert that the critical appraisal teaching has a positive effect on skills. However, when the size of this effect is considered the nature the impact on skills is very much more difficult to discern. Concentrating again on just those measures of skill which might be judged to give the most objective assessment of impact (results based on critical appraisal exercises and MCQs) reveals considerable variation in the size of effect. The most convincing change is found in the study by Bennett [41] where for the exercises on therapy the mean scores improved from 21% to 58% in the critical appraisal teaching group, but deteriorated from 32% to 27% in the control group. The net effect of the critical appraisal teaching was thus +42% [95% CI 24 to 60]. However in the same study, the impact on skills as judged by scores in the test on diagnosis were much less dramatic, the net effect being +13% [95% CI: 4 to 22]. At the other extreme was the study by Linzer [52], the only study to favour the control group. In this the scores on the critical appraisal test

exercise improved from 33% to 36% in the critical appraisal teaching group and from 24% to 33% in the control group, the net effect of CAT thus being –6%. In between these extremes, the size of effect was either very difficult to interpret, the results being based on correlation with expert assessments in the cases of the studies by Hicks [47] and Hillson [48], or the results showed small or moderate net effects, +2% in the case of Radack [53], +10% in the case of Gehlbach [46] and +22% or +20% in the case of Frasca [45]. In this situation it is tempting to suggest that meta-analysis (which would be possible) might help clarify the size of effect. This however ignores the fact that of the 16 comparisons available, only 7 contained information to allow quantification of the effect. Moreover the studies which could be expressed quantitatively, contained the only study indicating an effect favouring the control group.

Clearly, the above assessments of size of effect include self-rated assessments, which do not separate real changes in skills from misperceptions about skills. Our judgement was that the means by which this was measured does not give an accurate estimate of size of effect, but that that such scales were of value in assessing the direction of effect. However, even in this a note of caution needs to be introduced. In the study by Linzer, assessment of impact using self-perceived impact gave a result clearly favouring CAT, but when assessed using a relatively more objective measure involving scoring of performance on a test article, the result favoured the control.

Finally as far as the impact on skills is concerned it should be noted that although some of the included comparisons give an indication of what the range of sizes of effect might be, none attempts to define a level which would be significant in practice.

Skills – sensitivity analysis

Yet further caution in firmly concluding that critical appraisal teaching has a positive impact on skills is added when restricting analysis of the results to those studies and comparisons which were not open to major sources of bias – Bennett [41], Hicks [47] (for the assessment using a test article only) and Linzer [52]. This somewhat undermines the consistent pattern of benefit attributable to critical appraisal teaching with respect to skills emerging when openness to bias is not taken into account. Of the five relatively unbiased comparisons contributing information on impact on skills 4 favoured CAT and 1 favoured control. Three unequivocally statistically significant results were noted, all in differences favouring CAT. Thus although the overall balance of results remains favouring CAT, the overwhelming balance of evidence suggesting a positive impact on skills is reduced. Again the inconsistency within the results in the study by Linzer, where a positive effect is obtained when self-perceived impact on skills is used and a negative effect when assessed using performance in a test article, adds a further note of caution. It should be re-emphasised that the assessments of openness to bias were made completely independently of knowledge of the results.

Knowledge

Ten studies, providing information from 12 comparisons contributed to assessment of the impact on knowledge. 3 comparisons contributed by the studies by Cuddy [44] and Landry [51] included an element of skills. 10 comparisons assessed knowledge using responses to tests or MCQs ; and 2 comparisons assessed self-perceived knowledge. Despite considerable ambiguity in the exact timing of the outcome measures in a number of studies, the majority assessed knowledge change between 1 day and 10 months after the start of the critical appraisal teaching interventions. The greater representation of results measuring very early assessment of impact (<1 month) is a slight contrast to the results for the other outcome groups presented. The results, grouped by the way in which the outcome was measured, are presented in Table 9.

Table 9. Included comparisons; results for knowledge

i **Study (Year)**	ii **Outcome**	iii **Time**	iv **Pop**	v **Int & dur**	vi **Results (direction & stat signif)**	vii **Results (numerical)**
Performance in tests and MCQs						
Caudill (1993)	Epidemiology & biostatistics: test questions. *WG; change.*	>6m	Drs (Re)	Lects & sems (est. 11 h)	*% correct (15 questions):* **"No significant improvement detected."**	CAT (22/70) B: 37% A: N/S Δ: N/S P=NS
Cuddy (1984) (Lect)*	Basic concep-ts of lit eval: MCQ test. *WG; change.*	>1h	Med St	Lecture (1 h)	*% correct (20 questions):* **Greater after CAT.** Statistically significant.	CAT (9/9) B: 66% A: 83% Δ: +17% P<0.05 Results read from graph.
Cuddy (1984) (Slide-tape)*	Basic concep-ts of lit eval: MCQ test. *WG; change.*	>21 mins	Med St	Slide/ tape prog (0.33 h)	*% correct (20 questions):* **Greater after CAT.** Statistically significant.	CAT (9/9) B: 66% A: 83% Δ: +17% P<0.05 Results read from graph.
K'hens (1989) (Ph I)	Clin epi princs: T/F & MCQ test. *BG; end.*	21w	Drs (Re)	Sems (min 8.5 h)	*Mean % score:* **Favours CAT.** Not statistically significant.	CAT (48/51) A: 67% Con (31/32) A: 63% BG Δ: +4% P=0.2
K'hens (1989) (Ph II)*	Clinical epi-demiology principles: T/F & MCQ test. *BG; change.*	12w	Drs (Re)	Sem-inars (min 4 h)	*Mean % score:* ↑ CAT; ↓ control. **Favours CAT.** Difference Statistically significant.	CAT (29/32) B: 63% A:69% Δ: +5% Con (41/51) B: 66% A:65% Δ: -1% BG Δ: +7% P=0.02
Landry (1994)*	Basic research design: T/F test. *BG; change.*	5w	Med St	Sem-inars – large group (3 h)	*% questions correct:* ↑↑ CAT; ↑ control. **Favours CAT.** Difference Statistically significant.	CAT (65/65) B: 72% A: 82% Δ:+10% P=0.001 Con (81/81) B: 73% A: 74% Δ:+1% P=NS BG Δ: +9%
Linzer (1988)*	Epidemiology & biostatistics: test questions. *BG; change.*	Ave of 9.5m	Drs (Int)	Journal clubs (min 3h [actual attend.)	*Mean scores (max 15):* ↑↑ CAT; ↑ control. **Favours CAT.** Difference Statistically significant.	CAT (22/22) B: 9.3 A: 10.8 Δ: +1.5 Con (19/22) B: 10.0 A: 10.3 Δ: +0.3 BG Δ: +1.2 P=0.04

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iii) Indicates the time after the start of CAT when the outcomes were measured. mins=minutes d=days; w=weeks; m= months; y=years.
iv) Mult=multi-disciplinary (see Appx 6 for details) ; MW=midwives; Med St=medical students; Int=interns; Re=residents.
v) Gives the format used to teach critical appraisal and the planned total duration of the CAT intervention in hours. Where this varied, the minimum that all participants would have been exposed to is given.
vi) Gives the direction of effect stated in words and whether this was said to be statistically significant in the original paper [p<0.05 unless stated; if studies did not state, p<0.05 was assumed]. Where several measures contributed to the outcome eg specific items from a questionnaire, these are listed. In this case the overall direction of effect, taking into account the directions of effect in the specific measures are given in bold. For BG; *change* comparisons only: → indicates no change from before to after; ↑ indicates increase from before to after; ↓ indicates decrease from before to after; ↓↓ indicates the size of decrease was over twice as great as that in the other group. E/A=externally assessed outcome.
Vii) Gives the numerical information, as presented in the original papers, used to support the statements made in column 6. First line(s) generally indicate the number of participants providing information on the measure/outcome and the total numbers originally exposed to CAT or no CAT. B=value before; A=value after; Δ=(A-B); BGΔ=(Δ CAT)-(Δ control). The exact p values are given where available. NS=non-significant, as stated in article, assumed to be p>0.05. N/S=not stated.

Table 9 (continued)

i **Study (Year)**	Ii **Outcome**	iii **Time**	iv **Pop**	v **Int & dur**	vi **Results (direction & stat signif)**	vii **Results (numerical)**
Performance in tests and MCQs (continued)						
Reigel-Man (1986)	Study design & statistics: T/F questions. *BG; end.*	About 3y	Med St	Lect-ures + sem-inars (16 h)	*% students answering correctly in each of 4 questions:* For all questions. **Favours CAT.** 2/4 statistically significant.	CAT (91/150) Con (82/146) Q1 CAT A: 90% Con A: 63% BG Δ: +27% P<0.05 Q2 CAT A: 93% Con A: 78% BG Δ: +15% P<0.05 Q3 CAT A: 87% Con A: 81% BG Δ: +6% P=NS Q4 CAT A: 91% Con A: 82% BG Δ: +9% P=NS
Seelig (1991)	Basic principles of crit appr: test questions. *WG; change.*	4m	Drs (Re)	Sem-inar + journal clubs (8 h)	*Mean % correct in test:* **Greater after CAT.** Statistically significant	CAT (?/14) ie numerator N/S B: 42% A: 67% Δ: +25% P=0.02
Seelig (1993)	Basic principles of crit appr: test questions. *BG; change.*	4m	Drs (Int)	Sem-inar (1 h)	*Mean % correct:* → CAT; → control. **"Favours neither."** Statistical significance not stated.	CAT (?/18) ie numerator N/S B: N/S A: 56% Δ: N/S Con (?/12) ie numerator N/S B: N/S A: 54% Δ: N/S BG Δ: N/S P N/S

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More positive values in all cases indicate greater knowledge.

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iii) Indicates the time after the start of CAT when the outcomes were measured. d=days; w=weeks; m= months; y=years.
iv) Mult=multi-disciplinary (see Appx 6 for details) ; MW=midwives; Med St=medical students; Int=interns; Re=residents.
v) Gives the format used to teach critical appraisal and the planned total duration of the CAT intervention in hours. Where this varied, the minimum that all participants would have been exposed to is given.
vi) Gives the direction of effect stated in words and whether this was said to be statistically significant in the original paper [p<0.05 unless stated; if studies did not state, p<0.05 was assumed]. Where several measures contributed to the outcome eg specific items from a questionnaire, these are listed. In this case the overall direction of effect, taking into account the directions of effect in the specific measures are given in bold. For BG; *change* comparisons only: → indicates no change from before to after; ↑ indicates increase from before to after; ↓ indicates decrease from before to after; ↓↓ indicates the size of decrease was over twice as great as that in the other group. E/A=externally assessed outcome.
Vii) Gives the numerical information, as presented in the original papers, used to support the statements made in column 6. First line(s) generally indicate the number of participants providing information on the measure/outcome and the total numbers originally exposed to CAT or no CAT. B=value before; A=value after; Δ=(A-B); BGΔ=(Δ CAT)-(Δ control). The exact p values are given where available. NS=non-significant, as stated in article, assumed to be p>0.05. N/S=not stated.

Table 9 (continued)

i **Study (Year)**	Ii **Outcome**	iii **Time**	iv **Pop**	v **Int & dur**	vi **Results (direction & stat signif)**	vii **Results (numerical)**
Self-perceived assessment of knowledge						
Burls (1997)	Understanding of key terms in SRs: perception of own knowledge (crude score). *WG; change.*	1d	Mult	Work-shop (min-imum of 2.7 h)	*Mean rating in test questions (9):* For all questions. Greater after CAT. 9/9 statistically significant. *Mean rating in control questions (9):* For all questions. Greater after CAT. 9/9 statistically significant. **NB These results duplicate those of next entry.**	CAT (1315 to 1337/1880) Test questions: Q1 Δ: +0.5 Q2 Δ: +1.6 Q5 Δ: +0.8 Q10 Δ: +1.4 Q11 Δ: +1.1 Q12 Δ: +1.7 Q14 Δ: +1.2 Q17 Δ: +0.4 Q18 Δ: +0.8 Control questions: Q3 Δ: +0.2 Q4 Δ: +0.2 Q6 Δ: +0.4 Q7 Δ: +0.2 Q8 Δ: +0.4 Q9 Δ: +0.2 Q13 Δ: +0.5 Q15 Δ: +0.1 Q16 Δ: +0.2 B & A values N/S All P<0.0001
Burls (1997)	Understanding of key terms in SRs: percept'n of own k'ledge (overall impact score). *WG; change.*	1d	Mult	Work-shop (min-imum of 2.7 h)	*Overall impact score:* Range –200 to +200; 0 indicates no change; +30 judged as being a practically significant impact. **Greater after CAT.** Statistically significant.	CAT (1339/1880) Mean score +54 95% CI +51 to +56 St dev 44 86% >0 73% >30
Ibbot-son (1997)	Understanding of key terms in SRs: perception of own knowledge (crude score). *WG; change.*	1d	Mult	Work-shop (min-imum of 2.7 h)	*Mean rating in test questions (9):* For all questions. Greater after CAT. 9/9 statistically significant. *Mean rating in control questions (9):* For all questions. Greater after CAT. Statistical significance not stated. Overall: **Favours CAT.**	CAT (86/115) Test questions: B: 38/45 A: 42/45 Δ: +4 P<0.001 Control questions: B: 28/45 A: 30/45 Δ: +1 P N/S

GENERAL NOTES:
Shaded cells indicate data items about which there was ambiguity. Where there is more than one data item in the cell, the one underlined is that where there was uncertainty.
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More positive values in all cases indicate greater knowledge.

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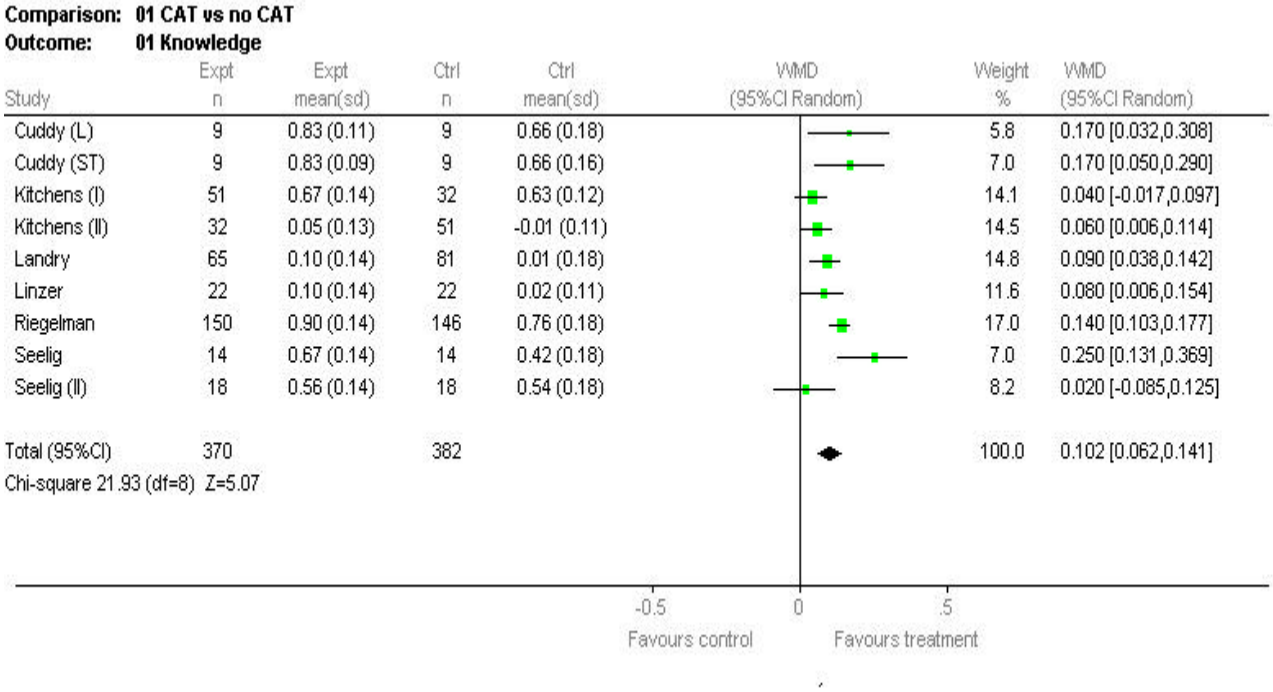
iii) Indicates the time after the start of CAT when the outcomes were measured. d=days; w=weeks; m= months; y=years.
iv) Mult=multi-disciplinary (see Appx 6 for details) ; MW=midwives; Med St=medical students; Int=interns; Re=residents.
v) Gives the format used to teach critical appraisal and the planned total duration of the CAT intervention in hours. Where this varied, the minimum that all participants would have been exposed to is given.
vi) Gives the direction of effect stated in words and whether this was said to be statistically significant in the original paper [p<0.05 unless stated; if studies did not state, p<0.05 was assumed]. Where several measures contributed to the outcome eg specific items from a questionnaire, these are listed. In this case the overall direction of effect, taking into account the directions of effect in the specific measures are given in bold. For BG; *change* comparisons only: → indicates no change from before to after; ↑ indicates increase from before to after; ↓ indicates decrease from before to after; ↓↓ indicates the size of decrease was over twice as great as that in the other group. E/A=externally assessed outcome.
Vii) Gives the numerical information, as presented in the original papers, used to support the statements made in column 6. First line(s) generally indicate the number of participants providing information on the measure/outcome and the total numbers originally exposed to CAT or no CAT. B=value before; A=value after; Δ=(A-B); BGΔ=(Δ CAT)-(Δ control). The exact p values are given where available. NS=non-significant, as stated in article, assumed to be p>0.05. N/S=not stated.

In this table it should be noted that in the study by Burls [42] an additional comparison ("crude score") is presented. This is to emphasise that when making assessments using self-perception of knowledge, or indeed any outcome, there will be a tendency for participants to respond in a way which they believe is desired. Thus, in the case in point, the crude results in the study by Burls show that not only was there an improvement in self-perceived knowledge in the nine questions relating to terms which had been addressed in the critical appraisal teaching, but also a positive change, although much less pronounced, in the self-perceived knowledge of terms which had not been addressed. However, in deciding what the overall pattern of results is, this comparison should not be considered as it would lead to double-counting of the results obtained in the Burls study, for which the main representation is the results as expressed in the overall impact score.

As for skills, there is a consistent pattern in favour of CAT with respect to the direction of effect on knowledge. All the included comparisons bar two, Caudill [43] and Seelig 1993 [56], favoured CAT. Even in the case of Seelig, although the results were reported as favouring neither CAT or control, the numerical results show a very small advantage for CAT. The reported results for Caudill, "no significant improvement detected", also suggest that there was improvement, but that it was not statistically significant. However, without the numerical results to confirm this, this interpretation is clearly debatable. Of the 10 comparisons clearly supporting an impact of CAT on knowledge, 7 were unequivocally statistically significant. Further in the study by Reigelman [54,57] two of the four components making up the overall assessment of impact on knowledge were statistically significant, and in the study by Ibbotson [49], it seems likely that the difference was statistically significant.

On this basis it thus seems reasonable to conclude that critical appraisal teaching does have a positive impact on knowledge. However, as for skills, the size of the effect on knowledge attributable to critical appraisal teaching is far more difficult to discern. Inspection of Table 9, focusing particularly on the results derived from tests, which we judged would give the best estimate of effect size, shows there is enormous variation in the impact on knowledge. This ranges from extremely small changes, as in the case of Seelig 1993, with an additional 2% in score attributable to CAT, to extremely large changes as in the case of Seelig 1991, with an additional 25% in score potentially attributable to CAT. In Figure 2 we have plotted the results of all comparisons that assessed knowledge through MCQ tests (excepti Caudill [43] which had no numerical data) using a standard Forest plot. The results as recorded in Table 9 have been converted to a % score or change in % score for the CAT period, and the same for the control. Differences between CAT and control values have then been calculated. Standard deviations were either taken from the original papers or estimated using values from other studies.

Figure 2. Included comparisons; results for knowledge measured by tests or MCQs (summary diagram)



The most notable feature in Figure 2 is the marked statistical heterogeneity in the results. An indication of this is given by the chi-square statistic, which at 21.93, and being greatly in excess of the number of studies, clearly indicates that there is a far greater spread in the results than could be accounted for by chance. For this reason the summary measure supplied cannot be taken as a true indication of a common measure of impact on knowledge. It seems likely that there are other important differences between studies (possibly in the outcomes assessed and the intervention tested) which will account for the variation. Unfortunately the relatively small number of studies available and the omission of important detail from the study reports limits our ability to identify exactly which of the many potential variables which might be responsible for this wide variation is actually at work, and importantly whether it relates to inadequacies of the studies, or real effects.

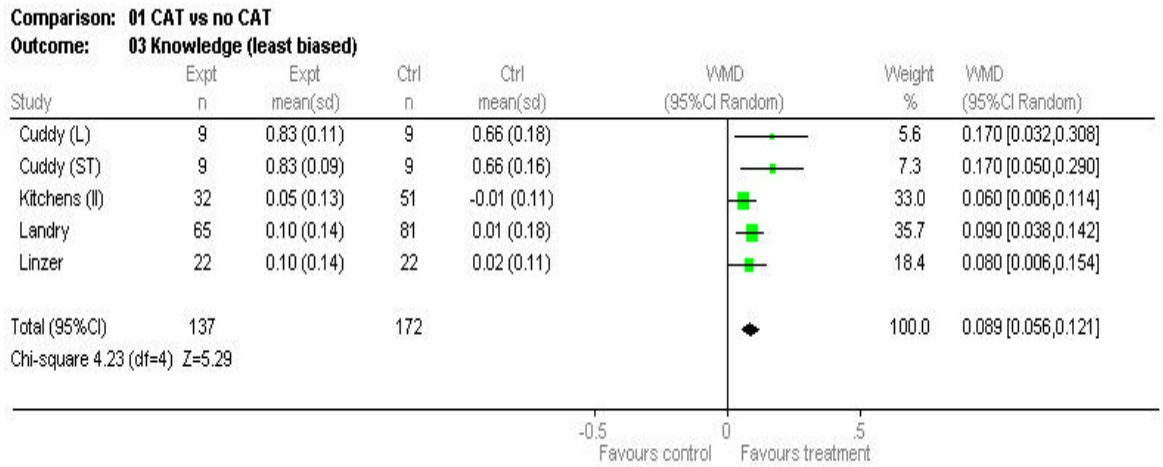
Finally, in the same way as for impact on skills, a further challenge beyond estimating the true size of the effect on knowledge is a definition of whether a particular level represents a change which is likely to be significant in practice. However, in contrast to the included comparisons on skills, one study assessing impact on knowledge (Burls [42]) did attempt to define a level of change in the overall impact score which was felt to represent a useful and important change. On this basis the study was able to identify that 73% of participants in the critical appraisal workshop programme

achieved a level of change felt to be useful in practice. Although the level chosen was not validated, the approach adopted seemed to be a useful one that could be applied more widely.

Knowledge – sensitivity analysis

Considering just those studies and comparisons least open to bias (Cuddy 44], Kitchens [50] (Phase II only), Landry [51] and Linzer [52]) generally makes little difference to the provisional conclusions about the direction of effect of critical appraisal teaching on knowledge. Indeed, removing the two most equivocal comparisons (Caudill and Seelig 1993) reinforces the impression that CAT has a positive effect on knowledge. Further, restricting the analysis to those studies judged least open to bias also clarifies the assessment of size of effect as is illustrated in Figure 3. The statistical heterogeneity is much reduced and generates a much more plausible summary measure, an increase in % score of 9% (95%CI 6 to 12%). However, even with increased confidence about the true size of the effect of critical appraisal teaching on knowledge, still leaves unanswered the question of whether an increase in knowledge of the size indicated is clinically important.

Figure 3. Included comparisons; sensitivity analysis of results for knowledge including just studies least open to bias (summary diagram)



Attitudes

Five studies, providing information from 5 comparisons should have contributed to assessment of the impact on attitudes. However one study , Seelig 1993 [56], although clearly indicating that it had collected information on attitudes, did not provide any results. Thus effectively there were only 4 studies contributing 4 comparisons. All of these comparisons measured attitudes using self assessed agreement/disagreement with series of statements. This outcome was generally assessed between 1 day and 6 months after the start of the critical appraisal teaching interventions. The results are presented in Table 10.

As for Table 10, in this table too it should be noted that in the study by Burls [42] an additional comparison ("crude score") is presented. Again as before this is to emphasise that when making assessments using self-perception there will be a tendency for participants to respond in a way which they believe is desired. The crude results for impact on attitudes in the study by Burls show that not only was there an improvement in agreement/disagreement in the desired direction in the six "test" statements, but also greater agreement in two "control" statements where no particular changes were being sought. However, in deciding what the overall pattern of results is with respect to impact on attitudes, this comparison should not be considered as it would lead to double-counting of the results obtained in the Burls study, for which the main representation is the results as expressed in the overall impact score.

The pattern of results across the included comparisons suggests a positive direction of effect on attitudes from critical appraisal teaching. Three comparisons unequivocally favour CAT; the other study (Seelig 1991) provides support from 4 of the 10 statements posed. The other six statements prompted no change following the CAT intervention. Two of the included comparisons (Burls [42] and Landry [51]) were of unequivocal statistical significance. The pronounced tendency for participants to change in a direction which they perceive to be desired clearly needs to be taken into account in assessing whether CAT truly has an impact on attitudes, but both the study by Burls and by Landry take this into account to a degree. In the first study the overall impact score adjusts for the change seen in the control questions; in the second the presence of a parallel control to some extent blinds the participants as to what is desired. However it is unlikely that either approach completely eliminates the phenomenon.

Table 10. Included comparisons; results for attitude

I **Study (Year)**	Ii **Outcome**	iii **Time**	iv **Pop**	v **Int & dur**	vi **Results (direction & stat signif)**	vii **Results (numerical)**
Burls (1997)	Need to use research: degree of agreement with statements (crude score). *WG; change.*	1d	Mult	Work-shop (min-imum of 2.7 h)	*Mean rating of agreement/disagreement with test statements (6):* Where greater agreement desired (3): Greater after CAT. 3/3 statistically significant. Where greater disagreement desired (3): Greater after CAT. 3/3 statistically significant. *Mean rating of agreement/disagreement with control statements (2):* (No greater agreement or disagreement desired) Greater agreement after CAT. 2/2 statistically significant. **NB These results duplicate those of next entry.**	CAT (1352 to 1383/1880) Test statements (agree): Q1 Δ: +0.1 † Q2 Δ: +0.1 † Q9 Δ: +0.1 † Test statements (disagree): Q5 Δ: +0.1 Q7 Δ: +0.1 Q10 Δ: +0.2 Control statements: Q4 Δ: -0.1 Q6 Δ: -0.1 B & A values N/S All P<0.0001, bar Q7 P<0.005 † NB: In paper ↓ in ratings indicates greater agreement & ↑ greater disagreement. Signs have been altered for Q 1,2 & 9 so + denotes a favourable change in attitude.
Burls (1997)	As above (overall impact score). *WG; change.*	1d	Mult	Work-shop (min-imum of 2.7 h)	*Overall impact score:* Range –100 to +100; 0 indicates no change; +15 judged as being a clinically significant impact. **Favours CAT.** Statistically significant.	CAT (1327/1880) Mean score +21 95% CI +19 to +24 St dev 42
Caudill (1993)	Limits to use of research literature: agreement with state-ments. *WG; change.*	>6m	Drs (Re)	Lects and sem-inars (estim-ated 11 h)	*Mean rating of agreement with 3 statements:* In all greater agreement was desired. **"Improvement" after CAT.** 0/3 statistically significant.	CAT (22/70) Statement 1 B: 3.5 A: N/S Δ: N/S P=NS Statement 2 B: 3.1 A: N/S Δ: N/S P=NS Statement 3 B: 3.4 A: N/S Δ: N/S P=NS

GENERAL NOTES:
Shaded cells indicate data items about which there was ambiguity. Where there is more than one data item in the cell, the one underlined is that where there was uncertainty.
CAT= critical appraisal teaching group. Con= control group (no CAT).
More positive values generally indicate more favourable attitudes.

SPECIFIC HEADING NOTES & ABBREVIATIONS:
i) * indicates one of least biased studies considered in the sensitivity analysis.
ii) BG = between-group comparison; WG = within-group comparison; *change* indicates that before-after differences were used as the outcomes; *end* (only relevant for BG comparisons) indicates that the outcome at the end of the observation period was compared in the CAT and control groups.
iii) Indicates the time after the start of CAT when the outcomes were measured. d=days; w=weeks; m= months; y=years.
iv) Mult=multi-disciplinary (see Appx 6 for details) ; MW=midwives; Med St=medical students; Int=interns; Re=residents.
v) Gives the format used to teach critical appraisal and the planned total duration of the CAT intervention in hours. Where this varied, the minimum that all participants would have been exposed to is given.
vi) Gives the direction of effect stated in words and whether this was said to be statistically significant in the original paper [p<0.05 unless stated; if studies did not state, p<0.05 was assumed]. Where several measures contributed to the outcome eg specific items from a questionnaire, these are listed. In this case the overall direction of effect, taking into account the directions of effect in the specific measures are given in bold. For BG; *change* comparisons only: → indicates no change from before to after; ↑ indicates increase from before to after; ↓ indicates decrease from before to after; ↓↓ indicates the size of decrease was over twice as great as that in the other group. E/A=externally assessed outcome.
vii) Gives the numerical information, as presented in the original papers, used to support the statements made in column 6. First line(s) generally indicate the number of participants providing information on the measure/outcome and the total numbers originally exposed to CAT or no CAT. B=value before; A=value after; Δ=(A-B); BGΔ=(Δ CAT)-(Δ control). The exact p values are given where available. NS=non-significant, as stated in article, assumed to be p>0.05. N/S=not stated.

Table 10 (continued)

i **Study (Year)**	Ii **Outcome**	iii **Time**	iv **Pop**	v **Int & dur**	vi **Results (direction & stat signif)**	vii **Results (numerical)**
Landry (1994)*	Value of research: Agreement with state-ments. *BG; change.*	5w	Med St	Sem-inars – large group (3 h)	*% agreeing/disagreeing with 4 statements:* Where greater agreement desired (2): ↑↑ CAT; ↑ or → in control. **Favours CAT.** 2/2 differences statistically significant. Where greater disagreement desired (2): ↑↑CAT; ↑ or ↓ in control. **Favours CAT.** 2/2 differences statistically significant. † NB: % agreeing quoted in paper used to derive % disagreeing ie (100-figure quoted in paper)	CAT (65/65) Con (81/81) Statement 1 CAT B: 52% A: 77% Δ: +25% P<0.05 Con B: 52% A: 54% Δ: +2% P=NS BG Δ: +23% P N/S Statement 2 CAT B: 79% A: 94% Δ: +15% P<0.05 Con B: 76% A: 76% Δ: 0% P=NS BG Δ: +15% P N/S Statement 3 † CAT B: 40% A: 70% Δ: +30% P<0.05 Con B: 55% A: 57% Δ: +2% P=NS BG Δ: +28% P N/S Statement 4 † CAT B: 57% A: 75% Δ: +18% P<0.05 Con B: 60% A: 59% Δ: -1% P=NS BG Δ: +19% P N/S
Seelig (1991)	Importance and purpose of reading journal articles: degree of agreement with state-ments. *WG; change.*	4m	Drs (Re)	Sem-inar + journal clubs (8 h)	*Mean rating of agreement with 10 statements:* Where greater agreement desired (6): **"No change" after CAT.** 0/6 statistically significant. Where greater disagreement desired (4): **Greater after CAT.** 0/4 statistically significant. † NB: Sign altered so + denotes favourable change in attitude.	CAT (?/14) ie numerator N/S Agreement desired 1. B: 5.3 A :N/S Δ: N/S 2. B: 5.2 A :N/S Δ: N/S 3. B: 5.0 A :N/S Δ: N/S 4. B: 4.9 A :N/S Δ: N/S 5. B: 4.7 A :N/S Δ: N/S 6. B: 3.8 A :3.8 Δ: 0 Disagreement desired 7. B: 5.7 A :4.9 Δ: +0.8 † 8. B: 5.2 A :5.1 Δ: +0.1 † 9. B: 4.8 A :4.3 Δ: +0.5 † 10. B: 4.4 A :4.3 Δ: +0.1 † All P=NS
Seelig (1993)	Importance and purpose of reading journal articles: degree of agreement with state-ments. *WG; change.*	4m	Drs (Int)	Sem-inar (1 h)	*Mean rating of agreement with 10 statements (as for Seelig 1993):* No results reported, although study claims to address this outcome in methods section. Statistical significance not stated.	CAT (?/18) ie numerator N/S Numerical results not given.

GENERAL NOTES:
Shaded cells indicate data items about which there was ambiguity. Where there is more than one data item in the cell, the one underlined is that where there was uncertainty.
CAT= critical appraisal teaching group. Con= control group (no CAT).
More positive values generally indicate more favourable attitudes.
See previous page for detailed heading notes and abbreviations.

As far as size of effect and its significance in practice is concerned the nature of the outcome and the way it is assessed in the included comparisons make these impossible to judge. Ideally some indication of the proportion of participants who had changed from being highly unreceptive to receptive to the need to incorporate use of research into practice would have been measured, but no measure equivalent to this was identified.

Attitudes – sensitivity analysis

Considering the single study by Landry judged open to least bias, makes little difference to the results on impact on attitudes as this was one of the studies which provided unequivocal, statistically significant support for a positive effect of CAT on attitudes.

Satisfaction

To re-emphasise, no comparisons from included studies contained information on satisfaction meeting the criteria for this review.

4.6 Influence of nature of participants on study outcomes

Variation in the results has been highlighted for three of the four general outcome groups for which data from included studies was available – behaviour, skills and knowledge. A priori we felt strongly that variation in openness to bias was likely to account for much of this variation. We believe that the analysis of results for knowledge in particular confirms that openness to bias is likely to be a major contributor to variation in results from one study to the next. However, even in the case of knowledge, openness to bias does not completely account for the variation. The nature of participants has been put forward as a potential explanatory variable, particularly that there is a difference in the effectiveness of teaching critical appraisal teaching between undergraduate and post-graduate participants [30]. Fortunately even for those outcomes such as knowledge where there is greatest information on impact, there is still relatively limited amounts of evidence for the purpose of explaining variation. This prohibits attempts to reliably detect whether variation is truly attributable to variables like nature of the participant and nature of the intervention (see next section 4.7). Acknowledging this, we nonetheless tentatively explored whether there was any evidence for their influence. In this we accept that these attempts are hypothesis-generating rather then hypothesis-proving exercises.

The first point to note is that at the level of direction of effect for the outcomes where this is clear- skills probably, and knowledge and attitudes certainly- there appears to be no influence of variables accounting for variation. Thus with reference to Table 9, in the case of nature of participants' relation to impact on knowledge, a positive effect was found irrespective of whether the participants were medical students, post-graduate doctors (interns and residents) or multi-disciplinary including

substantial proportions of non-medically qualified health care workers. A similar pattern is repeated for attitudes – see Table 10.

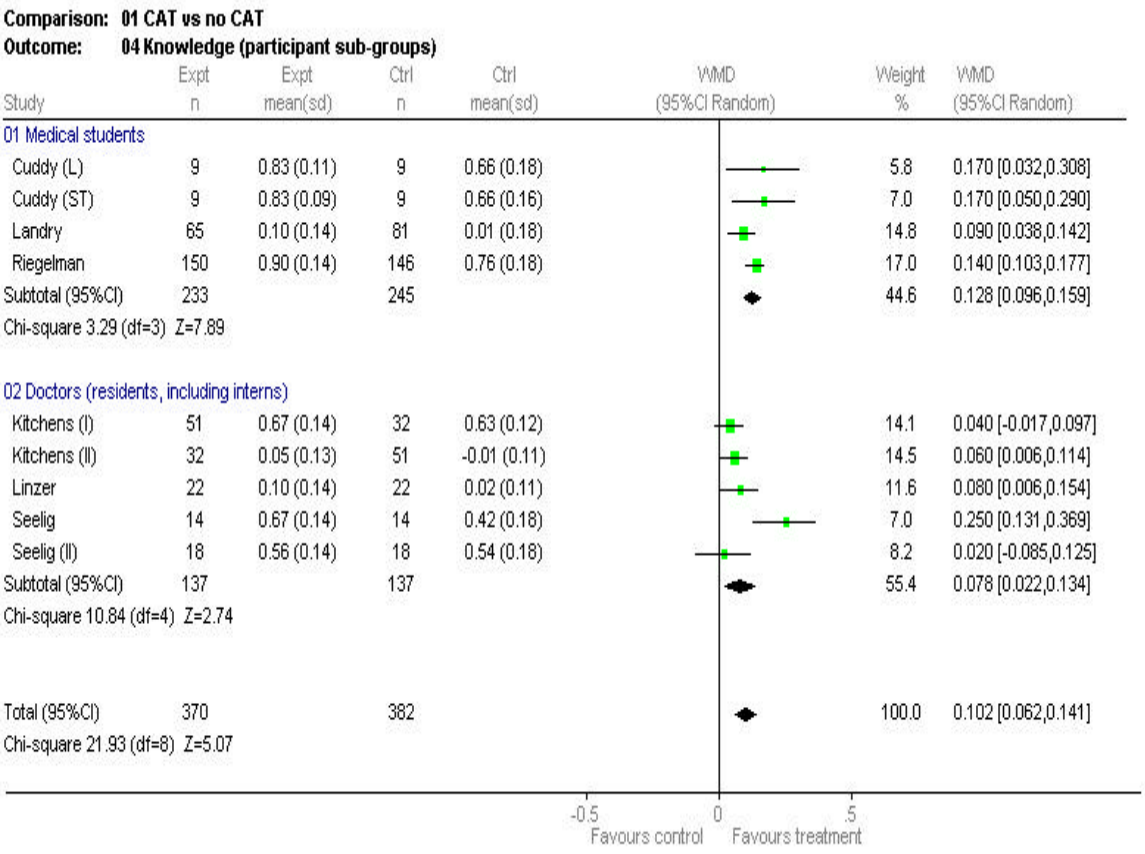
Even for skills (see Table 8), positive effects were obtained in all the main groups of participants examined - medical students, post-graduate doctors (residents) and midwives. The two studies not conforming to the overall pattern of benefit for skills by Linzer [52] and Seelig 1993 [56] *were* both performed on post-graduate medics (interns). However, in the context of the pattern of results for other outcomes, it seems as likely that the reduced effectiveness of CAT observed in interns is a chance phenomenon, as it does that the results for Linzer and Seelig 1993 are reflecting a true difference in effectiveness. In this respect it should be noted first that there is internal inconsistency in the results for the study by Linzer, one measure of skills favouring control and the other CAT, and second, that the study by Seelig has a number of very important short-comings.

Again in the case of behaviour (see Table 7) the studies on interns by Linzer and Seelig 1993 apparently stand out as indicating negative impact on behaviour, in contrast to other studies in other participant groups where positive results predominate. However, this too does not bear close scrutiny. Negative results were not restricted to those studies where the participants were interns. For instance one of the four components of the assessment of behaviour by Landry [51] on medical students was negative; the study by Reigelman [54,57] on medical students favoured the control; and one of four components of the evaluation of impact on behaviour in the study by Caudill [43] on residents was negative. Thus, in behaviour, as for skills, against a background of greater intrinsic variability in results, it is as likely that the studies on interns by Linzer and Seelig 1993 showed negative results by chance, as it is that they truly indicate a different level of effectiveness for this participant group. Finally in terms of the relationship between the participant group and any outcomes, it should be noted that the relationship is likely to be confounded by duration of the intervention. Both the studies by Linzer and Seelig 1993 have relatively short durations of input. In the case of Seelig this is unequivocally so; in the case of Linzer the point has previously been made that it is the only study which reports the number of sessions actually attended, and thus 3 hours is likely to be an underestimate of the input relative to other studies. This observation also needs to take into account the acknowledged imprecision of the assignment of duration and an inability to take into account the quality of the intervention which is likely to be as important as duration.

All the foregoing does not exclude the possibility that there is truly a difference between the effectiveness of CAT in interns, and post-graduates doctors generally, as opposed to other groups. Indeed sub-grouping the results for knowledge by nature of the participants as presented in Figure 4 does provide some very tentative support for the assertion, although the highly speculative nature of

this analysis needs to be borne in mind. The point we do wish to emphasise is that a sub-group effect is not the only cogent explanation for the apparently divergent results of the two studies where the participants were interns. Final proof of the assertion that the effectiveness of CAT differs in interns requires a much larger data-set of evaluations than that currently available. It is debatable whether further research to allow this question alone to be answered is justified when the basic evidence of effectiveness of CAT in all groups still has important areas of doubt.

Figure 4. Included comparisons; results for knowledge sub-divided by participant sub-groups (summary diagram)



4.7 Influence of nature of intervention on study outcomes

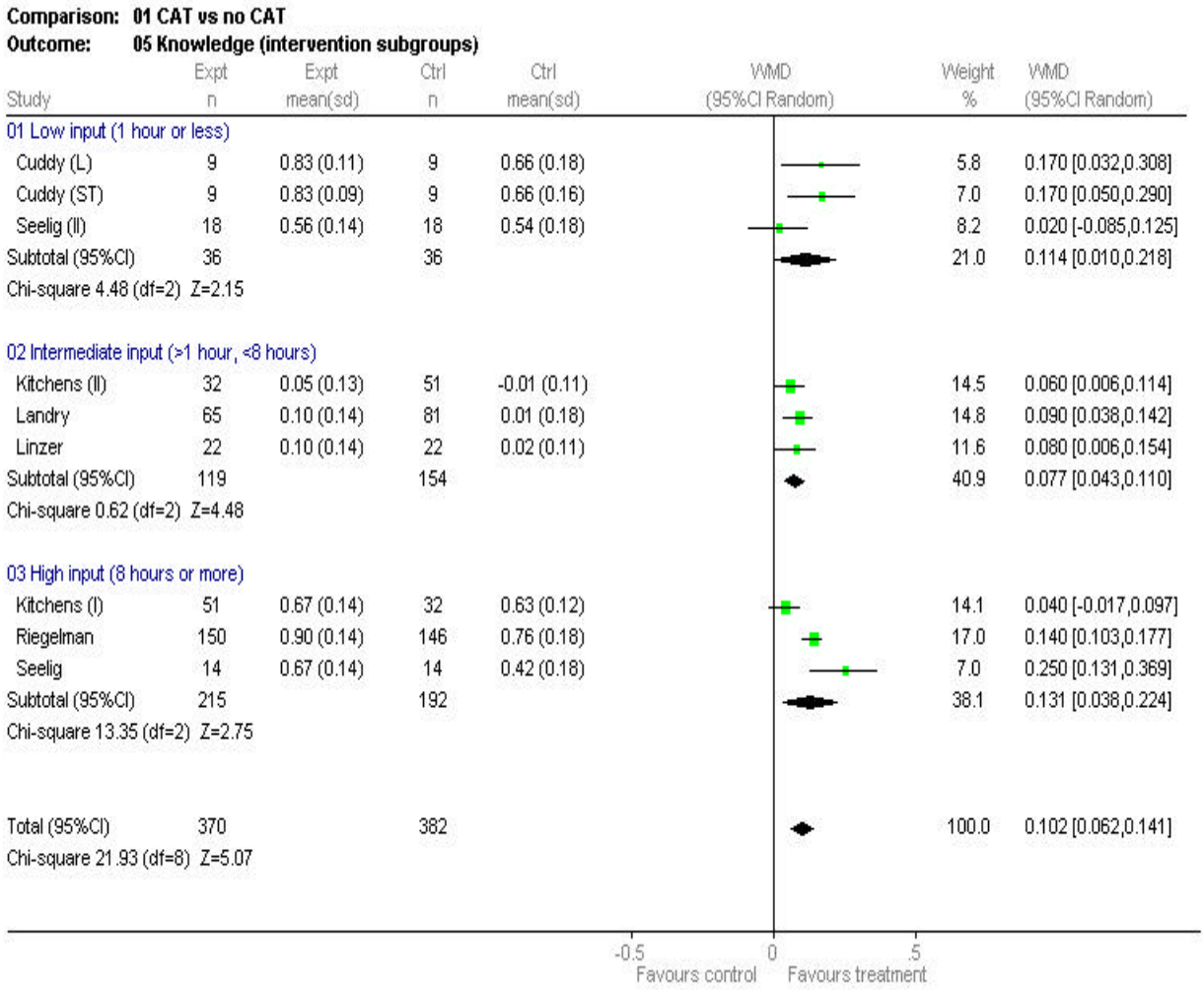
Many of the arguments already put forward in the previous section also apply to consideration of whether there is any evidence that the nature of the CAT intervention has any influence on outcome. In particular the noted consistency of direction of effect on knowledge and attitudes appears to be

independent of the wide range of formats and intervention durations in the studies providing information on these outcomes (see Table 9 & Table 10). An issue of concern is that descriptions used to convey the likely impact of the intervention are imperfect. Even the durations quoted may be misleading owing to the inconsistent way in which they were reported and the lack of information on attendance.

They certainly do not capture potentially important aspects of the quality of the intervention, which although hinted at in the descriptions provided in the included studies, were impossible to capture in a reliable manner. These points alone may explain why there is no evidence of any clear relationship between duration of the intervention (divided into three sub-groups of minimal, intermediate and high input) and impact on knowledge measured by MCQs and their equivalents, presented in Figure 5.

Thus we can only conclude that the evidence reviewed provides no indication of a duration and format of critical appraisal teaching which offers the prospect of being more effective than another. A better way of assessing this would be to consider direct comparisons of different methods of critical appraisal teaching. A small group of such studies were identified in the searches for this review, but their analysis was outside our scope. Thus systematically reviewing this pool of studies is an obvious area for further research.

Figure 5. Included comparisons; results for knowledge sub-divided by duration of intervention (summary diagram)



4.8 Publication bias

A key issue which we have not been able to tackle is the possibility that the noted consistencies in direction of effect on knowledge and attitudes, and to a certain extent skills may have been accentuated by a tendency for small evaluations of teaching critical appraisal which showed negative effects, particularly non-significant negative effects, not to reach the public domain. A priori it seems highly plausible that such studies might not be published. We believe the rigour of our search and our strenuous attempts to track down unpublished material should have provided defence against this. However, such measures are not infallible. Funnel plots can provide a crude check on whether publication bias is likely to be present, but the accuracy of the technique is dependent on the number of studies available and variability in their sample sizes. Even if all sixteen included studies had

provided information on the same outcome using comparable measures it is debatable whether we could have obtained reliable conclusions on the whether publication bias was likely.

5 Discussion

5.1 Statement of principal findings

Critical appraisal seems intuitively to be a useful and even necessary skill in the face of pressures facing health care professionals and decision makers: increasing information overload, the need to improve quality, the wish to bridge the gap between research and practice. Studies of teaching critical appraisal do show benefit, particularly with respect to knowledge and attitudes, but the picture is not consistent.

5.2 Summary of the review process

Over 4000 references were considered and 16 studies finally met the inclusion criteria. Other groups of studies were identified which could be usefully reviewed, particularly studies directly comparing different methods of critical appraisal teaching. A number of important studies which will contribute information on this topic in the future are ongoing.

The 16 included studies covered a wide range of intervention formats and durations, and participant groups. They contained information on 58 relevant comparisons. Fifteen of these were duplicative, leaving 43 for inclusion in the analysis.

Reporting of key information in respect of the nature of the interventions and the actual attendance by participants was poor, limiting precise categorisation. None of the studies was completely bias free. Thirty of the 43 studies included comparisons conducted in ways where we judged there to be at least one major threat to validity.

The poor reporting of included studies was also apparent in ambiguity about many items of abstracted data. The main method of data analysis was qualitative, with conclusions mainly drawn on the basis of patterns in tabulated results. Sensitivity of the conclusions to the observed variation in study quality was undertaken. The inter-relationship between the results and the type of participants and the nature of the intervention were explored.

5.3 Answers to main questions

Chapter two set out the seven questions around which the review was structured. A summary of answers to these questions is given below.

Does teaching critical appraisal produce beneficial effects on patient health, which are not outweighed by *negative effects*?

We found no evidence addressing this question.

Does teaching critical appraisal result in behaviour that is more up to date in relation to current good practice?

We found no evidence addressing this question.

Does teaching critical appraisal change clinical decision making or health seeking behaviour?

The impact of critical appraisal teaching on clinicians' behaviour, particularly self-assessed reading behaviour, was mixed. Only one study provided an objective measure of impact on behaviour, through assessment of actual use of literature in patient write-ups; this favoured critical appraisal teaching. Despite this, no clear conclusions on whether critical appraisal teaching does or does not have an impact on behaviour can be drawn. We found no evidence looking at clinicians' decision-making or patients' health-seeking behaviour.

Does teaching critical appraisal result in change of skills of the learner?

At first sight, critical appraisal teaching appears to have a consistently positive effect on skills. This is irrespective of how this is measured: by assessment through performance in critical appraisal exercises; by MCQs requiring application of critical appraisal or library skills; or by self-assessment of skills. However, closer scrutiny of those studies least open to bias suggests a note of caution: the balance between studies showing a positive and negative effect shifts, although those showing a positive effect still predominate.

Even if the generally positive direction of effect of critical appraisal teaching on skills is accepted, the size of this effect is highly variable and difficult to summarise. Further, the practical importance of the changes measured is very difficult to discern.

Does teaching critical appraisal result in change in knowledge of the learner?

The impact of critical appraisal teaching on knowledge is consistently positive. This seems to be independent of the measure of knowledge used, the nature of the participants and the quantity and

quality of the intervention. No difference in pattern emerges if the analysis is restricted to those studies judged to be least open to bias.

Although consistently positive, the size of the effect of critical appraisal teaching on knowledge is highly variable. The variability of results was reduced by concentrating on comparisons that used the most objective assessment of the size of effect –formal tests and MCQs – and excluding the studies most open to bias.

One study tried to define a threshold above which changes in knowledge would have significance in practice. This was not one of the studies providing the most reliable measures of size of effect referred to above, and so did not help gauge significance in practice directly. It does however indicate a useful approach that might be applied in future research.

Does teaching critical appraisal result in a change of attitudes of the learner?

The impact of critical appraisal teaching on attitudes, universally measured as agreement with series of statements, is also consistently positive. This again is independent of the nature of the participants, the nature of the intervention and the openness to bias of the comparisons analysed. However, the size of effect on attitudes and its practical importance is unclear. The analysis of results for impact on attitudes highlights the problems associated with the use of self-assessed measures. Such measures were also widely encountered in assessing other outcomes.

Does teaching critical appraisal skills lead to increased satisfaction in the teacher and learner?

No sufficiently rigorous information was identified on the impact of critical appraisal teaching on participant or teacher satisfaction.

Additional question: is there an optimum method for teaching critical appraisal?

We identified no suitable evidence to investigate whether that different interventions were associated with different changes in outcomes. The main reasons for this were the limited amount of data available on any specific outcome and the impossibility of accurately classifying the quantity and particularly quality of the interventions in included studies.

Further question: is critical appraisal teaching more effective with different participants?

Beyond the eight stated questions, we also investigated whether the effectiveness of teaching critical appraisal differs depending on the nature of the target audience.

No strong evidence was identified substantiating a relationship between the nature of participants and the outcomes achieved. In particular, we could not test the suggestion that the effectiveness of critical appraisal teaching is reduced when directed at qualified doctors such as interns, as has been suggested previously [30]. Our belief, however, is that an apparent relationship between negative findings and teaching interns is likely to be a chance phenomenon and most of the variation between study results is due to variable openness to bias of the included comparisons (rather than to true differences in the effectiveness of critical appraisal teaching by participant group).

5.4 Strengths of the review

The relative strengths of this review include the following:

Background and focusing the question

(a) The review took full account of and built on existing systematic reviews of critical appraisal teaching.

(b) Critical appraisal was considered in a conceptual context (chapter 1).

(c) A broad range of outcomes was considered (see the 'hierarchy of outcomes' in section 2.1). This is desirable because teachers and learners of critical appraisal may have differing needs. Teachers and course innovators may see critical appraisal as a way of coping with information overload, with implementing evidence in practice, with keeping up to date. Students and clinicians may pursue the acquisition of critical appraisal skills/knowledge in order to illuminate clinical decision making. Both perspectives (and more) are legitimate. Evaluations therefore need to consider a variety of outcomes.

(d) The review was inclusive with respect to study design, ensuring that we maximised the amount of data we could incorporate into the systematic review.

Minimising bias

(e) The review aimed to reduce the problem of publication bias. This was achieved by conducting a very thorough search strategy and made use of sources often not used in systematic reviews. We also made extensive use of direct contact and networks to identify unpublished material. This is reflected by the fact that of the 16 studies, one quarter were unpublished or published as abstracts with unpublished full manuscripts. We followed up abstracts rigorously and finally included 4 unpublished studies, all in full manuscript form rather than as abstracts. It remains possible that the noted consistencies in direction of effect on knowledge and attitudes, and to a certain extent skills,

may have been accentuated by a tendency for small evaluations of teaching critical appraisal which showed negative effects, particularly non-significant negative effects, not to reach the public domain. A priori it seems highly plausible that such studies might not be published and the author of one of the unpublished studies we included commented to us that he had tried hard but unsuccessfully to get his paper published. We believe the rigour of our search and our strenuous attempts to track down unpublished material should have provided defence against this. However, such measures are not infallible. Funnel plots can provide a crude check on whether publication bias is likely to be present, but the accuracy of the technique is dependent on the number of studies available and variability in sample size. Even if all sixteen included studies had provided information on the same outcome using comparable measures it is debatable whether we could have obtained reliable conclusions on the whether publication bias was likely. We decided in the end not to do a funnel plot, since any asymmetry would be more readily attributable to the variable quality of the studies and their heterogeneity than to publication bias.

(f) Assessments of retrieved studies (to apply inclusion criteria) were undertaken independently in triplicate because of the difficulties encountered in defining many of the concepts of critical appraisal and teaching. The level of agreement achieved between the three reviewers demonstrated that our definitions were reliable and likely to be reproducible.

(g) Validity was assessed at the level of each outcome considered in each included study (rather than considering the study as a whole). This is important because loss to follow-up may be suffered to different degrees by different outcomes within the same study.

(h) The ambiguity of the data and our judgements was graded- we have indicated items and data from the studies of which we are not certain or could not agree throughout the review, or that the authors reported inconsistently. We have also indicated the validity items where we could not agree on their likely impact.

(i) Special emphasis was placed throughout on checking data extraction and quality assessment processes.

Useful outputs

In addition to the production of this report, the findings of this review will be published on the Cochrane Library through the Effective Practice and Organisational Care collaborative review group.

5.5 Limitations of the review

Some of the limitations of this review process include:

(a) The amount of time it would take to conduct the review was underestimated (both reviewer time and senior supervision time). This review was undertaken with only six months research assistant funding from NHS R&D.

(b) The objectives of this study were limited to the evaluation of the impact of critical appraisal teaching on satisfaction, attitudes, skills, behaviour etc. It is not therefore an evaluation of critical appraisal skills programmes, centres for evidence based healthcare, clinical effectiveness, clinical governance or any of the more "macro" uses to which this "micro" intervention might be harnessed [58]. We do however think it likely that we would have found studies addressing this issue if they had been there and the fact that these issues are not covered is more due to the lack of relevant research than to restricted scope.

(c) The review is in some ways already out of date. We are aware of at least one UK trial that has been submitted for publication [59]. Because this is a fast moving field [60], evaluations of teaching programs are turning to the issue of how, rather than whether, to teach critical appraisal skills

Methods of primary studies

A systematic review depends for its value mainly on the primary studies it includes. The 16 studies examined here were very varied. There are important points to note in terms of the participants, interventions and outcomes studied and the methods used which limit the validity, generalisability and usefulness of the results; these are highlighted below.

The participants studied

(d) The wide range of professional groups, in particular noting that seven studies were of medical students. These may differ from the other groups, making external validity difficult to assess.

(e) We found only one study [42] that included any healthcare consumers (3%) and none that reported results separately for consumers.

The interventions studied

(f) The enormous variety of interventions, in terms particularly of methods of teaching and duration (range from 20 minutes to 16 hours).

The outcomes studied

(g) Overall, there is a lack of medium or long-term outcomes and no patient relevant outcomes are reported. Many studies used self-assessed outcome measures, which have limitations. None of the studies assessed costs. Only two mentioned consent or other ethical issues.

(h) We found no valid evidence on participant satisfaction. One proxy measure of satisfaction is attendance rates. These were rarely reported and were sometimes poor.

(i) An issue discussed previously is whether the authors' interpretations of the direction of effect is always appropriate. For instance, Riegelman found that critical appraisal training was associated with a slightly lower level of regular reading of research journals [54,57]. In Table 6 this is interpreted as (e.g.) 'favouring controls'. The implication of that is that an objective of critical appraisal teaching is the more regular reading of research journals. An alternative view would be that it does not matter if people read less so long as they read more critically. On this view, Riegelman's results might actually be seen as favouring the intervention group.

(j) A related issue is the possibility of adverse effects (not considered by most of the studies). Several of the included studies highlighted a mismatch between self-perceived skills and externally assessed skills. This might be construed as an adverse event (the implication being that critical appraisal teaching merely creates an illusion of greater skills) as much as a problem of measurement.

The methods used

(k) Most of the studies involved small sample sizes: all but two had fewer than 200 participants, the median size was 57 and ranged from 14 to 1880 participants.

(l) Only two studies reported a power calculation. The size of the improvement in knowledge and skills is generally small. There is insufficient evidence cited to define what amount of educational change would result in a teaching intervention being deemed "successful" or what are the practical consequences of that "success". Note that Burls [42] sought to define a level of improvement that was "educationally significant"; this has not been validated.

5.6 Lessons to draw from the included studies

Issues relating to study design

There was a wide range of study designs, with both between-group comparisons (where the effect in a group exposed to critical appraisal teaching is compared to another group not so exposed) and within-group comparisons (where an outcome measure before the critical appraisal teaching intervention is

compared to a measure after it). The existence of a randomised controlled trial demonstrates the feasibility of applying this study design to an educational intervention.

Many important limitations of within-group comparisons were identified; however the main reason that many within-group comparisons in this review were felt to be open to bias related to high losses to follow-up rather than the lack of concurrent controls.

The main threat to validity associated with between-group comparisons is lack of equivalence in the two groups assessed. Randomisation is the advised way of avoiding confounding from this, but was rarely used. In the one case where it was (Linzer [52]), it is unlikely that sufficient numbers (22 in each arm) were actually randomised to ensure comparability. Matching can also help ensure comparability, but again this was rarely employed. On this basis we would have predicted that most of the between-group comparisons would have been open to confounding. Although this was indeed the case for the studies by Gehlbach [46] and Riegelman [54,57], most between-group comparisons minimised confounding by using a controlled before-and-after study design comparing before-after changes between groups. This provides a powerful method of adjusting for non-comparability of base-line characteristics which directly effect the outcome measure in question. This simple observation is worth highlighting as using before-after changes is rarely suggested as a method for controlling for confounding. This may be because it is not possible to measure many biomedical outcomes before an intervention e.g. death. Nonetheless many of the outcomes of interest in assessing the impact of critical appraisal teaching and other educational interventions can be measured both before and after the intervention. This may highlight that assessment of change is a possible adjunct to randomisation, and should be considered particularly where the number of participants available for randomisation is limited, or randomisation is not feasible.

As far as within-group comparisons are concerned, little problem is generated from difference in characteristics of the subjects, provided analysis is restricted to paired before and after data, as each subject acts as their own control. There is a problem, however, in attributing any change in outcome to the intervention. One protection against bias from this is to assess the before-after change in the context of a long-term trend – an interrupted time-series. This approach was not however encountered, possibly because many of the measures used would have been subject to learning effects with repeated use. Most of the included studies relied on the use outcomes measured immediately before and immediately after the intervention in question, leaving as little opportunity as possible for extraneous influences to be invoked as explanations for any changes observed. Even with this however, residual problems remain where the intervention occurs over a long period of time, often the case in educational courses. Of extreme frustration, given that timing of the outcomes is an important feature in attributing change,

was the often vague information about exactly when the before and after outcomes were assessed. A further surprising omission from virtually all the included studies relying on within-group comparisons was any attempt to describe what else participants might be exposed to at the same time as the intervention, in order to reassure that any change could reasonably be attributed to the critical appraisal teaching intervention of interest. What clearly emerges from considering the included studies with within-group comparisons in this review is that as a source of evidence on longer term outcomes, distant from the end of the intervention, simple uncontrolled before-after studies alone are likely to be unconvincing.

Issues relating to outcome assessment and data analysis

As well as specific observations about the validity of the included studies arising from consideration of the means by which outcomes were measured and analysed, there are a number of general issues. The first is a justification of the re-assessment of study validity for each outcome for each included study, in contrast to considering the study as a whole. This was undertaken for several reasons. First, loss to follow-up may occur to different degrees for different outcomes within the same study. A clear example of this is found in Hicks [47] where, depending on the outcome considered, loss to follow-up ranged from 0% to 47%. Openness to detection bias may also vary with the nature of the outcome under consideration. For instance, in Landry [51] it was easy to accept that behaviour change assessed by consideration of patient write-ups with reference to defined criteria was likely to be assessed in an independent and blind manner. In contrast, it was more debatable whether assessing attitudes measured by self-assessed agreement with various statements about the value of research would be. Again, for the assessment of impact on knowledge by Burls [42], it was easier to make a judgement that detection bias would be more likely in the crude score than in an overall impact score, where the impact on test questions had been down-graded to take account of changes in control questions which had not been addressed by the critical appraisal teaching.

Second, study design makes a considerable contribution to helping assure that an outcome has been assessed independently and blindly. Without a control group it is very difficult to envisage how a participant or investigator would not be aware that they were part of an experimental study, and that they might in turn modify their responses to take account of this. This would be particularly true for self-assessed outcomes attempting to measure impact on behaviour and attitudes. This raises the question of whether any outcome which is not highly objective can be accurately measured in a within-group comparison. The only innovative approach identified in a within-group comparison, to make a the impact of a self-assessed outcome more convincing, was the attempt in Burls [42] to adjust improvement in test questions for smaller improvements observed in control questions which had not been addressed by the critical appraisal workshops in question.

Who conducts evaluations of critical appraisal?

The evaluations we have reviewed have usually been conducted by clinicians, enthusiastic about critical appraisal. They are typically opportunistic and follow quickly on the establishment of a course by pioneers. The reports are analogous therefore to reports of phase II or early phase III trials of drugs. One possible consequence of the fact that some authors have written for their colleagues rather than for educational researchers is that many published evaluations have appeared in mainstream healthcare journals.

There are several disadvantages to this situation. Many authors appear to lack expertise in educational research methods, contributing to the marked heterogeneity of studies (in terms of their time, setting, participants, interventions, outcomes, evaluation method), their poor quality and poor reporting. The research has usually been a one-off (rather than part of an ongoing programme). Authors seldom show familiarity with the evidence base in the area they are evaluating; and they have not located the findings of their studies in the context of a systematic review of all the available and relevant evidence.

5.7 Strengths and limitations in relation to other reviews, discussing particularly any differences in results.

When we started on this review, we were aware of one previous published review (Audet [29]). A strength of this review, published in 1993, was its rigorous assessment of included studies but it needed updating. In addition, we were aware of an unpublished review by Norman and Channon which was subsequently published [30] In addition, during the course of the review, two other UK investigators prepared reviews (see chapter 1 for a fuller discussion of the previous reviews) [31-32].

We attempted to take account of these studies and to build on them, by producing an up-to-date systematic review, that looked for studies of critical appraisal outwith a narrowly medical framework, that employed exhaustive search methods and rigorously assessed the included studies' methods. We also sought to provide more informative summaries of the characteristics and results of included studies.

We broadly concur with the findings of these earlier reviews, but we have succeeded in taking the evidence base and the debate forward. In particular, this review has included more primary studies than the earlier reviews; and it highlights more clearly the methodological problems of the primary studies and therefore the uncertainties in our knowledge.

5.8 Meanings of the review: possible mechanisms and implications for commissions or policy makers.

Much effort and resource is already being devoted to teaching critical appraisal skills. Whether the amount of human effort from teachers and students, or opportunity cost, or actual costs of running courses are considered, the amount of investment is such that the impact of CAT needs to be justified. Increasing the amount of CAT in response to increasing demand, accentuates further the need for justification.

This review provides reassurance to those who have invested in such activities, that they are likely to have had a positive impact. We have certainly not identified any information to suggest that current investment in CAT should be diverted elsewhere.

The key issue is whether there is sufficient evidence to encourage further expansion of CAT. Our view is that the evidence alone is not enough for such encouragement. Not only are there important limitations on validity and the significance in practice of results on outcomes where we have some information, but there are many important outcomes on which we have no information at all.

In chapter 1, we discussed a number of 'rationales' for critical appraisal teaching (1.4). We note that none of the studies included here assessed how far critical appraisal teaching helped achieve these.

In the next section we outline the types of research which would create an evidence-base which would convince more teachers, clinicians and policy-makers whether they should invest more in CAT. We also provide some guidance on the methods which such research should employ to overcome the problems of interpretation we encountered in this review.

A subsidiary question on which we also make suggestions is to identify the best method of delivering CAT. However, until the basic value of CAT is elucidated with greater clarity, research on the relative effectiveness of different approaches should remain a second priority, even though such research may obviously be of greater interest to those who have already convinced themselves that the benefits of CAT justify the costs.

The studies looked at in this review provide a historical overview of the recent development of critical appraisal. Sackett and Parkes [60] comment that events may have passed to some degree this debate by. Critical appraisal is increasingly seen, not in isolation, but as one part of practising evidence based medicine or as one part of the undergraduate curriculum.

Educational research has not acquired the prestige of pure or applied medical science and may attract inadequate funding, with little effect on career advancement, thus inspiring temporary enthusiasms [61]. All of these may help to explain the paucity of the literature. This picture will have to change if any of the outstanding questions are to be answered by high quality research.

We will need much better information if any educational interventions in health care are ever to be included in the same decision making framework as healthcare resource allocation decisions. (This is especially important for new interventions and for those to do with the practice of an evidence-based approach: both are relevant to critical appraisal teaching.) Increasingly, cost per QALY is used as the calculus in this area. Could cost-utility analysis be applied to critical appraisal teaching? To do this would necessitate careful estimation of costs (both direct costs of teaching and the opportunity costs of attendance/learning) and of benefits (in utility weighted life expectancy gains). This means that health outcomes have to be measured, particularly when critical appraisal teaching is happening in the postgraduate or continuing professional development setting, where the opportunity costs of participants' time are much clearer. The will move the evaluation of such teaching from (from the perspective of health services research) being a peripheral topic of interest of educationalists to a central concern of health services research.

5.9 Unanswered questions and future research.

Unanswered questions

- How much predefined improvement in specified outcome measures would be significant in practice? Adult educationists may be well placed to help answer this questions. Their input would be invaluable also in determining the amount of teaching that is required (a) to change knowledge, skills and attitudes and then (b) professional behaviour.
- What impact does critical appraisal teaching have on patient outcomes or on clinicians keeping up to date?
- If critical appraisal teaching has an influence on knowledge, skills and attitudes, what is its impact on patient care? This has not yet been assessed and, given the complexities of the present systems of healthcare and healthcare education, this will have to be assessed using proxy indicators [62].
- What is the impact of recent developments in electronic publishing and the provision of journals of secondary publication on the need for critical appraisal training for all healthcare professionals?
- What is the impact of changes in the availability of evidence (principally through the internet revolution) on the need for critical appraisal skills among the general population and health care professionals?

Specific research questions

(a) For skills and knowledge, what is the size of the effect of critical appraisal teaching and is it of practical importance
(b) What is the best time to begin to teach critical appraisal to health professionals?
(c) What is the best method to teach critical appraisal to students and qualified healthcare workers?
(d) Does critical appraisal have any effect on clinical behaviour?
(e) Does critical appraisal teaching of health professionals improve the quality of patient care?
(f) How effective is teaching critical appraisal to postgraduates and as part of continuing professional development? Does such teaching represent good value for money for the health service?

From our knowledge of the evidence base and its trajectory, it is our assessment that the present systematic review should be updated in 2001.

Specific research methods

- There are many centres around the world teaching critical appraisal to their healthcare students and postgraduate workers and we have contacted many of them during the course of this review. Considerable work and effort are being put into this area but it is usually accompanied by little evaluation. That which exists often uses poorly validated instruments, poor controls or no comparator groups. It must be possible to plan and even co-ordinate the work done in this field to increase study numbers and obtain valid results of measurable outcomes, using consistent, valid instruments. This could facilitate the production of more homogeneous results, that could be combined to give an overall effect direction and size of effect.

Preferred research question and design

- On the basis of this review and our knowledge of the evolution of critical appraisal teaching, our view is that the top priority should be a multicentre randomised controlled trial of teaching critical appraisal to postgraduates/as part of CPD.
- This should be preceded by and take account of a quick update of our systematic review, taking into account all studies completed since our searching finished.
- It should define participant groups, interventions and outcomes precisely.
- It should define in advance changes in outcomes that are ‘significant in practice’.
- It should include a consideration of costs and attempt to answer the value for money question.
- Multi-centre, methodologically rigorous, controlled before and after studies in comparable groups with the same valid instruments, measuring the same outcomes, may be able to give answers of reasonable validity when randomisation is infeasible.

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7 Appendices

Appendix 1. Initial protocol (4/3/97)

Long Title: The effectiveness of teaching critical appraisal skills.

Short Title: Critical appraisal

BACKGROUND

New developments in health care and medicine are often communicated through reports of scientific studies being presented at conferences and in academic journals. When health care professionals are faced with a dilemma concerning the effectiveness of an intervention for a particular patient, one option for them to follow is to locate such a relevant scientific study. However reliable interpretation generally requires a basic understanding of scientific and statistical methods, together with the adoption of an inquisitive and sceptical approach. Formal training in these critical appraisal skills may assist health care workers in interpreting studies, recognising potential biases, increasing comprehension of numerical results, and helping in the decision whether articles are relevant, valid, and how they should influence the care of their patients. This not only applies to health care professionals but to anyone who is making a decision regarding health care for example health authority managers, users of health care and the media who disseminate information about health care issues.

Over the past few decades, there has been a revolution in the teaching of critical appraisal, in undergraduate medical school curricula, as a tool in the continued medical education offered to qualified health professionals, in determining the purchase of health care, in the assessment of higher professional training. There is a need to determine how effective this teaching is, and whether acquisition of critical appraisal skills has any effect on health care worker behaviour or patient related outcomes.

OBJECTIVE

To summarise the effects of teaching critical appraisal on knowledge, skills, behaviour and patient outcomes, by locating and reviewing published and unpublished evaluations of critical appraisal training.

DEFINITION

Critical appraisal is the application of rules of evidence to clinical, paraclinical, and published data in order to determine their validity and applicability (Sackett).
It involves determining the validity of those appropriate studies' that are identified, interpreting their results and deciding the applicability to the identified question.
(or critical appraisal is the process of assessing and interpreting evidence, by systematically considering its validity, results and relevance to the individuals own work.)

HYPOTHESES

1. Teaching critical appraisal results in ability to perform this skill.
2. Teaching critical appraisal to health care workers changes their clinical behaviour.
3. Teaching critical appraisal is an effective way of keeping up to date with current good practice.
4. Teaching critical appraisal has a long term effect.
5. Teaching critical appraisal has an effect on patient health.
6. Teaching critical appraisal to managers of health care leads to more rational decision making.
7. Critical appraisal skill teaching to users/consumers of health care leads to increased satisfaction in these end-user groups.

OUTCOMES

Reaction: satisfaction after training in critical appraisal
Learning: demonstration of new /improved knowledge and skills of critical appraisal for example, how well can people perform in critical appraisal after teaching.
Behaviour: transfer learning to every day routine use of critical appraisal skills in professional practice which involves a change in health care worker behaviour
Results: change in health care worker behaviour leading to effects on outcomes for patients or the organisation (Kirkpatrick's hierarchy of evaluation 1975).

PHASE 3 LITERATURE SEARCHING

Electronic database searching:
Search strategies will be developed using text words as well as indexing terms. Validated search strategies will be used to optimally identify studies of certain designs.
Databases to be searched:
Medline
FAMLI
ERIC
LISA
NTIS
EMBASE
PsychLit
Social Science Citation Index
Cinahl
SIGLE
DISSABS
Cochrane database

Other elements of searching:
Bibliographies of original and review articles will be scanned for other suitable studies
Hand searching J Med Education
Evidence-based health mailbase and other relevant mailing lists
Consultation with experts in the field by contact through letter
Cochrane networks
Clinical epidemiology networks in North America, UK and Europe
Contact of lead authors of all included trials
Consultation with medical educators network

PHASE 4 ASSESSMENT OF STUDIES FOR INCLUSION

Criteria for including studies:
Types of participants and setting: Any clinical setting, any health care professional, any health care manager, any health care purchaser, any health care user.
Types of studies: Randomised controlled trials, non randomised controlled trials, controlled before and after studies and interrupted time series.
Types of outcomes:
1. Educational satisfaction after teaching critical appraisal - pupil / teacher.
2. Demonstration of proficiency in critical appraisal skills.
3. Change in behaviour of health professional/health care user after critical appraisal teaching.
4. Patient outcomes: patient mortality; patient quality of life; patient satisfaction.

Criteria for excluding studies:
Methodological weakness.

Does not meet criteria for inclusion.

PHASE 5 ASSESSMENT OF THE VALIDITY OF THE INCLUDED STUDIES

Included studies will be assessed according to validity criteria which will address:

For randomised controlled studies;
Was the assignment of participants randomised
Was randomisation list concealed
Were all participants who entered the study accounted for at its conclusion and were they analysed in the groups to which they were randomised
Were outcomes measured in the same way in the compared groups
Were groups similar at beginning of study
Were groups treated equally except for the intervention
Was follow up sufficiently long and complete
For interrupted time series;
Was there a clearly defined point in time when the intervention occurred?
Was there at least two data points before and after the intervention?
For controlled before and after studies;
Was there contemporaneous data collection?
Was there appropriate choice of control site/activity. For studies using untargeted activities as controls, are the study and control activities comparable with respect to characteristics of the targeted behaviour?

At least two reviewers will independently select the studies to be included in the review according to the criteria stated above. Any disagreement will be settled by negotiation. The validity of each of the studies will be assessed by the same reviewers, and will be performed blind to the study results. The studies will be broadly ranked according to study design and according to criteria of validity met in a hierarchy of evidence. Further assessment will follow the suggestions of Detsky et al.

PHASE 6 METHODS USED TO COLLECT DATA FROM INCLUDED STUDIES

Data extraction will be completed independently by the same reviewers, using a checklist developed by CCEPP, modified and amended for the purposes of this review. This will include the above categories used to assess the methodological quality and data on outcome measures.

PHASE 7 METHODS USED TO SYNTHESISE THE DATA COLLECTED FROM INCLUDED STUDIES

All data will be synthesised using qualitative methods, bearing in mind the validity and size of the studies, the exact nature of the interventions and participants in the programmes and any other differences which may impact on the results. Where studies appear suitable homogeneous and assess similar outcomes formal methods of meta-analysis will be used to combine the results. When choosing statistical methods, appropriate attention will be paid to the choice of effect measure and evidence of heterogeneity between studies.

PHASE 8 CONCLUSIONS and REPORT WRITING

Conclusions will be drawn from the qualitative and quantitative synthesis of the research studies considering both the strength and magnitude of the evidence of effectiveness of critical appraisal teaching in the identified client groups, the appropriateness of the outcomes that have been assessed, and the differences between the studies. Where the evidence is strong and complete, recommendations on educational methods will be produced; where it is weak recommendations on future research will be made.

PHASE 9 PEER REVIEW

The report will be peer reviewed by experts in the field and end users to assess its completeness, scientific validity and appropriateness. CCEPP review will be reviewed by the CCEPP editorial team.

PHASE 10 FINALISATION OF REPORT and DISSEMINATION

The completed report will be submitted to the NHS Advisory group on promoting the implementation of research findings in the NHS. The review will also be published in peer reviewed journals, and disseminated on the Cochrane Database of Systematic Reviews.
A summary of the report will be produced which will be suitable for dissemination to other groups involved in medical and health education

Appendix 2. Further detail on searching

A. Electronic database search strategies

Medline 1966-1997
Search terms used: teach*(mh), read*(mh), education*(mh explode), learn*(mh), critical* apprais* (ft), critical* read*(ft), journal* club*(ft)

Embase 1980-1997
Search terms used: education(mh), teach*(mh), critical* apprais*(ft), critical* read*(ft), learn*(mh).

Cochrane Library 1997
Search terms used: critical appraisal(ft), teaching(mh), education graduate(mh), continuing medical education(mh), problem based learning(mh), education medical graduate(mh), reading(mh), medical undergraduate(mh), critical reading (ft), journal club(ft)

PsychLit 1974-1997
Search terms used: critical* apprais* (ft), critical read*(ft), teach*(mh)

LISA
Search terms used: critical appraisal and teach

ERIC 1966-1997
Search terms used: critical appraisal and teaching

CINAHL 1982-1997
Search terms used: critical* apprais*(ft), critical read*

SIGLE 1980-1997
Search terms used: critical* appraisal*, critical read*

Social Science Citation Index 1981-1997
Search terms used: critical appraisal (ft), journal club (ft), critical reading (ft)

Science Citation Index 1981-1997
Search terms used: critical appraisal (ft), journal club (ft), critical reading (ft)

Forward citation searches were conducted using the following names taken from leading publications in the field: Linzer, Sackett, Bennett, Reigelman.

B. WWW search strategy

Webcrawler search engine using and search terms (critical appraisal + teaching + medicine)

Medical matrix and **pages of institutions and sites** known to have interest in critical appraisal eg SCHARR, CASP, McMaster, CEBM Oxford, Harvard.

C. Individuals contacted for unpublished data

Dr Nicole Audet
Dr Amanda Burls
Dr Trish Greenhalgh
Prof Mark Linzer
Prof Geoff Norman
Dr William Rosenberg
Prof Dave Sackett
Prof Ken Schulz

Each of the main authors of this report also indicated unpublished studies.

Further, although mainly contacted for clarification of their study's data, the lead authors of each of the 16 included studies were also able to indicate the existence of unpublished studies.

Appendix 3. Inclusion/exclusion proforma

Extractors Initials __ __ __ Date _____

Study Eligibility Form

PLEASE RING ONE ANSWER FOR EACH QUESTION

FIRST AUTHOR _____ YEAR _____

(1) Are the participants health care related people?

Yes No Unsure

(2) Are they taught critical appraisal?

Yes No Unsure

(3) Is there a comparison with no training in CA?
(either a separate group, or before/after)

Yes No Unsure

(4) Does the paper report any of …

student/teacher satisfaction	Y N U
proficiency in CA skills	Y N U
behaviour	Y N U
knowledge or attitudes	Y N U
patient outcomes	Y N U

Any? Yes No Unsure

(*) INCLUSION DECISION
If all 1-4 are yes include **If any are no then exclude**

Yes **No** **Unsure**

(5) Is it critical appraisal alone (or combined with something else)?

CA alone	Y N U
If combined, is CA separately extractable	Y N U

If combined, with what? _____

(6) Is the study a

randomised controlled trial	Y N U
controlled trial	Y N U
controlled before-and-after	Y N U
before-and-after (ITS)	Y N U

Appendix 4. Details of studies excluded after detailed discussion and reasons for exclusion

1. Alarcón PE, Velázquez LV. Efecto de una estrategia educativa sobre la lectura crítica de estudiantes de medicina. [Effect of an educational intervention in the critical reading of medical students.] Rev Invest Clin 1994;46:447-56.

This was a Mexican study. On the basis of an English abstract this appears to be a controlled before-after study measuring the effect on critical appraisal skills of an educational intervention consisting of "guided housework for text interpretation" and group work consisting of "debate and confrontation of viewpoints of the individual work".

The study was provisionally included pending clarification of the nature of the intervention which did not clearly seem to consist of teaching critical appraisal. Further it was not clear what the control group had received. Unfortunately no clarification was received and the study was effectively excluded, despite clearly being of potential relevance.

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2. Burstein JL, Hollander JE, Barlas D. Enhancing the value of journal club: use of a structured review instrument. Am J Emergency Medicine 1996;14(6)561-563.

This before-after study in emergency medicine residents assessed the impact of a structured review instrument in a journal club, on overall satisfaction, perceived educational value, attendance and workload.

It was excluded as the instrument did not constitute teaching of critical appraisal.

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3. Domholdt E, Flaherty JL, Phillips JM. Critical appraisal of research literature by expert and inexperienced physical therapy researchers. Physical Therapy 1994;74(9):853-60.

This study compared the critical appraisal skills of inexperienced and expert physical therapists and examined factors influencing critical appraisal skills.

It was excluded as the impact of teaching of critical appraisal was not evaluated.

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4. Dorsch JL, Frasca MA, Wilson MA,Tomsic ML. A multidisciplinary approach to information and critical appraisal instruction. Bull Med Lib Assoc 1990;78(1):38-44.

Description of the development of a critical appraisal teaching intervention for the included study by Frasca.

It was excluded because it was as duplicative.

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5. Fowkes FGR, Gehlbach SH, Farrow SC, West RR, Roberts CJ. Epidemiology for medical students: a course relevant to clinical practice. International Journal of Epidemiology 1984;13(4):,538-541.

This before-after study evaluated an epidemiology course for medical students which included teaching critical appraisal.

It was excluded on confirmation that there was no separable data for that part of the course teaching critical appraisal.

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6. Gehlbach SH, Farrow SC, Fowkes FGR, West RR, Roberts CJ. Epidemiology for medical students: a controlled trial of three teaching methods. International Journal of Epidemiology 1985;14:178-181.

This controlled trial compared teaching an "Epidemiology for Clinical Practice" course delivered by lectures, or small group seminars, or self-learning packages.

It was excluded because there was no comparison with no critical appraisal teaching. It was identified as a potentially useful study outside the immediate context of this review.

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7. Globerman J. Teaching critical appraisal of the social work literature. Journal of Teaching in Social Work 1993;7(2):63-80.

This describes the development of a course to teach critical appraisal skills to social workers. The main focus is descriptive, but there is reference to evaluation.

It was excluded because there was no comparison group and no pre-course assessment.

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8. Griffith OW, Goss MEW, Tardiff K, Cassell EJ, Pardee JD, Weinstein AM. An elective course for first-year students based on the New England Journal of Medicine. Journal of Medical Education 1988; 63:559-561.

This study reported a course that focused on teaching critical appraisal skills to medical students.

It was excluded because there was no comparison group and no pre-course assessment.

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9. Heller RF, Peach H. Evaluation of a new course to teach the principles and clinical applications of epidemiology to medical students. International Journal of Epidemiology 1984;13(4):533-37.

This controlled trial assessed the impact of a general epidemiology and public health course to medical students.

Although the course included the development of a critical approach to information, it was excluded because it was judged to be a small component, the effect of which could not be separated.

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10. Heiligman R. Resident evaluation of a family practice residency journal club. Family Medicine 1991; 23:152-3.

This study identified attitudes of family practice residents toward a journal club and the identification of factors contributing to the success of the journal club.

It was excluded because there was no comparison group and no pre-course assessment.

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11. Herbert CP. Teaching prevention by debate. Family Medicine 1990; 22:151-3.

This study reported a course teaching critical appraisal to residents and its application in an innovative debate format in making a clinical decisions.

It was excluded because no comparative evaluative data were presented, the absence of which was confirmed by the author.

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12. Inui T. Critical reading seminars for medical residents. Medical Care 1981;19(1):122-124.

This described a seminar series for teaching critical appraisal skills to second year residents.

It was excluded because no comparative data were presented.

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13. Johnson JM, Reineck C, Daigle-Bjerke A, Goupil NM, Captain C. Understanding research articles. A pilot study of Critical reading of research publications. Journal of Nursing Staff Development 1995;11(2):95-99.

See Reineck C.

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14. Kerrison S, Rosenthal J, Wallace P. An evaluation of the North Thames Research Appraisal Teaching project. London: Department of General Practice and Primary Care, Royal Free Hospital School of Medicine, June 1995. Unpublished manuscript.

This study assessed the impact of a series of 23 workshops involving an estimated 130 participants, including managers, clinicians and researchers. The main focus of the evaluation was qualitative; some quantitative data was collected.

It was excluded because no comparative data was presented. Confirmation of this from the lead author was sought but not obtained.

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15. Konen JC, Fromm B. A family practice residency curriculum in critical appraisal of the medical literature. Family Medicine 1990; 22:284-7.

This describes five years of experience with a curriculum teaching critical appraisal skills to family practice residents.

It was excluded as no comparison group data were available, a fact confirmed by the author.

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16. Langkamp DL, Pascoe JM, Nelson DB. The effect of a medical journal club on residents' knowledge of clinical epidemiology and biostatistics. Family Medicine 1992;24:528-30.

This controlled before-after study assessed the impact of two didactic sessions on research design, clinical epidemiology and biostatistics followed by 8 monthly journal club sessions to 27 paediatric residents at two institutions.

It was provisionally included pending confirmation that the intervention was critical appraisal teaching, and that it was being compared to no teaching. Unfortunately no clarification was received and the study was effectively excluded, despite clearly being of potential relevance.

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17. Linzer M, DeLong ER, Hupart KH. A comparison of two formats for teaching critical reading skills in a medical journal club. Journal of Medical Education 1987;62:690-692.

This quasi-randomised controlled trial compared a journal club for residents teaching clinical epidemiology and biostatistical skills co-ordinated by a general medicine faculty member with a special interest and training in clinical epidemiology, biostatistics and critical appraisal, versus one co-ordinated by a chief resident.

It was excluded because it did not assess the impact of teaching critical appraisal, but rather two alternative approaches to teaching of critical appraisal. It was identified as a potentially useful study outside the immediate context of this review.

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18. Macauley D. Critical reading using the READER acronym at an international workshop. Family Practice 1996;13:104-105.

This study was excluded because it evaluates an instrument to aid critical appraisal and not the impact of teaching it.

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19. MacAuley D, Sweeney KG. Critical reading using the READER acronym by experienced general practitioners (G.P.s) and by G.P. Registrars in Southern and Northern Ireland. IJMS 1997;166(3):121-3.

This study was excluded because it evaluates an instrument to aid critical appraisal and not the impact of teaching it.

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20. Markert R. A research methods and statistics journal club for residents. Academic Medicine 1989;64:223-224.

This described the development of a journal club teaching medical residents how to read critically appraise the medical literature.

It was excluded because there was no comparison group and no pre-course assessment.

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21. Milne R, Oliver S. Evidence-based consumer health information: developing teaching in critical appraisal skills. Int J Qual Health Care 1996;5(8):439-445.

This study evaluated critical appraisal workshops designed to develop skills needed to make sense of evidence about effectiveness for people who give health information to the public esp staff in consumer health information services and members of maternity self-help groups.

It was excluded because there was no comparison group and no pre-course assessment.

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22. Mulvihill MN, Wallman G, Blum S. A seven-year retorspective view of a course in epidemiology and biostatistics. Journal of Medical Education 1980;55:457-459.

This study describes a course in epidemiology and biostatstics to medical students.

It was excluded because teaching critical appraisal did not appear to be a major component of the course. Further there was only minimal data on evaluation.

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23. Mulvihill MN, Banta HD. A clinical approach to teaching epidemiology and biostatistics. Journal of Medical Education 1973;48:591-593.

See previous reference by same author.

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24. Novick LF, Greene C, Vogt RL. Teaching medical students epidemiology: utilizing a state health department. Public Health Reports 1985;100(4):401-405.

The second part of the epidemiology course described was concerned with the teaching of critical appraisal skills.

It was excluded because there was no comparison group and no pre-course assessment.

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25. O'Sullivan P, Pinsker J, Jeremiah J, Wartman S. A learner centred journal club. Teaching and Learning in Medicine 1995;7(2):121-124.

This assessed general internal medicine residents perception of how two methods of teaching critical appraisal affected their reading habits, presentation skills and critical appraisal skills.

It was excluded as no comparison with no critical appraisal teaching was provided. It was identified as a potentially useful study outside the immediate context of this review.

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26. Reineck CA. Pilot testing an independent study series on research. Journal Of Continuing Education In Nursing 1995;26(6):249-252.
This described a pilot study of a critical reading of research programme over 6 sessions for nurses following on from the preliminary work by Jean Johnson.

It was excluded because there was no comparison group and no pre-course assessment, although it was indicated that the latter had been collected in the associated paper by Johnson.

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27. Romm FJ, Dignan M, Herman JM. Teaching clinical epidemiology: a controlled trial of two methods. Am J Prev Med 1989;5(1):50-51.

This randomised controlled trial compared teaching critical appraisal using either small group formats or lectures.

It was excluded as it had no comparison group not being taught critical appraisal. It was identified as a potentially useful study outside the immediate context of this review.

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28. Salmi LR, Collet JP. Lecture critique des articles médicaux. Rev Prat (Paris) 1991;41:2598-2605.

This paper in French was a tutorial on the critical appraisal process and was excluded because it was not an evaluation.

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29. Sandifer Q.D, Lo SV, Crompton G. Evaluation of a journal club as a forum to practise critical appraisal skills. J Roy Coll Phys Lond 1996;30(6):520-522.

This was set in a department of public health in S Glamorgan Health Authority and assessed the use of a journal club as a learning environment to practise critical appraisal skills. The proxy outcome indicators used were impact on commissioning policy and publication of letters to the editor of the journal from which the appraisers articles were selected.

It was excluded because there was no comparison group and no pre-course assessment.

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30. Stern D, Linzer M, O'Sullivan P, Weld L. Evaluating medical residents' literature appraisal skills. Academic Medicine 1995;70(2):152-154.

This was excluded as it was developing and validating an instrument to evaluate the abilities of residents to critically appraise a journal article and not the teaching of critical appraisal skills.

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31. Viniegra L, Espinosa P. Lectura crítica en groupos escogidos de estudiantes de medicina. [Critical reading in select groups of medical students.] Rev Invest Clin 1994; 46(5):407-15.

By the same authors as excluded study 1, this Mexican study involved the evaluation of critical appraisal skills in medical students and an attempt to relate differences observed to other characteristics such as years of medical training.

It was excluded as it did not involve teaching critical appraisal.

Appendix 5. Details of studies in progress

The following on-going and planned studies were identified:

- Taylor R, Exeter, UK. Undertaking an RCT looking at the effectiveness of teaching critical appraisal. In particular they are assessing longer term outcomes, including change in professional behaviour.
- Simon and Gillman, Harvard Medical School, USA. Have designed a critical reading of the medical literature tutorial-based course supplemented by occasional large group teaching. They have piloted the course and have extended it for the year 1997/8 to all first year Harvard medical students. They plan an evaluation of the impact of the course on students' critical appraisal skills when they reach their clinical years (years III and IV) beginning in summer 1998.
- Schulz and Grimes. Presently writing the results of a decade of evaluations of critical appraisal teaching courses that they have run under the auspices of the Berlex Foundation. The courses consist of week long tuition for academics in obstetrics and gynaecology run three times a year.
- Bob Cook, Sheffield Medical School, UK. Studies are in progress following the introduction of a McMaster-like, problem based learning curriculum.

In addition, there were many centres teaching critical appraisal, sometimes with sophisticated prepared teaching packages, that had no evaluation processes or data available when contacted.

Appendix 6. Included comparisons; further detail on nature of participants

Author (year)	Participants	Number (individuals unless stated)	Further details
Linzer (1988)	Doctors (interns)	44	Internal medicine interns at single hospital during outpatient clinic rotations (CAT 22; Control 22).
Seelig (1993)	Doctors (interns)	30	Practising internists with medical staff privileges at one hospital belonging to two essentially identical internal medicine group practices (CAT 18; Control 12).
Caudill (1993)	Doctors (residents)	70	Residents in single hospital's Dept of Internal Medicine residency program.
G'lbach (1980)	Doctors (residents)	35	Y 1-3 family medicine residents at one hospital (23 CAT; 12 Control).
Hillson (1993)	Doctors (residents)	29	Second year internal medicine residents taking part in 2m ambulatory care block rotation at one hospital.
Kitchens (1989) Phase I	Doctors (residents)	83	Y1-3 residents in internal medicine at one hospital attending eight ambulatory care clinics for ½ day per week (CAT 51; Control 32).
Kitchens (1989) Phase II	Doctors (residents)	83	Same population as above. Control group rotated to the four ambulatory care clinics teaching CA in pre-clinic conferences (CAT 32; Control 51).
Seelig (1991)	Doctors (residents)	14	Y1-3 residents in internal medicine training programme at one community hospital.
Bennett (1987)	Medical students	92	Final year medical students from four teaching hospitals in one area (49 CAT; 43 Control).
Cuddy (1984)	Medical students	18	Two of 28 randomly selected groups of medical students containing all levels of the six-year program (9 slide-tape programme; 9 lecture).
Frasca (1992)	Medical students	92	Third year medical students rotating through medical clerkship at two hospitals in one area (48 CAT; 44 Control).
Landry (1994)	Medical students	146	Third year medical students doing second six week block of 12w core medicine rotation at four centers in same area (CAT 65; Control 81).
Radack (1986)	Medical students	34	Fourth year clerks on three consecutive 2m inpatient medicine clinical rotations at two hospitals in one area (CAT 22; Control 12).
R'lman (1986)	Medical students	296	All "Class of 81" & all "Class of 85" medical students in one university – each tested in final year (Y4) (CAT 150; Control 146).
Hicks (1994)	Midwives	19	Experienced clinical midwife volunteers.
Burls (1997)	Multi-disciplinary	Circa 1,880	First time attenders at 94 standard format workshops, on appraisal of a systematic review and using standard evaluation questionnaires between 17/12/93 & 25/9/96. Total number of attenders had to be estimated because detailed records not kept on all those attending. Estimate based on average first time attendance rate at each workshop being 20. Justification for this using ancillary data is provided. A broad indication of the mix of disciplines can only be derived from a wider data-set for all workshops undertaken up to December 96 (172). In this the proportion of participants in particular groups was: • 30% Other/unknown • 20% Purchasing managers • 18% GPs • 9% Public health doctors • 6% Clinical audit staff • 5% Researchers • 5% Hospital consultants • 4% Librarians • 2% Consumer groups • 1% Consumer information
Ibbotson (1997)	Multi-disciplinary	115 (attenders)	All attenders at three workshops for which evaluation data were available (four originally planned). This represents 76 individuals, as some attended more than one of the three workshops. The backgrounds of these 76 were: • 43% Medical • 29% Research • 21% Managerial • 3% Nursing • 4% Other

Shaded cells indicate data items on which there was ambiguity.

Appendix 7. Included comparisons; further detail on nature of intervention considering both critical appraisal content and teaching method

STUDY	Teaching Format	Stud/ tutor ratio	Content	CA model	Quantity	Intensity	Motivation/ preselection	Attendance	Control	Intervention tested
BenN	Tutorials	4-5 S: 1 T	"Training for tutors and provision of special problem based educational materials that emphasise the critical appraisal of clinical evidence".	Mc Master	16h	2h /w	Unselected final yr medical students.	Not stated.	Usual tutorials. No tutor training/ CA teaching.	Greater crit app content + enhanced teaching method.
BuRLS	Workshops; CASP type (94)	5-8 S : 1 T for small groups 20-30 S: 1T other	Preparation, reading pre-workshop pack. Workshop timetable: 5-10 min intro; 45-60 min lecture; 45-60 min small group work appraising an article; 45-60 min plenary feedback; 15 min evaluation; 5 min conclusion.	Mc Master	2.7h to 3.5h	One -off	Wanted to attend workshop.	Not stated.	No parallel control group.	Greater crit app content + novel teaching method.
Caud	Lectures + seminars	Not stated	1. Printed self-directed learning material. 2. Monthly journal reading conference series (4 lectures). 3. Critical appraisal seminar series (7) – problem based; small group.	Mc Master (EBM)	Not stated Estimated 11h over 4m		All residents in a residency prog. Optional	31% at least one session.	No parallel control group.	Greater crit app content only.
CuddY	Slide/ tape program	No tutor	Pre-reading of high quality clinical trial. Self-administered slide-tape illustrating main sections of paper and guidelines for evaluating each of these sections.	None	21 mins	One -off	Randomly selected medical students.	100%	No parallel control group.	Greater crit app content + novel teaching method.
	Lecture	9 S: 1 T	Lecture on "literature evaluation skills" covering same topics as slide-tape programme.	None	1h	One -off		100%		Greater crit app content only.
FRASCA	Sem-Inars	9-13 S: 1T	Integrated library and critical appraisal skills course to teach location, evaluation & application of new information to clinical problems. Problem-based, facilitated small-group learning.	Mc Master	15h	1.2h /w	All Y3 medical students in a medical rotation.	Not stated.	Usual training for same rotation at another hosp.	Greater crit app content. Probably enhanced teaching.
GehLB'h	Seminars	4-6 S: 1-2 T	"Improving residents ability to read and interpret medical literature" Sessions: 1-3 Tutor led; 4-7 Resident presentations of articles; 8 Discussion of take-home exercise – not that used in evaluation.	None	8h	1h /w	All fam med residents in a 2m O-P rotation.	Not stated.	Y1residents in rotation. No epi seminar series.	Greater crit app content + gen Y2&3 content + enhanced teaching.
HICKS	Study day	19 S: 1 T	Obj 1 To make more accurate, informed and valid assessments of published research literature Obj 2 To increase use of published research. Workshop: 2h intro lecture; 2h present an ongoing research project; approx 3h use guidelines in relation to article.	None	7h	One -off	Experienced clinical midwife volunteers.	100%.	No parallel control group.	Greater crit app content + novel teaching method.
HLLS'n	Lectures + journal club Sessions	Lect & jc: 5-7 S: 1-2 T	Sessions: 1 Lecture on critical review methods; 2 Demonstration of critical review on an article; 3+ Residents present and have a facilitated discussion on their chosen article.	None	7h to 13.5 h	0.9h /w to 1.5h /w	All Y2 int med residents in a 2m rotation.	Not stated.	No parallel control group.	Greater crit app content + novel teaching method.
IBb	Workshops; CASP Type (4)	Assume identical to Burls		CASP (& so McMaster)	2.7h to 3.5h	One -off	Wanted to attend workshop.	Not stated.	No parallel control group.	Assume as for Burls

Shaded cells indicate data items on which there was ambiguity. Where cells contain several items of information the ambiguous item is underlined.

Study	Teaching Format	Stud/ tutor ratio	Content	CA model	Quantity	Intensity	Motivation/ preselection	Attendance	Control	Intervention tested
Kitchens	Seminars (Ph I)	Unknown	"To teach key principles of clinical epidemiology that are necessary to read critically the medical literature." At each pre-clinic conference resident led discussion of current article in relation to relevant McMaster guideline. Explicit involvement of students and use of small group interactive formats.	Mc Master	8.5h to 12.8 h	0.5h /w to 0.75 h/w	All Y1-3 residents in int med at one hospital.	Not stated.	Same rotation. Clinics with standard pre-clinic conference.	Greater crit app content. Probably enhanced teaching.
Kitchens	Seminars (Ph II)	Unknown	As above but modified in response to feed back after Phase I. 1. Decreased number of sessions 2. Each conference supplemented with written questions to emphasise important clinical epidemiology principles. Explicit involvement of students and use of small group interactive formats.	Mc Master	4h to 6h	0.5h /w to 0.75 h/w	All Y1-3 residents in int med at one hospital.	Not stated.	CAT arm above rotates to clinics with standard teaching.	Greater crit app content. Probably enhanced teaching.
Landry	Seminars (large group)	65 S: 1 T	"Improve medical student attitudes towards, knowledge about and clinical use of medical literature" Sem 1. Types of articles and study design; Sem 2. Reading the literature critically emphasising McMaster guidelines. Seminars interactive.	Mc Master	3h	1.5h /w	All Y3 med students on 12w core med rotation.	Not stated.	Same rotation; centres with no seminar & assoc material.	Greater crit app content only.
Linzer	Journal club sessions	Unknown	General medical journal club that emphasises epidemiologic methods and critical appraisal of medical evidence. Intern chooses article; article circulated; intern presents & critiques at journal club; tutor facilitates discussion & emphasises clinical utility.	Mc Master	3h to 6h (actually attended)	Unknown duration	All int medicine interns during O-P clinic rotation.	JC: 100% Con: 45% - both for 3h or more.	Same rotation, standard conferences in ambulatory care.	Greater crit app content. Probably enhanced teaching.
Radack	Seminars	4-7 S: 1T	"To teach the critical evaluation of journal articles by presenting students with methodologic criteria developed to help determine the validity and usefulness of the evidence presented in the published data." Under tutor supervision article appraised by student with reference to clinical scenario and guidelines.	Several influences inc Mc Master	4.2h	0.5h /w	All Y4 clerks on three consecutive 2m I-P med clinical rotations.	50% to 85% depending on the rotation.	Same rotation, different hospital with no CA & no seminars offered.	Greater crit app content. Probably enhanced teaching.
Reigel	Lectures + seminars	Lect: >100 S: 1 T Sem: Unknown	Comprehensive course on study design and statistics. 12 lectures; 4 seminars. Emphasis on, "what the student needs to know to understand medical journal articles and apply them in practice".	None	16h	Unknown duration	All "Class of 85" medical students.	Not stated.	"Class of 81". No course, but prob had some biostats.	Greater crit app content only.
Seel 91	Seminar + journal club sessions	Sem: 14 S: 1 T JC: Unknown	Seminar incorporating principles of adult education – 5 specified objectives relating to need and skills required to use medical literature. Reinforced with learner participation, written assignments, active feed back and follow-up in journal clubs.	Mc Master	8h	0.5h /w	All Y1-3 residents in int med training programme.	Not stated.	No parallel control group.	Greater crit app content + novel teaching method.
Seel 93	Seminar	18 S: 1 T	As for Seelig (1991) No follow-up in journal clubs possible.	Mc Master	1h	One -off	Internists with medical staff privileges at one hospital.	Not stated.	Same status; different practice. No lect (or other education)	Greater crit app content. Probably enhanced teaching.

Shaded cells indicate data items on which there was ambiguity. Where cells contain several items of information the ambiguous item is underlined.

Appendix 8. Detail on outcome information available in each of the included studies

Study ID [ref]	Comparison		General outcome assessed	Specific measure	Within-/ between-group *
Bennett 87 [1]	A	1	Skills	Scored response to problem on therapy	B (b-a change ^{i} vs b-a change ^{c})
	B	2	Skills	Scored response to problem on diagnosis	B (b-a change ^{i} vs b-a change ^{c})
	C	3	Skills	Scored response to problem on therapy	W (b ^{i} vs a ^{i})
	D	4	Skills	Scored response to problem on diagnosis	W (b ^{i} vs a ^{i})
Burls 97 [2]	A	5	Knowledge	Self-perceived understanding and ability to explain key terms (adjusted, "impact score")	W (b ^{i} vs a ^{i})
	B	6	Knowledge	Self-perceived understanding and ability to explain key terms (adjusted, "impact score")	W (b ^{i} vs a ^{i})
	C	7	Attitudes	Degree of agreement with key statements on need to use research (crude)	W (b ^{i} vs a ^{i})
	D	8	Attitudes	Degree of agreement with key statements on need to use research (adjusted, "impact score")	W (b ^{i} vs a ^{i})
Caudill 93 [3]	A	9	Behaviour	Self-perceived reading behaviour esp of research articles	W (b ^{i} vs a ^{i})
	B	10	Skills	Self-perceived confidence in critical appraisal	W (b ^{i} vs a ^{i})
	C	11	Knowledge	Score in epidemiology and biostatistics test	W (b ^{i} vs a ^{i})
	D	12	Attitudes	Degree of agreement with statements on limits to use of research literature	W (b ^{i} vs a ^{i})
Cuddy 84 [4]	a (Lect)	13	Knowledge (element of skills)	Score in MCQ on course content	W (b ^{i} vs a ^{i})
	b (Slide–tape prog)	14	Knowledge (element of skills)	Score in MCQ on course content	W (b ^{i} vs a ^{i})
Frasca 92 [5]	A	15	Skills	Score in test to measure application of library skills	B (a ^{i} vs a ^{c})
	B	16	Skills	Score in test to measure application of appraisal skills	B (a ^{i} vs a ^{c})
Gehlbach 80 [6]	A	17	Skills	Score in MCQs relating to interpretation of journal article	B (a ^{i} vs a ^{c})

Shaded cells indicate data items on which there was ambiguity.

* This column provides a description of the comparison used to provide the information on the outcome in question. The conventions used were:
B = between-group comparison, the outcome in the CAT group being compared to that in a parallel control group
W = within-group comparison, the outcome after the CAT being compared to that before
b^{i} = before measurement in the intervention (CAT) group
b^{c} = before measurement in the control (no CAT) group
a^{i} = after measurement in the intervention (CAT) group
a^{c} = after measurement in the control (no CAT) group
a_2^{i} = where the after measurement is made at more than one point in time, subscripts are used
b-a change = where in a between-group comparison, the change in outcome in the intervention (CAT) group is compared to the control (no CAT) group [as opposed to just comparing the after measures]

Study ID [ref]	Comparison		General outcome assessed	Specific measure	Within-/ between-group *
Hicks 94 [7]	A	18	Behaviour	Self-perceived frequency of reading research articles	W (b^i vs a_2^i)
	B	19	Behaviour	Self-perceived frequency of research prompting change in practice	W (b^i vs a_2^i)
	C	20	Skills	Concordance of appraisal of research article on 8 criteria with that of experienced appraisers	W (b^i vs a_1^i)
	D	21	Skills	Self-perceived confidence in critical appraisal	W (b^i vs a_2^i)
Hillson 92 [8]	A	22	Skills	Concordance of appraisal of research article on 15 criteria with that of experienced appraisers	W (b^i vs a^i)
	B	23	Skills	Self-perceived confidence in critical appraisal	W (b^i vs a^i)
Ibbotson 97 [9]	A	24	Knowledge	Self-perceived understanding and ability to explain key terms	W (b^i vs a^i)
Kitchens 89 [10]	A (P I)	25	Knowledge	Score in clinical epidemiology test	B ** (a_1^i vs a_1^c)
	B (PII)	26	Knowledge	Score in clinical epidemiology test	B ** (a_1-a_2 change^i vs a_1-a_2 change^c)
	C (PII)	27	Knowledge	Score in clinical epidemiology test	W ** (a_1^i vs a_2^i)
Landry 94 [11]	A	28	Behaviour (referred to as skills in paper)	Assessment of patient write-ups	B (b-a change ^{i} vs b-a change ^{c})
	B	29	Behaviour (referred to as skills in paper)	Assessment of patient write-ups	W (b^i vs a^i)
	C	30	Knowledge (element of skills)	Score in test of research design and critical appraisal skills	B (b-a change ^{i} vs b-a change ^{c})
	D	31	Knowledge (element of skills)	Score in test of research design and critical appraisal skills	W (b^i vs a^i)
	E	32	Attitudes	Agreement with statements on value of research	B (b-a change ^{i} vs b-a change ^{c})
	F	33	Attitudes	Agreement with statements on value of research	W (b^i vs a^i)

Shaded cells indicate data items on which there was ambiguity.

* This column provides a description of the comparison used to provide the information on the outcome in question. The conventions used were:
B = between-group comparison, the outcome in the CAT group being compared to that in a parallel control group
W = within-group comparison, the outcome after the CAT being compared to that before
b^i = before measurement in the intervention (CAT) group
b^c = before measurement in the control (no CAT) group
a^i = after measurement in the intervention (CAT) group
a^c = after measurement in the control (no CAT) group
a_2^i = where the after measurement is made at more than one point in time, subscripts are used
b-a change = where in a between-group comparison, the change in outcome in the intervention (CAT) group is compared to the control (no CAT) group [as opposed to just comparing the after measures]

** Kitchens is a cross-over trial. a_1 is the outcome measured after completion of phase I; a_2 is the outcome measured after completion of phase II. Thus for phase II the before measure is a_1 and the after measure a_2.

Study ID [ref]	Comparison		General outcome assessed	Specific measure	Within-/ between-group *
Linzer 88 [12]	A	34	Behaviour	Self-perceived reading habits	B (b-a change ^{i} vs b-a change ^{c})
	B	35	Behaviour	Self-perceived reading habits	W (b ^{i} vs a ^{i})
	C	36	Skills	Score in critical appraisal exercise	B (b-a change ^{i} vs b-a change ^{c})
	D	37	Skills	Score in critical appraisal exercise	W (b ^{i} vs a ^{i})
	E	38	Skills	Self-perceived confidence in critical appraisal	B (b-a change ^{i} vs b-a change ^{c})
	F	39	Skills	Self-perceived confidence in critical appraisal	W (b ^{i} vs a ^{i})
	G	40	Knowledge	Score in epidemiology and biostatistics test	B (b-a change ^{i} vs b-a change ^{c})
	H	41	Knowledge	Score in epidemiology and biostatistics test	W (b ^{i} vs a ^{i})
Radack 86 [13]	A	42	Skills	Score in critical appraisal exercise	B (b-a change ^{i} vs b-a change ^{c})
	B	43	Skills	Score in critical appraisal exercise	W (b ^{i} vs a ^{i})
Reigelman 86 [14, 17]	A	44	Behaviour	Self-perceived extent and type of reading of medical literature	B (a ^{i} vs a ^{c})
	B	45	Behaviour	Self-perceived extent and type of reading of medical literature	W (b ^{i} vs $a_2{}^{i}$)
	C	46	Skills	Self-perceived competence in critical appraisal skills (5)	B (a ^{i} vs a ^{c})
	D	47	Skills	Self-perceived competence in critical appraisal skills (5)	W (b ^{i} vs $a_1{}^{i}$ vs $a_2{}^{i}$)
	E	48	Knowledge	Correct answers to questions on study design and statistics	B (a ^{i} vs a ^{c})
	F	49	Knowledge	Correct answers to questions on study design and statistics	W (b ^{i} vs $a_2{}^{i}$)

* This column provides a description of the comparison used to provide the information on the outcome in question. The conventions used were:
B = between-group comparison, the outcome in the CAT group being compared to that in a parallel control group
W = within-group comparison, the outcome after the CAT being compared to that before
b^{i} = before measurement in the intervention (CAT) group
b^{c} = before measurement in the control (no CAT) group
a^{i} = after measurement in the intervention (CAT) group
a^{c} = after measurement in the control (no CAT) group
$a_2{}^{i}$ = where the after measurement is made at more than one point in time, subscripts are used
b-a change = where in a between-group comparison, the change in outcome in the intervention (CAT) group is compared to the control (no CAT) group [as opposed to just comparing the after measures]

Study ID [ref]	Comparison		General outcome assessed	Specific measure	Within-/ between-group *
Seelig 91 [15, 16]	A	50	Behaviour	Self-perceived extent and type of reading of medical literature	W (b^i vs a^i)
	B	51	Skills	Self-perceived confidence in critical appraisal	W (b^i vs a^i)
	C	52	Knowledge	Score in test of the principles of critical appraisal	W (b^i vs a^i)
	D	53	Attitudes	Degree of agreement with statements on importance and purpose of reading journal articles	W (b^i vs a^i)
Seelig 93 [16]	A	54	Behaviour	Self-perceived extent and type of reading of medical literature	W (b^i vs a^i)
	B	55	Skills	Self-perceived confidence in critical appraisal	W (b^i vs a^i)
	C	56	Knowledge	Score in test of the principles of critical appraisal	B (b-a change ^{i} vs b-a change ^{c})
	D	57	Knowledge	Score in test of the principles of critical appraisal	W (b^i vs a^i)
	E	58	Attitudes	Degree of agreement with statements on importance and purpose of reading journal articles	W (b^i vs a^i)

* This column provides a description of the comparison used to provide the information on the outcome in question. The conventions used were:
B = between-group comparison, the outcome in the CAT group being compared to that in a parallel control group
W = within-group comparison, the outcome after the CAT being compared to that before
b^i = before measurement in the intervention (CAT) group
b^c = before measurement in the control (no CAT) group
a^i = after measurement in the intervention (CAT) group
a^c = after measurement in the control (no CAT) group
a_2^i = where the after measurement is made at more than one point in time, subscripts are used
b-a change = where in a between-group comparison, the change in outcome in the intervention (CAT) group is compared to the control (no CAT) group [as opposed to just comparing the after measures]

Appendix 9. Explanation of noted threats to validity arising from study design employed

Study (Year)	Comparison type (Between- or within-group) Design	Openess to confounding?			Sample size
		Was allocation conceal-ed?	Were the groups compared similar? Major or minor differences noted? Adjusted for?	Was CAT the only "intervention" possibly operating to explain any change in outcome observed?	
		Only applicable to RCTs	Between-group: • Time • Location • Experience • Baseline var-iables (number examined) • Adjustment Within-group: • Paired responses	Between-group: • CAT the only difference • Contamination Within-group: • Immediate post CAT assessment • If delayed, exclusion of other interventions	
Bennett (1987)	Between-group CT	N/A	No - minor - but adjusted for. Same time. Different hospitals. Same rotation (experience). Imbalance in measured baseline characteristics (2). Comparison of b-a changes adjusts for imbalances.	Yes. Contamination unlikely.	92 CAT = 49 Con = 43
Burls (1997)	Within-group BA	N/A	Yes. Paired responses used.	Yes. Immediate post-intervention assessment. CAT workshop lasted ½ day.	Approx 1880
Caudill (1993)	Within-group BA	N/A	Yes. Paired responses used.	Unknown. Exact timing of post-intervention assessment not stated.	70
Cuddy (1984) (Lecture)	Within-group BA	N/A	Yes. Paired responses used.	Unknown. Students allowed to take post-intervention assessment when convenient to them. CAT lasted 1h.	9
Cuddy (1984 (Sl-tape)	Within-group BA	N/A	Yes. Paired responses used.	Unknown. Students allowed to take post-intervention assessment when convenient to them. CAT lasted 21mins.	9
Frasca (1992)	Between-group CT	N/A	No - minor - not adjusted for. Same time. Different hospitals. Same experience. Some imbalance in measured baseline characteristics (4). No adjustment.	Yes. Contamination unlikely.	92 CAT = 48 Con = 44

Shaded cells indicate data items on which there was ambiguity or where there was uncertainty about the degree to which the feature constituted a threat to validity.
Cells outlined in bold indicate those features considered to constitute a major threat to validity.

Study (Year)	Comparison type (Between- or within-group) Design	Openess to confounding?			Sample size
		Was allocation conceal-ed?	Were the groups compared similar? Major or minor differences noted? Adjusted for?	Was CAT the only "intervention" possibly operating to explain any change in outcome observed?	
		Only applicable to RCTs	Between-group: • Time • Location • Experience • Baseline var-iables (number examined) • Adjustment Within-group: • Paired responses	Between-group: • CAT the only difference • Contamination Within-group: • Immediate post CAT assessment • If delayed, exclusion of other interventions	
Gehl-bach (1980)	Between-group CT	N/A	No - major - not adjusted for. Same time and location. Different experience, Y2 & Y3 residents compared to Y1. No measured baseline characterist-ics. No adjustment.	No. CAT groups had also been exposed to one to two years additional resident training.	35 CAT = 23 Con = 12
Hicks (1994)	Within-group BA	N/A	Yes. Paired responses used.	For behaviour, and skills as measured by "Confidence in appraisal skills" - No. Post-intervention assessment 2m after workshop. Other interventions in this period not excluded. For skills as measured by "Concordance with expert appraisal" – Yes. Immediate post-intervention assessment. Workshop lasted 1d.	19
Hillson (1994)	Within-group BA	N/A	Yes. Paired responses used.	Yes. Immediate post-intervention assessment. CAT program lasted 2m.	29
Ibbotson (1997)	Within-group BA	N/A	Yes. Paired responses used.	Yes. Immediate post-intervention assessment. CAT workshop lasted ½ d.	115 attenders (76 individuals)
Kitchens (1989) (Ph I)	Between-group CT	N/A	No - minor - not adjusted for. Same time, hospital and experience. Some imbalance in measured baseline characteristics (2). No adjustment.	Yes. However, some possibility of contamination.	83 CAT = 51 Con = 32
Kitchens (1989) (Ph II)	Between-group CT	N/A	No - minor - but adjusted for. Same time, hospital and experience. Some imbalance in measured baseline characteristics (2). Comparison of b-a changes adjusts for imbalances.	Yes. Contamination unlikely. Control group had previously received a similar, longer CAT program.	83 CAT = 32 Con = 51

Shaded cells indicate data items on which there was ambiguity or where there was uncertainty about the degree to which the feature constituted a threat to validity.
Cells outlined in bold indicate those features considered to constitute a major threat to validity.

Study (Year)	Comparison type (Between- or within-group) Design	Openess to confounding?			Sample size
		Was allocation conceal-ed?	**Were the groups compared similar? Major or minor differences noted? Adjusted for?**	**Was CAT the only "intervention" possibly operating to explain any change in outcome observed?**	
		Only applicable to RCTs	Between-roup: • Time • Location • Experience • Baseline var-iables (number examined) • Adjustment Within-group: • Paired responses	Between-group: • CAT the only difference • Contamination Within-group: • Immediate post CAT assessment • If delayed, exclusion of other interventions	
Landry (1994)	Between-group CT	N/A	No – minor - but adjusted for. Same time. Different hospitals. Same experience. Some imbalance in measured baseline characteristics (5). Comparison of b-a changes adjusts for imbalances.	Yes. Contamination unlikely.	146 CAT = 65 Con = 81
Linzer (1988)	Between-group RCT	Unknown. Method of randomis-ation not stated.	No - minor - but adjusted for. Same time, location and experience. Some imbalance in measured baseline characteristics (5). Comparison of b-a changes adjusts for imbalances.	Yes. However, some possibility of contamination.	44 CAT = 22 Con = 22
Radack (1986)	Between-group CT	N/A	No - minor - but adjusted for. Same time. Different hospitals (CAT in affiliated hospital; control in non-affiliated hospital). Same experience. No measured baseline characteristics. Comparison of b-a changes adjusts for imbalances.	Yes. Contamination unlikely.	34 CAT = 22 Con = 12
Reigel-man (1986)	Between-group CT	N/A	No – potentially major - not adjusted for. Same location and experience (Y4 students). Intervent-ion & control arms from different intakes ("Class of 1981" compared to "Class of 1985"). No imbalance in measured baseline characteristics (3). No adjustment.	Yes. No contamination possible.	296 CAT = 150 Con = 146

Shaded cells indicate data items on which there was ambiguity or where there was uncertainty about the degree to which the feature constituted a threat to validity.
Cells outlined in bold indicate those features considered to constitute a major threat to validity.

Study (Year)	**Comparison type (Between- or within-group) Design**	**Openess to confounding?**			**Sample size**
		Was allocation conceal-ed?	**Were the groups compared similar? Major or minor differences noted? Adjusted for?**	**Was CAT the only "intervention" possibly operating to explain any change in outcome observed?**	
		Only applicable to RCTs	Between-group: • Time • Location • Experience • Baseline var-iables (number examined) • Adjustment Within-group: • Paired responses	Between-group: • CAT the only difference • Contamination Within-group: • Immediate post CAT assessment • If delayed, exclusion of other interventions	
Seelig (1991)	Within-group BA	N/A	Yes. Paired responses used.	Yes. Immediate post-intervention assessment. CAT programme lasted 4m.	14
Seelig (1993)	Between-group CT (Knowledge)	N/A	No - minor- but adjusted for. Different group practices. Same time and experience. No imbalance in measured baseline characteristics (2). Comparison of b-a changes adjusts for imbalances.	Yes. Contamination unlikely.	30 CAT = 18 Con = 12
Seelig (1993)	Within-group BA (Behaviour, skills & attitudes)	N/A	Yes. Paired responses used.	No. Post-intervention assessment 4m after CAT lecture. Other interventions in this period not excluded.	18

Shaded cells indicate data items on which there was ambiguity or where there was uncertainty about the degree to which the feature constituted a threat to validity.
Cells outlined in bold indicate those features considered to constitute a major threat to validity.

Appendix 10. Explanation of noted threats to validity arising from methods of outcome assessment and data analysis.

Study (Year)	**i What**	**ii Timing**	**iii Tools used**	**iv Same tool**	**v Validation**	**vi Ind & Blind**	**vii F/up**	**viii Stats**	**ix Other bias**
Bennett (1987)	SKILLS (BG) Critical appraisal: exercises on therapy & diagnosis. *Change.*	Precise timing of before and after assess-ments not stated. CAT lasted 8w.	E/A Score in one of 9 written take home exercises comprising two of six therapy and one of three diagnosis questions. Each question required critical appraisal with reference to a specific article. Exercises scored against pre-set criteria.	Different exercises, allocated randomly, given to CAT & control and b-a. Potential for bias limited by random allocation and the standardised way in which exercises were developed.	Exercises pre-tested on graduate epidemiology students and shown to differentiate between levels of methodological expertise. Intra & inter-observer agreement of scoring tested on 30% random sample. Cohen's κ 0.84 & 0.74 (therapy) & 1.0 & 0.83 (diagnosis).	Yes. Assessment by non-faculty members blind of whether exercise was from CAT or control group before or after and whether.	13/92 (14%) CAT 4/49 Con 9/43	No power calculation. CI & p values used. Appropriate statistical tests used.	Yes. Use of parallel control group accounts for these.

Cells outlined in bold indicate major threats to validity. Shaded cells indicate data items on which there was ambiguity or uncertainty about the extent of any threat to validity.
HEADING NOTES: i) What was assessed? Were changes over study period assessed *[Change]* or were states at end of study compared *[End]* ?
ii) Timing of assessment/s with reference to start of period of CAT, which = time 0.
iii) Further details of assessment tools used. Were they primarily dependent on assessment by the participant themselves (S/A), or by the investigator or 3rd party (E/A)?
iv) Was the same assessment tool used in CAT & control and/or before & after? If no, was the risk of bias high or low?
v) Was the assessment tool validated? Complete validation = 2+ validation exercises on a specific outcome; partial validation = 1 exercise, or validation on assessment tool overall.
vi) Was assessment independent and double blind of whether outcome was in CAT/control group, or before/after? If no or unstated, was the risk of bias high or low with reference to: Was the study objective apparent to participants?, if S/A; & Were there clear assessment criteria?, if E/A.
vii) Loss to follow-up as % of original number of participants, including losses to follow-up in CAT and control groups where applicable.
viii) Was the statistical analysis generally appropriate? Specific consideration of a) power calculation b) whether CI or p values stated c) whether correct statistical tests used.
ix) Were other sources of bias excluded? In particular was the possibility of the following taken into account of a) background trend especially where time >6m b) learning effect.

Study (Year)	i What	ii Timing	iii Tools used	iv Same	v Valid	vi Ind & Blind	vii F/up	viii Stats	ix Other bias
Burls (1997)	KNOWLEDGE(WG) Understanding of key terms used in systematic reviews: perception of own knowledge (crude score & overall impact score). *Change.*	2w before and immed-iately after CAT.	S/A As part of self-completed questionnaire. Crude score: Uses five point Likert scale (1= unaware of term, 5= understand it and could define it now) to self-report perceived knowledge of 9 terms covered in CAT. Same tool used to assess knowledge of 9 "control" terms not covered in CAT. Overall impact score: Uses same data, but takes into account small shifts in score not indicating meaningful change, the tendency to improve even in those terms not addressed in the CAT (by subtracting change in "control" terms from change in "test" terms), and the ceiling effect of a scale with limited numbers of points.	Same tool used b-a.	Intra-observer variability of whole question-naire assessed (n=29). Weighted $\kappa = 0.69$ (95% CI 0.64 to 0.74). As above	KNOW & ATTITUDE Crude Score: No. Without a control group participants would realise that CAT was "new", and using a S/A outcome would be free to provide the answer post-CAT which they felt was socially acceptable. The crude score makes no adjustment for this. KNOW & ATTITUDE Overall Impact Score: No. High potential for bias reduced by taking into account the tendency to give the "desired" answer in the post-CAT response manifest in the changes in the "control" questions/statements which were not addressed by the CAT workshop.	Circa 570/ 1880 (30%)	No power calcul-ation. CI and p values used. Approp-riate stat-istical tests used.	Yes. Background trend highly unlikely over time period of outcome assessment. Data on intra-observer variation also provides reassurance that learning effect from doing questionnair e twice is likely to be negligible.
	ATTITUDES (WG) Need to use research: deg-ree of agree-ment with state-ments (crude score). *Change.*		S/A Part of self-completed questionnaire. Crude score using five point Likert scale (1= strongly agree, 5= strongly disagree) to self-report degree of agreement with 3 converse pairs of statements (6 in all). Same tool used to assess agreement with 2 statements which were not intended to be influenced by the CAT.				Circa 530/ 1880 (28%)		

Cells outlined in bold indicate major threats to validity. Shaded cells indicate data items on which there was ambiguity or uncertainty about the extent of any threat to validity.
HEADING NOTES: i) What was assessed? Were changes over study period assessed *[Change]* or were states at end of study compared *[End]* ?
ii) Timing of assessment/s with reference to start of period of CAT, which = time 0.
iii) Further details of assessment tools used. Were they primarily dependent on assessment by the participant themselves (S/A), or by the investigator or 3rd party (E/A)?
iv) Was the same assessment tool used in CAT & control and/or before & after? If no, was the risk of bias high or low?
v) Was the assessment tool validated? Complete validation = 2+ validation exercises on a specific outcome; partial validation = 1 exercise, or validation on assessment tool overall.
vi) Was assessment independent and double blind of whether outcome was in CAT/control group, or before/after? If no or unstated, was the risk of bias high or low with reference to: Was the study objective apparent to participants?, if S/A; & Were there clear assessment criteria?, if E/A.
vii) Loss to follow-up as % of original number of participants, including losses to follow-up in CAT and control groups where applicable.
viii) Was the statistical analysis generally appropriate? Specific consideration of a) power calculation b) whether CI or p values stated c) whether correct statistical tests used.
ix) Were other sources of bias excluded? In particular was the possibility of the following taken into account of a) background trend especially where time >6m b) learning effect.

Study (Year)	i What	ii Timing	iii Tools used	iv Same	v Validation	vi Ind & Blind	vii F/up	viii Stats	ix Other bias
Caudill (1993)	BEHAVIOUR (WG) Reading behaviour. *Change.*	Precise timing of before and after assess-ments not stated. CAT lasted 6m.	S/A Part of self-completed questionnaire with four parts. Total no of journals subscribed to and no of journal articles read, critically appraised and discussed with colleagues.	Same tool used b-a.	None stated for these components of questionnaire.	No. Without a control group participants would realise that CAT was "new", and using a S/A outcome would be free to provide the answer post-CAT which they felt was socially acceptable.	48/70 (69%)	No power calcul-ation. No CI. P values used. Approp-riate stat-istical tests used.	No. Background trend over the >6m period of study is possible and could account for any b-a change observed. Learning effect possible and not accounted for in measurement of knowledge; learning effect unlikely for self perceived reading behaviour, skills and attitudes.
	SKILLS (WG) Critical appraisal: perception of own skill. *Change.*		S/A Part of self-completed questionnaire with four parts. Five point Likert scale used (1= not at all confident, 5= very confident) to assess perceived skill in research design, identification of study population, statistics and generalization.						
	KNOWLEDGE (WG) Epidemiology and bio-statstics: test questions. *Change.*		E/A Part of self-completed questionnaire with four parts. Score in 15-item test as used in Linzer (1988).		As for Linzer (1988).	No. Potential for bias reduced by almost certainly having clearly defined correct/incorrect answers.			
	ATTITUDES (WG) Limits to use of research literature: degree of agree-ment with state-ments. *Change.*		S/A Part of self-completed questionnaire with four parts. Five point Likert scale (1= not at all, 5= extremely) used to assess degree of agreement with assertion that research literature is credible, applicable and available.		None stated. Tool said to be previously developed, a reference for which is provided.	As for entry for behaviour and skills.			

Cells outlined in bold indicate major threats to validity. Shaded cells indicate data items on which there was ambiguity or uncertainty about the extent of any threat to validity.
HEADING NOTES: i) What was assessed? Were changes over study period assessed *[Change]* or were states at end of study compared *[End]* ?
ii) Timing of assessment/s with reference to start of period of CAT, which = time 0.
iii) Further details of assessment tools used. Were they primarily dependent on assessment by the participant themselves (S/A), or by the investigator or 3rd party (E/A)?
iv) Was the same assessment tool used in CAT & control and/or before & after? If no, was the risk of bias high or low?
v) Was the assessment tool validated? Complete validation = 2+ validation exercises on a specific outcome; partial validation = 1 exercise, or validation on assessment tool overall.
vi) Was assessment independent and double blind of whether outcome was in CAT/control group, or before/after? If no or unstated, was the risk of bias high or low with reference to: Was the study objective apparent to participants?, if S/A; & Were there clear assessment criteria?, if E/A.
vii) Loss to follow-up as % of original number of participants, including losses to follow-up in CAT and control groups where applicable.
viii) Was the statistical analysis generally appropriate? Specific consideration of a) power calculation b) whether CI or p values stated c) whether correct statistical tests used.
ix) Were other sources of bias excluded? In particular was the possibility of the following taken into account of a) background trend especially where time >6m b) learning effect.

Study (Year)	**i What**	**ii Timing**	**iii Tools used**	**iv Same tool**	**v Valid**	**vi Ind & Blind**	**vii F/up**	**viii Stats**	**ix Other bias**
Cuddy (1984) (Lecture & slide-tape prog-rammes)	KNOWLEDGE (WG) Basic concepts of literature evaluation: MCQ test. *Change.*	Precise timing of before and after assessments not stated. Students were allowed to take tests at convenient times. CAT lasted 1h or 21 mins.	E/A Correct responses to 20 computer based MCQs covering CAT course content. Exact format not stated. Element of skills may also have been measured in addition to knowledge.	Same tool used b-a (and in both arms of study).	None stated.	No. Potential for bias reduced by having clearly defined correct/ incorrect answers for questions – MCQs were computer marked.	Lecture 0/9 (0%) S-tape 0/9 (0%)	No power calculation. No CI. P values used. Unusual but appropriate statistical test used.	No. However unlikely, unable to completely exclude possible background trend in absence of information on when post-CAT assessments were made. Learning effect also possible and not accounted for.
Frasca (1992)	SKILS (BG) Critical appraisal and library skills: MCQ test. *End.*	Immediately after each of the four 3m clerkships during which CAT or control offered.	E/A Score in 20 MCQ questions (13 critical appraisal, 7 library) – 20 mins allowed to complete; no warning given of test. Required application of skills to a practical situation. None required rote memory alone.	Same test given to CAT & control. No b-a change employed.	None stated.	Not stated. Potential for bias reduced by having clearly defined correct/ incorrect answers.	0/92 (0%) CAT 0/48 Con 0/44	No power calculation. No CI. P values used. Appropriate statistical tests used.	Yes. Use of parallel control group accounts for these.

Cells outlined in bold indicate major threats to validity. Shaded cells indicate data items on which there was ambiguity or uncertainty about the extent of any threat to validity.
HEADING NOTES: i) What was assessed? Were changes over study period assessed *[Change]* or were states at end of study compared *[End]* ?
ii) Timing of assessment/s with reference to start of period of CAT, which = time 0.
iii) Further details of assessment tools used. Were they primarily dependent on assessment by the participant themselves (S/A), or by the investigator or 3rd party (E/A)?
iv) Was the same assessment tool used in CAT & control and/or before & after? If no, was the risk of bias high or low?
v) Was the assessment tool validated? Complete validation = 2+ validation exercises on a specific outcome; partial validation = 1 exercise, or validation on assessment tool overall.
vi) Was assessment independent and double blind of whether outcome was in CAT/control group, or before/after? If no or unstated, was the risk of bias high or low with reference to: Was the study objective apparent to participants?, if S/A; & Were there clear assessment criteria?, if E/A.
vii) Loss to follow-up as % of original number of participants, including losses to follow-up in CAT and control groups where applicable.
viii) Was the statistical analysis generally appropriate? Specific consideration of a) power calculation b) whether CI or p values stated c) whether correct statistical tests used.
ix) Were other sources of bias excluded? In particular was the possibility of the following taken into account of a) background trend especially where time >6m b) learning effect.

Study (Year)	**i What**	**ii Timing**	**iii Tools used**	**iv Same tool**	**v Valid**	**vi Ind & Blind**	**vii F/up**	**viii Stats**	**ix Other bias**
Gehl-bach (1980)	SKILS (BG) Critical appraisal: MCQ test. *End.*	Precise timing of assessment after start of CAT not stated. Likely to vary depending on when in the year the 2m experimental out-patient rotation was done. Min 2m after start; max 1y.	E/A Score in 7 MCQs included as part of a 218 item in-training end of year examination. The MCQs required interpretation of a specially prepared one page abstract of a medical journal article.	Same test given to CAT & control. No b-a change employed	None stated.	Not stated. Potential for bias reduced by having clearly defined correct/incorrect answers.	0/35 (0%) CAT 0/23 Con 0/12	No power calculation. No CI. P values used. One-tailed statistical tests used.	Yes. Use of parallel control group accounts for these.

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HEADING NOTES: i) What was assessed? Were changes over study period assessed *[Change]* or were states at end of study compared *[End]* ?
ii) Timing of assessment/s with reference to start of period of CAT, which = time 0.
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iv) Was the same assessment tool used in CAT & control and/or before & after? If no, was the risk of bias high or low?
v) Was the assessment tool validated? Complete validation = 2+ validation exercises on a specific outcome; partial validation = 1 exercise, or validation on assessment tool overall.
vi) Was assessment independent and double blind of whether outcome was in CAT/control group, or before/after? If no or unstated, was the risk of bias high or low with reference to: Was the study objective apparent to participants?, if S/A; & Were there clear assessment criteria?, if E/A.
vii) Loss to follow-up as % of original number of participants, including losses to follow-up in CAT and control groups where applicable.
viii) Was the statistical analysis generally appropriate? Specific consideration of a) power calculation b) whether CI or p values stated c) whether correct statistical tests used.
ix) Were other sources of bias excluded? In particular was the possibility of the following taken into account of a) background trend especially where time >6m b) learning effect.

Study (Year)	i What	ii Timing	iii Tools used	iv Same	v Validation	vi Ind & Blind	vii F/up	viii Stats	ix Other bias
Hicks (1994)	BEHAVIOUR (WG) Reading behaviour [RB] & frequency of review of current practice prompted by articles read [PR]. *Change.*	Immed-iately before, and 2m after start of CAT.	S/A Part of self-completed questionnaire. Five point ordinal scale used (1=infrequent or low influence) to assess frequency of reading articles as a routine activity and the influence these articles had in reviewing aspects of clinical practice.	Same tool used b-a.	None stated for questionnaire.	No. Without a control group participants would realise that CAT was "new", and using a S/A outcome would be free to provide the answer post-CAT which they felt was socially acceptable.	RB 2/19 (11%) PR 9/19 (47%)	No power calculat-ion. No CI. P values used. One-tailed tests used.	Yes. Background trend unlikely over 2 months. Impact of learning effect on self-perceived reading behaviour, practice review and critical appraisal skills also unlikely.
	SKILLS (WG) Critical appraisal: perception of own skill. *Change.*		S/A Part of self-completed questionnaire. Five point ordinal scale used (1=low confidence) assessing confidence in evaluating articles.				Skills 6/19 (32%)		
	SKILLS (WG) Critical appraisal: of test article. *Change.*	Immed-iately before and after CAT.	E/A Single article rated using VAS on 8 critical appraisal criteria. Change in rating and concordance with gold standard response.	Same article and tool used b-a.	Gold standard response derived from Independent appraisal by 2 experienced researchers. Inter-rater reliability assessed and found to be high. VAS scores for each expert averaged to give gold standard response for each criterion.	No. Assessors of gold standard unlikely to be influenced by participants' CA results – stated to be independent. Quantified nature of their decision suggests that assessment of concordance could be achieved in a relatively bias free manner, even though attempt to blind not mentioned.	0/19 (0%)	No power calculat-Ion. No CI. P values used. One-tailed tests used.	No. Background trend not relevant over 1d. Learning effect through repeated use of same article/tool to assess skills (and to illustrate teaching points in CAT workshop) could account for some of change in outcome observed. No parallel control group to assess the magnitude of this in this study.

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Study (Year)	**i What**	**ii Timing**	**iii Tools used**	**iv Same tool**	**v Validation**	**vi Ind & Blind**	**Vii F/up**	**viii Stats**	**ix Other bias**
Hillson (1992)	SKILLS (WG) Critical appraisal: of test article. *Change.*	Immed-iately before and at the end of each of the five 2m clinical rotations during which CAT was delivered .	E/A Two articles rated by responses to 15 questions eg "The study appears likely to be biased", using five point Likert scales. Concordance with gold standard response.	Different articles used b-a; order in which received allocated randomly. Potential for bias limited by random allocation and the standardised way in which exercises were developed.	Gold standard response on 15 quality criteria derived from independent appraisal by the 2 course faculty members. Differences resolved by consensus, and gold standard response derived from this.	No. No explicit mention that marking was done in an independent &/or blind manner. Quantified nature of participant and gold standard response reduces potential for bias in assessment of concordance.	6/29 (21%)	No power calcul-ation. No CI. P values used. Approp-riate statist-ical tests used.	Yes. Background trend unlikely over 2 months. Use of different article b-a provides some protection from any influence of a learning effect.
	SKILLS (WG) Critical appraisal: perception of own skill. *Change.*		S/A Self-completed questionnaire. Five point Likert scale (1= not competent) used to assess confidence in 7 specific aspects of journal reading skill.	Same tool used b-a.	None stated for this measure.	No. Without a control group participants would realise that CAT was "new", and using a S/A outcome would be free to provide the answer post-CAT which they felt was socially acceptable.			Yes. Background trend unlikely over 2 months. Impact of learning effect on self-perceived critical appraisal skills also unlikely.

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v) Was the assessment tool validated? Complete validation = 2+ validation exercises on a specific outcome; partial validation = 1 exercise, or validation on assessment tool overall.
vi) Was assessment independent and double blind of whether outcome was in CAT/control group, or before/after? If no or unstated, was the risk of bias high or low with reference to: Was the study objective apparent to participants?, if S/A; & Were there clear assessment criteria?, if E/A.
vii) Loss to follow-up as % of original number of participants, including losses to follow-up in CAT and control groups where applicable.
viii) Was the statistical analysis generally appropriate? Specific consideration of a) power calculation b) whether CI or p values stated c) whether correct statistical tests used.
ix) Were other sources of bias excluded? In particular was the possibility of the following taken into account of a) background trend especially where time >6m b) learning effect.

Study (Year)	**i What**	**ii Timing**	**iii Tools used**	**iv Same tool**	**v Validation**	**vi Ind & Blind**	**vii F/up**	**viii Stats**	**ix Other bias**
Ibbotson (1997)	KNOWLEDGE (WG) Understanding of key terms used in systematic reviews: perception of own knowledge (crude score). *Change.*	2w before and immed-iately after CAT.	S/A As for Burls (1997). Only crude scores for "test" & "control" questions used. No attempt to calculate an adjusted overall impact score.	Same tool used b-a.	As for Burls (1997)	No. Without a control group participants would realise that CAT was "new", and using a S/A outcome would be free to provide the answer post-CAT which they felt was socially acceptable. The crude score makes no adjustment for this.	For attend-ances 29/ 115 (25%) For individ-uals 32/ 76 (42%)	No power calculation. p values used. No Cis. Appro-priate statistical tests used.	Yes. Background trend highly unlikely over time period of outcome assessment. Data on intra-observer variation from Burls (1997) also provides reassurance that learning effect from doing this questionnaire twice is likely to be negligible.

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vii) Loss to follow-up as % of original number of participants, including losses to follow-up in CAT and control groups where applicable.
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Study (Year)	**i What**	**ii Timing**	**iii Tools used**	**iv Same tool**	**v Validation**	**vi Ind & Blind**	**vii F/up**	**viii Stats**	**ix Other bias**
Kitchens (1989) (Phase I)	KNOWLEDGE (BG) Clinical epidemiology principles: T/F & MCQ test. *End.*	21w after start of Phase I CAT or control (4w after final session)	E/A Score in 18 T/F & 4 MCQ questions.	Same tool in CAT and control. No b-a change employed.	None stated.	Not stated. No mention of independent or blind assessment. Potential for bias reduced by having clearly defined correct/incorrect answers.	4/83 (5%) CAT 3/51 Con 1/32	No power calculation. No CI. P values used. Appropriate statistical tests used.	Yes. Use of parallel control group accounts for these. NB Size of learning effect is actually quantified in this study. NNB Use of b-a changes for CAT and control groups in Ph II allows conclusions to be drawn about CAT Ph II intervention, even though control had previously been exposed to the CAT Ph I intervention.
Kitchens (1989) (Phase II)	KNOWLEDGE (BG) Clinical epidemiology principles: T/F & MCQ test. *Change.*	12w after start of Phase II CAT or control (4w after final session)	E/A Before test as for Kitchens (1989) (Ph I). After test same format - 16 questions unchanged.	Same tools in CAT and control. B-a tests differed in respect of 6/22 questions.			13/83 (16%) CAT 3/32 Con 10/51		

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Study (Year)	**i What**	**ii Timing**	**iii Tools used**	**iv Same**	**v Validation**	**vi Ind & Blind**	**vii F/up**	**viii Stats**	**ix Other bias**
Landry (1994)	BEHAVIOUR (BG) Use of medical literature in patient write-ups. *Change.*	1w before and 5w after first CAT sem-inar.	E/A Assessment of number of references used, type of literature referenced, whether reference was directly cited in the body of the write-up (or just listed at end) & whether commented on study quality.	Same tools/ questions used in CAT & control and b-a.	BEHAVIOUR None stated for this outcome. KNOWLEDGE Developed by study authors and tested on experienced faculty members Some questions taken from test used by Riegelman (1986). ATTITUDES None stated for this element of study.	BEHAVIOUR Yes. Assessors not those who delivered seminar. Assessor blind to whether write-up from CAT or control or whether before or after. Students unaware that write-up would be used as outcome. KNOWLEDGE No. No mention of independent or blind assessment. Potential for bias reduced by probably having clearly defined correct/incorrect answers for most questions. ATTITUDES Not stated. Even with a control group participants may still realise, unless specifically blinded, that CAT was "new". If using a S/A outcome they would be free to provide the answer post-CAT which they felt was socially acceptable. The effect might be differential in CAT & control groups, particularly where the latter was perceived as normal teaching.	0/146 (0%) CAT 0/65 Con 0/81	Power calculation for change in knowledge. No CI. P values used. Deficiencies in statistical tests used-pairing of measures not accounted for for categorical outcomes. No tests comparing differences between groups.	Yes. Use of parallel control group accounts for these.
	KNOWLEDGE (BG) Basic research design: T/F test. *Change.*	6w before and 5w after first CAT sem-inar.	E/A 10 item test. Minimal detail on format – some T/F. Mainly on study design and basic statistics. Element of critical appraisal skills with questions referring to short summaries and skeletons of published articles.						
	ATTITUDES (BG) Value of research: agreement with statem'ts. *Change.*		S/A Self-completed questionnaire. Agreement (Y/N) with four statements eg "Medical literature is critical to patient care".						

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Study (Year)	**i What**	**ii Timing**	**iii Tools used**	**iv Same**	**v Validation**	**vi Ind & Blind**	**vii F/up**	**viii Stats**	**ix O'r bias**
Linzer (1988)	BEHAVIOUR (BG) Reading behaviour. *Change.*	Immed-iately before CAT prog-ramme and on ave-rage 9.5m after its start.	S/A Part of self-completed questionnaire Articles read per month, no of journal subscriptions and proportion of articles read completely vs "skimmed".	Same quest-ionnaire used in CAT & control and b-a, bar some add-itional quest-ions on change in reading habits after inter-vention.	BEHAVIOUR None stated for this component of questionnaire. SKILLS – TEST ARTICLE Gold standard critique for test article derived by consensus using Delphi method among faculty members and scoring system devised from this. Intra and inter-observer variability of "graders" assessed – 0.8 & 1.4 marks. SKILLS – SELF-ASSESSED None stated for this component of questionnaire. KNOWLEDGE Questions carefully selected from an established question bank. Designed so that perfect score would theoretically allow 81% of medical literature to be understood. ALL The whole assessment instrument was validated for content by a panel of experts who modified content using the Delphi method to gain final consensus. Whole assessment tool pre-tested and shown to discriminate different levels of methodological expertise.	BEHAVIOUR No. Potential for bias reduced by participants not being informed that CAT was the new educat-ional format under investigation. SKILLS – TEST ARTICLE Yes. Graders appear to be indep-endent of those delivering CAT. Graders blind to whether critique from CAT or control or whether before or after. Participants not informed that CAT was the new educational format under investigation. SKILLS – SELF-ASSESSED No. Potential for bias reduced by participants not being informed that CAT was the new educat-ional format under investigation. KNOWLEDGE No. No mention of independent blind assessment of test question answers. Potential for bias reduced by almost certainly having clearly defined correct/incorrect answers for questions.	3/44 (7%) CAT 0/22 Con 3/22	Power calcul-ation for change in know-ledge. No CI. P values used. Approp-riate statist-ical tests used, except for within group change s (not used in review).	Yes. Use of parallel control group accounts for these.
	SKILLS (BG) Critical appraisal: test article. *Change.*		E/A Score (max 18) in critique of a test article. Scoring against pre-set criteria.						
	SKILLS (BG) Critical appraisal: perception of own skill. *Change.*		S/A Part of self-completed questionnaire. Exact format of the questions not stated.						
	KNOWLEDGE (BG) Epidemiology and biostatstics: test questions. *Change.*		E/A Part of self-completed questionnaire. Score in 15 test questions, exact format not stated.						

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Study (Year)	**i What**	**ii Timing**	**iii Tools used**	**iv Same tool**	**v Validation**	**vi Ind & Blind**	**vii F/up**	**viii Stats**	**ix Other bias**
Radack (1986)	SKILLS (BG) Critical appraisal: exercise on diagnosis. *Change.*	Immed-iately before and at the end of each of the three 2m clinical rotations during which CAT or control were offered.	E/A Score in written test based on a case scenario with relevant text from a published article. No detail on scoring system, other than that a pre-set level of b-a change was decided on to distinguish significant from insignificant improvement.	Same test used in CAT & control and b-a.	None stated.	Not stated. Without reassurance that assessors were blind to allocation &/or b-a status, or that well defined criteria were used to mark the exercises, possibility of bias could be high.	13/34 (38%) CAT 9/22 Con 4/12	No power calculation. Complete absence of any statistical testing.	Yes. Use of parallel control group accounts for these.

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Reigelman (1986)	BEHAVIOUR (BG) Reading behaviour. *End.*	2.7 to 3.7 years after start of CAT or control. Dependent on when in Y4 test took place.	S/A Part of self-completed questionnaire with four parts. Subscribed or read regularly any medical research journal.	Same tool in CAT and control. No b-a change employed.	None stated.	Not stated. With a non-parallel control group participants would realise that CAT was "new", and using a S/A outcome would be free to provide the answer post-CAT which they felt was socially acceptable. Potential for bias would be off-set somewhat by the distance of outcome assessment from period of CAT.	123/ 296 (42%) CAT 59/ 150 Con 64/ 146	No power calculation. No CI. P values used. Appear to be errors in application of statistical tests- reported test values cannot be regenerated from data provided.	No. Y4 "Class of 85" (CAT) compared to Y4 "Class of 81". Background trend over 4 years highly plausible for all outcomes. CAT group did questionnaire 3 times; control did it once. Thus for KNOWLEDGE with only 4 questions differential learning effect is highly likely.
	SKILLS (BG) Critical appraisal: perception of own skill. *End.*		S/A Part of self-completed questionnaire with four parts. Six point scale used (1= very competent; 6= not very competent) for evaluation of study design, assignment of patients to study & control groups, evaluating outcomes of studies, methods of interpreting results, and methods of extrapolating to individuals not included in the study.						
	KNOWLEDGE (BG) Study design and statistics: T/F questions. *End.*		E/A Part of self-completed questionnaire with four parts. Correct responses to 4 T/F questions, full text of which given in paper.			Not stated. Potential for bias reduced by having clearly defined correct/incorrect answers for questions.			

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Seelig (1991)	BEHAVIOUR (WG) Reading behav-iour. *Change.*	Precise timing of before assess-ment not stated. After assess-ment 4m post start of CAT.	S/A Part of self-completed questionnaire. No of hours reading per week.	Same quest-ion used b-a.	None stated	No. Without a control group participants would realise that CAT was "new", and using a S/A outcome would be free to provide the answer post-CAT which they felt was socially acceptable.	Not stated	No power calcul-ation. No CI. P values used. Appro-priate statistical tests used.	Yes. Background trend unlikely over 4 months. Impact of learning effect on self-perceived reading behaviour also unlikely.
	SKILLS (WG) Critical appraisal: perception of own skill. *Change.*		S/A Part of s-completed questionnaire. 6-point Likert scale (1= not at all, 6= very able) used to assess ability to critically assess research articles and medical journals in general.						
	KNOWLEDGE (WG) Basic principles of critical appr-aisal: test quest-ions. *Change.*		E/A Part of self-completed questionnaire. % correct answers. No detail on number of questions or format.			No. Potential for bias reduced by probably having clearly defined correct/incorrect answers for questions, although lack of detail on questions is a concern.			No. Background trend unlikely over 4m. Learning effect is possible and not accounted for in absence of a parallel control group.
	ATTITUDES (WG) Importance and purpose of reading journal articles: degree of agreement with statements. *Change.*		S/A Part of self-completed question-naire. Six point Likert scale (1= not at all important, 6= very important) used to assess degree of agreement with value of five alternative sources and five most important reasons for reading journals.			No. Without a control group participants would realise that CAT was "new", and using a S/A outcome would be free to provide the answer post-CAT which they felt was socially acceptable.			Yes. Background trend unlikely over 4 months. Impact of learning effect on self-perceived attitudes also unlikely.

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Seelig (1993)	BEHAVIOUR (WG) Reading behaviour. *Change.*	Precise timing of before assess-ment not stated. After assess-ment 4m post start of CAT.	S/A As part of self-completed quest-ionnaire. No of hours reading per week.	Same question used b-a.	None stated. Quest-ion-naire used prev-iously in Seelig (1991).	No. Seelig 1993 has a control group, even though not used in this out-come. Even with a control group participants may still realise, unless specifically blinded, that CAT was "new". If using a S/A outcome they would be free to provide the answer post-CAT they felt was socially acceptable. The effect might be differential in CAT & control groups, particularly where the latter was perceived as normal teaching.	Not stat-ed	No power calcul-ation. No CI. P values used. Approp -riate statistic al tests used.	Yes. Background trend un-likely over 4 m. Impact of learning effect on self-perceiv-ed reading behaviour and critical appraisal skills also unlikely.
	SKILLS (WG) Critical appraisal: perception of own skill. *Change.*		S/A As part of self-completed quest-ionnaire. Stated to be same as Seelig (1991), but some ambig-uity. Suggestion that only a single post-intervention measure of "change in literature reading abilities" was ascertained. If so study's results for this outcome would be ineligible for this review.	Unclear if tool was administ-ered b-a.					
	KNOWLEDGE (BG) Basic principles of critical appraisal: test questions. *Change.*		E/A Stated to be same measure as used in Seelig (1991). % correct answers. No detail on number of questions or format.	Same tool in CAT & con-trol and b-a, but some ambiguity		Not stated. Potential for bias reduced by probably having clearly defined correct/incorrect answers. Lack of detail on questions is a concern.			Yes. Use of par-allel control accounts for these.
	ATTITUDES (WG) Importance and purpose of reading articles: degree of agreement with statements. *Change.*		S/A Part of self-completed questionnaire. Stated to be same measure as Seelig (1991), but some ambiguity in text.	Same tool used b-a.		As for BEHAVIOUR & SKILLS.			As for BEHAV-IOUR & SKILLS.

Cells outlined in bold indicate major threats to validity. Shaded cells indicate data items on which there was ambiguity or uncertainty about the extent of any threat to validity.
HEADING NOTES: i) What was assessed? Were changes over study period assessed *[Change]* or were states at end of study compared *[End]* ?
ii) Timing of assessment/s with reference to start of period of CAT, which = time 0.
iii) Further details of assessment tools used. Were they primarily dependent on assessment by the participant themselves (S/A), or by the investigator or 3rd party (E/A)?
iv) Was the same assessment tool used in CAT & control and/or before & after? If no, was the risk of bias high or low?
v) Was the assessment tool validated? Complete validation = 2+ validation exercises on a specific outcome; partial validation = 1 exercise, or validation on assessment tool overall.
vi) Was assessment independent and double blind of whether outcome was in CAT/control group, or before/after? If no or unstated, was the risk of bias high or low with reference to: Was the study objective apparent to participants?, if S/A; & Were there clear assessment criteria?, if E/A.
vii) Loss to follow-up as % of original number of participants, including losses to follow-up in CAT and control groups where applicable.
viii) Was the statistical analysis generally appropriate? Specific consideration of a) power calculation b) whether CI or p values stated c) whether correct statistical tests used.
ix) Were other sources of bias excluded? In particular was the possibility of the following taken into account of a) background trend especially where time >6m b) learning effect.

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Archived ARIF Request

Immunoreactive Trypsin Screening (IRT)
Cystic Fibrosis

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the evidence base of a proposal to introduce regionwide neonate screening for cystic fibrosis using immunoreactive trypsin?

ARIF was asked to examine the evidence-base of a document submitted to support this proposal.

Reviews Identified

- Farrell PM, Mischler EH, The cystic fibrosis neonatal screening study group. Newborn screening for cystic fibrosis. Advances in Pediatrics 1995;39:35-70

Trials Identified

Trial as reported in text of review above. (Wisconsin study, 1985)

- Chatfield S et al. Neonatal screening for cystic fibrosis in Wales and the West Midlands: clinical assessment after five years of screening. Archives of Diseases of Childhood 1991;66:29-33
- Dankert-Roelse SE, te Meerman GJ. Long term prognosis of patients with cystic fibrosis in relation to early detection by neonatal screening and treatment in a cystic fibrosis centre. Thorax 1995;50:712-71

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Comments

The review identified is not systematic, but does provide useful background on the issue of screening for cystic fibrosis.

Considering the primary research, particularly those studies listed above, we identified sufficient conflict and uncertainty about the effects of IRT screening for cystic fibrosis, to suggest that a formal systematic review was required to gauge the true effects/effectiveness. Interpretation of the study by Dankert-Roelse, which claims to demonstrate improved survival, was particularly problematic as bias in the analysis could have contributed significantly to the observed result.

ARIF identified two groups who were undertaking relevant systematic reviews as part of the National

HTA Programme. The most directly relevant review is being undertaken by Prof H Cuckle, with an estimated completion date of 30/6/97.

This is an area prone to need for regular updating as new information is continually becoming available.

Request Carried Out: June 1996

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Archived ARIF Request

Day Hospitals
Mental Illness
Psychiatric Disorders

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence on the effectiveness/cost effectiveness of day hospitals in the treatment of people with mental illness in comparison with other NHS or social services models of provision?

Reviews Identified

- Marshall M, Crowther R, Almaraz-Serrano A, Creed F, Sledge W, Kluiter H, Roberts C, Hill E, Wiersma D. Day hospital versus admission for acute psychiatric disorders. The Cochrane Database of Systematic Reviews: Reviews 2003, Issue 1. Art No: CD004026. DOI: 10.1002/14651858.CD004026
- Marshall M, Crowther R, Almaraz-Serrano AM, Tyrer P. Day hospital versus out-patient care for psychiatric disorders. The Cochrane Database of Systematic Reviews: Reviews 2001, Issue 2. Art No: CD003240. DOI: 10.1002/14651858.CD003240

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Comments

Marshall et al (2003) assess the effectiveness of day hospitals in comparison with inpatient admission for patients suffering from an acute episode of psychiatric illness. A formal appraisal of the paper indicates the review was clearly focused, well-executed and contained a cogent statement of method sufficient to permit its replication. Marshall et al (2003) make the following conclusions:

- At least 20% of patients currently admitted to inpatient care could realistically be treated in acute day hospitals
- Day hospitals afford the possibility of substantial cost savings as day hospital care is cheaper than inpatient care
- Cost reductions could be achieved without increasing the burden on carers as there is no difference in carer burden between the day hospital and inpatient groups
- Day hospital patients experience a greater sense of satisfaction with treatment
- Patients may benefit from a more rapid improvement in their mental state
- Overall day hospital care does not reduce readmission rates or lead to improvements in social

functioning (however the studies included have limited statistical power and report wide 95% confidence intervals which include the possibility of both clinical benefits and harms

Marshall et al (2001) assess the effectiveness of day hospitals for patients suffering mainly from the more chronic forms of psychiatric illness in comparison with outpatient care. A formal appraisal of the paper indicates the review was also clearly focused and conducted in a thorough, explicit manner. However the rationale for this review is difficult to understand. Essentially it encompasses three specific populations each with its own specific intervention and might easily have formed the basis for three separate systematic reviews. The following comparisons with outpatient care are assessed:

- Day treatment programmes for patients with non-psychotic disorders
- Day care centres for patients with severe long term disorders
- Transitional day hospital care for patients discharged from acute psychiatric wards

The authors conclude that overall there is insufficient evidence to determine whether any of the three types of day hospital care are better than outpatient care. The authors state that as more community orientated forms of care have now largely superseded day care centres it is doubtful that further research is needed in this area. However the review highlights the need for more rigorous research into the effectiveness of day treatment programmes and transitional day hospitals.

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Day Hospitals
Elderly Patients

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence on the effectiveness/cost effectiveness of day hospitals in the treatment of the elderly in comparison with other NHS or social services models of provision?

Reviews Identified

- Forster A, Young J, Langhorne P for the Day Hospital Group. Medical day hospital care for the elderly versus alternative forms of care. The Cochrane Database of Systematic Reviews 1999, Issue 3. Art No: CD001730. DOI: 10.1002/14651858.CD001730

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Comments

A formal appraisal of the paper indicates the review was clearly focused, well executed and contained a cogent statement of method sufficient to permit its replication. However whilst the results of the review seem to represent the best available evidence at the time of its completion the studies included relate mainly to the 1980's and 90's and an assessment of their relevance to present service provision should take this into account. Furthermore as the included studies have limited statistical power and report wide confidence intervals one cannot rule out a clinical benefit/disbenefit.

The review focuses on medical day hospital care for the elderly (defined as an outpatient facility where older patients attend for a day or near full day and receive multidisciplinary rehabilitation in a health care setting). Medical day hospital care is compared with (i) comprehensive elderly care (access to a range of inpatient and outpatient geriatric medical services), (ii) domiciliary care, and (iii) no comprehensive care.

Forster et al (1999) make the following conclusions:

- Patients attending day hospitals display more favourable outcomes in comparison with those receiving no comprehensive elderly care
- Day hospitals have a generally similar impact on patient outcomes as other forms of care such as inpatient, outpatient and domiciliary services
- Day hospital attendance may have a favourable impact on the need for long-term institutional care in

comparison with other forms of care

- A trend towards the reduced use of hospital beds is evidenced amongst the day hospital attendees in comparison with those utilizing other services/no service
- Day hospitals appear to be more expensive than other forms of comprehensive elderly care however more stringent costing analyses are required to assess the extent to which these higher costs may be offset by reduced demands on hospital and institutional care resource

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Archived ARIF Request

D-Dimer Test
Pulmonary Embolism (PE)
Deep Venous Thrombosis (DVT)

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The Problem Submitted for ARIF to Advise Upon:

In the diagnosis of DVT and PE, what is the effectiveness and cost effectiveness of undertaking serum D-Dimer tests and, based on the result, progressing to ultrasound or V/Q scan for the final diagnosis?

Reviews Identified

- Becker DM, Philbrick JT, Bachuber TL et al. D Dimer testing and acute venous thromboembolism. Archives of Internal Medicine 1996;156:939-946
- Kearon C, Julian JA, Newman TE et al. Noninvasive diagnosis of deep vein thrombosis. McMaster Diagnostic Imaging Practice Guidelines Initiative. Annals of Internal Medicine 1998;128 (8):663-677
- Kraaijenhagen RA, Lensing AW, Lijmer JG et al. Diagnosis strategies for the management of patients with clinically suspected deep vein thrombosis. Current Opinion in Pulmonary Medicine 1997; 3 (4): 268-274

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Comments

Three relevant systematic reviews were identified. All are fairly good systematic reviews, but the validity of their results is limited by the poor methodological quality of the primary studies. Becker et al compares the performance of the D-Dimer test with other tests in the diagnosis of PE and DVT. The other two reviews evaluate different diagnostic strategies for the diagnosis of DVT.

The results of the Becker review are extremely heterogenous, due in part to the study quality, but also to the considerable variation between the study characteristics, in terms of the test itself, the reference test, and the study populations. The D-Dimer results appear favourable but the authors stress the need for further research evaluating the outcomes of clinical decisions based on the test, and/or strategies which include the test, relative to other tests and strategies.

Taken together, the other two reviews suggest that strategies incorporating the D-Dimer test may fare better than those that do not. However, there are questions around the validity of some of the summary analyses, such as the use of indirect comparisons.

In summary the D-Dimer test appears to have promise but many unanswered questions remain and further research is required.

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Archived ARIF Request

Deep Brain Stimulation
Pallidotomy
Parkinson's Disease

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The Problem Submitted for ARIF to Advise Upon:

What are the effects of:

- thermocoagulation (pallidotomy)
- deep brain stimulation

in the treatment of movement disorders, especially Parkinson's Disease?

Reviews Identified

There is a wealth of evidence which can be considered in addressing the question posed. The following three citations represent a starting point only.

- Robert G. Pallidotomy for Parkinson's disease. Winchester: Wessex Institute of Public Health, 1996. (DEC Report No 51). pp7
- Siegfried J. Therapeutic Sterotactic Procedures on the Thalamus for Motor Movement Disorders. Acta Neurochirurgica (Wien) 1993; 124: 14-18
- McLellan DL. Implants for tremor. Ballieres Clinical Neurology 1995; 4(1): 115-129

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Comments

Although none of the reviews are completely systematic, the three reviews quoted provide excellent starting points to consider the research information available on these two neurosurgical approaches to extremely serious and debilitating conditions resistant to other forms of therapy, particularly drugs.

The conclusion of the Development & Evaluation Committee on pallidotomy on the basis of the report by the Wessex Institute of Public Health, "Not proven. But the treatment held potential and randomised controlled trials should be undertaken to evaluate the technique." seems well founded and on the basis of the information provided in the second and third reviews a similar conclusion, particularly in respect of the need for further rigorous evaluation, also holds for deep brain stimulation.

(Further detailed advice on the topic may be available from the Authority who made this request. Contact should, however, be with ARIF in the first instance.)

Request Carried Out: February 1996

Update: March 2000

This request was updated in the context of a subsequent request on Deep Brain Stimulation (DBS). The 1996 DEC report has now been superseded by a subsequent report published in 1999:

- Nicholson T, Milne R.
  Pallidotomy, thalamotomy and deep brain stimulation for severe Parkinson's disease.
  Southampton: Wessex Institute for Health Research and Development, 1999.
  (DEC Report No. 105)

This new review covers pallidotomy, thalamotomy and DBS in severe Parkinson's disease that has not responded to medical treatment. As well as being up-to-date, this is a well reported review. It was clearly well conducted and its results are almost certainly reliable. However, as far as DBS is concerned, its findings do not alter our conclusions at the time of the original request. There was insufficient evidence to enable the committee to make a judgment on the overall effectiveness of DBS given that the evidence on its efficacy is weak, and it is an expensive treatment the benefits of which may be offset by potentially serious adverse effects.

Additional information relevant to this request is available in the requests entitled Spinal Cord Stimulation/Chronic Pain, Intraspinal Drug Delivery/Chronic Pain.

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Archived ARIF Request

Deep Brain Stimulation Dystonia

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of deep brain stimulation for dystonia?

Dystonia is a movement disorder characterised by sustained muscle contractions which cause twisting and repetitive movements and/or abnormal postures over which a person has no control.

Deep brain stimulation is a neurosurgical procedure in which electrodes are implanted into the brain. The electrodes can be on one side (unilateral) or both sides (bilateral) and they can be removed. They are connected to a neurostimulator (electric impulse generator) which is inserted near the collar-bone or the abdomen.

Reviews Identified

- Medical Advisory Secretariat Ontario Ministry of Health and Long-Term Care. Deep Brain Stimulation for Parkinson's Disease and Other Movement Disorders: Health Technology Literature Review. Ontario Health Technology Advisory Committee, Toronto. 2005

Controlled Trials

- Vidailet M, Vercueil l, Houeto J-L, Krystowiak P, Benabid A-L, Cornu P, Lagrange C, Tezenas du Montcel S, Dormont D, Grand S, Blond S, Detante O, Pillon B, Ardouin C, Agid Y, Destee A, Pollak P, for the French Stimulation du Pallidum Interne dans la Dystonie (SPIDY) Study Group. Billateral Deep-Brain Stimulation of the Globus Pallidus in Primary Generalized Dystonia. New England Journal of Medicine. 2005; 352:459-67

Uncontrolled Trials

- Coubes P, Cif L, El Fertit H, Hemm S, Vayssiere N, Serrat S, Picot MC, Tuffery S, Claustres M, Echenne B, Frerebeau P. Electrical stimulation of the globus pallidus internus in patients with primary generalized dystonia: long-term results. J Neurosurg. 2004; 189-94
- Krause M, Fogel W, Kloss M, Rasche D, Volkmann J, Tronnier V. Pallidal stimulation for dystonia. Neurosurgery. 2004; 55(6): 1361-8
- Bittar R, Yianni J, Wang S, Liu X, Nandi D, Joint C, Scott R, Bain P, Gregory R, Stein J, Aziz T. Deep brain stimulation for generalised dystonia and spasmodic torticollis. J of Clinical Neuroscience.

2005; 12(1): 12-16

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Comments

The review by the Medical Advisory Secretariat of the Ontario Ministry of Health and Long-Term Care assessed the effectiveness of bilateral deep brain stimulation of the globus pallidus internus in patients with primary generalised dystonia (PGD). This reasonably-well conducted review excluded uncontrolled trials and hence only identified one controlled trial (Vidailet M. et al). In addition, we identified three uncontrolled trials addressing the same question.

Generally, the studies indicate a significant improvement in the disability and movement scores of patients with PGD following surgery. This improvement appears to be sustained over a 2-year period however, longer-term effectiveness is not clear. Adverse events were observed (particularly infections) but they generally resolved and seemed to be outweighed by the effects on movement.

These results need to be interpreted with some caution as they originate from non-randomised, mainly uncontrolled trials which are susceptible to selection and assessment bias. Furthermore, they are of small sample size which may make the results more susceptible to chance.

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Archived ARIF Request

Deep Vein Thrombosis
Low Molecular Weight Heparin

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The Problem Submitted for ARIF to Advise Upon:

What evidence is there that low molecular weight heparin for the treatment of deep vein thrombosis/ venous thrombo embolism can safely and successfully be used in a community setting?

Reviews Identified

- Lensing AWA et al. Treatment of deep vein thrombosis with low molecular weight heparins. A meta-analysis. Archives of Internal Medicine 1995;155:601-07
- Leizorovicz A et al. Comparison of efficacy and safety of low molecular weight heparins and unfractioned heparin in initial treatment of deep vein thrombosis: A meta-analysis. British Medical Journal 1994;309:299-304

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Comments

Both the above are systematic reviews.

They reach different conclusions about the whether the efficacy of low molecular weight heparin has actually been demonstrated in secondary care. As the data presented in each do not differ substantially, the difference is accounted for by differing judgements made on the meaning of the research identified. The second reference presents the research evidence in a way which is much more open to external inspection and is suggested as the reference which best allows a reader to make their own judgement. ARIF's view is that the available evidence presented in these reviews upholds the suggestion that significant doubt does remain about the efficacy of low molecular weight heparin in secondary care, particularly the magnitude of any effect.

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Archived ARIF Request

Low Molecular Weight Heparin (LMWH) Deep Venous Thrombosis (DVT)

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The Problem Submitted for ARIF to Advise Upon:

How effective and cost-effective is LMWH relative to other treatments, particularly unfractionated heparin, in the prevention of deep venous thrombosis (DVT)?

Reviews Identified

- Howard AW, Aaron SD. Low molecular weight heparin decreases proximal and distil deep venous thrombosis following knee arthroplasty. A meta-analysis of randomised trials. Thrombosis and Haemostasis 1998;79(5):902-906
- Nurmohamed MT, Rosendaal FR, Buller HR et al. Low molecular weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis. Lancet 1992;340(8812):152-156
- Leizorovicz A, Haugh MC, Chapuis FR et al. Low molecular weight heparin in the prevention of peri-operative thrombosis. British Medical Journal 1992;305(6859):913-920

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Comments

There are a large number of good systematic reviews, of equivalent quality, available on this subject. On this occasion, those that are recommended represent a selection of these and their results are not necessarily more reliable than those not cited. There is a considerable degree of ambiguity between the results and conclusions of the different reviews, that may be due to differences in the characteristics and quality of the primary studies, as well as some methodological problems pertaining to the topic as a whole.

Our overall impression is that, relative to other forms of prophylaxis, LMWH may decrease the occurrence of DVT and these reductions may be greatest in orthopaedic patients. However, this impression is not overwhelming and, when some of the methodological limitations of the evidence are taken into account, it is difficult to reach an overall judgment on whether these benefits are sufficient to outweigh the risks and costs of treatment. In addition, the superiority of LMWH over unfractionated heparin and other forms of chemical prophylaxis is not as firmly established as is commonly supposed.

This is an area prone to need for regular updating as new information is continually becoming available. The topic is one of several currently being reviewed by the West Midlands DEC Programme.

Additional information relevant to this request is available in the requests entitled: LMWH/Unstable Angina; LMWH/Treatment of Thromboembolic Disease; LMWH/Prevention and Treatment of Thromboembolic Disease and Management of Unstable Angina; Physical Prophylaxis/Deep Venous Thrombosis

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Physical Prophylaxis Deep Vein Thrombosis

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The Problem Submitted for ARIF to Advise Upon:

How effective are foot pumps and other physical devices for preventing thromboembolism following elective hip and knee surgery?

Question Reformulated

Our interpretation of the question was that it largely concerns the relative risks and benefits of physical and chemical methods of prophylaxis in orthopaedics, with a particular focus on intermittent pneumatic compression (IPC) devices relative to LMWH. We therefore searched for reviews which compared physical devices with other methods of DVT prophylaxis.

Reviews Identified

- Handoll HHG, Farrar MJ, McBirnie J et al. Heparin, low molecular weight heparin and physical methods for preventing deep vein thrombosis and pulmonary embolism following surgery for hip fractures (Cochrane Review). In: The Cochrane Library, Issue 1, 2000. Oxford: Update Software.
- Vanek VW. Meta-analysis of effectiveness of intermittent pneumatic compression devices with a comparison of thigh-high to knee-high sleeves. American Surgeon 1998; 64(11): 1050-1058.

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Comments

The Cochrane review is a broad but well-conducted review, the results of which can almost certainly be trusted. It concludes that, compared with no prophylaxis, mechanical pumping devices may reduce the incidence of DVT but that the results of their meta-analysis should be viewed with caution due to the methodological limitations of the included studies. No comparisons with chemical prophylaxis were included and there was insufficient data to draw robust conclusions for other outcomes and major adverse effects.

The review by Vanek is a reasonably good systematic overview of the relative effectiveness of different IPC devices. However, the review may be susceptible to a significant degree of publication bias and has a number of methodological limitations. For example, it fails to clearly state the inclusion and exclusion criteria and to provide sufficient information on the characteristics of the included studies to allow an assessment of the validity of the meta-analysis.

The evidence on DVT prophylaxis is notoriously difficult to interpret. With this in mind, alongside the fact that a robust evidence comparing physical devices with chemical prophylaxis does not exist, it is difficult to make an overall judgment at this stage.

Additional information relevant to this request is available in the requests entitled: LMWH/Unstable Angina; LMWH/Deep Venous Thrombosis (DVT); LMWH/Treatment of Thromboembolic Disease; LMWH/Prevention and Treatment of Thromboembolic Disease and Management of Unstable Angina

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Identification of Mild Cognitive Impairment in patients presenting with Subjective Cognitive Impairment.

Synopsis

Question:	Is there evidence indicating the best diagnostic tool for identifying mild cognitive impairment in patients presenting with subjective cognitive impairment?
Evidence Identified:	This report is based on evidence from four reviews. Holsinger T, Deveau J, Boustani M, Williams JW, Jr. Does this patient have dementia? JAMA 2007; 297(21):2391-2404. Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA. A review of screening tests for cognitive impairment. J Neurol Neurosurg Psychiatry 2007; 78(8):790-799. Wild K, Howieson D, Webbe F, Seelye A, Kaye J. Status of computerized cognitive testing in aging: a systematic review. Alzheimers Dement 2008; 4(6):428-437. Howe E. Update on Alzheimers: Initial screening of patients for Alzheimer's Disease and Minimal Cognitive Impairment Psychiatry 2007.
Comments:	In summary, four reviews were identified that describe a number of tests that could be used to detect people with mild cognitive impairment. However, to identify the 'best' test for use in clinical practice, a more detailed assessment of each test to determine test accuracy and external validity is required, therefore the information contained in the reviews can only act as a starting point in searching for the best test for identifying mild cognitive impairment in patients presenting with subjective cognitive impairment.
Date Completed:	July 2010

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ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Identification of Mild Cognitive Impairment in patients presenting with Subjective Cognitive Impairment.

Request completed: July 2010

Question

Is there evidence indicating the best diagnostic tool for identifying mild cognitive impairment in patients presenting with subjective cognitive impairment?

Question clarification

The reason for this request was to identify a tool, preferably computerised, that could be used to screen patients with subjective cognitive impairments (SCI) to see if they have mild cognitive impairment (MCI). Some patients with MCI are likely to progress to Alzheimer's disease (AD).[5] Screening tests which could identify those patients with MCI, particularly those who are likely to progress to AD, may allow assessment of interventions which could potentially prevent or attenuate progression to severe AD.

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol www.arif.bham.ac.uk/strategy.shtml. The search was inclusive rather than exclusive. Text and index terms were used to represent the population and the intervention. Sources were searched from their inception to May 2010. No language restriction was applied to the searches. As an example, the MEDLINE search can be found in Appendix A. The following criteria were used for study selection:

Population/ setting	Patients with subjective cognitive impairment. Age from 35* years. Community setting with computer facilities available. Excluding memory clinics.
Intervention	Screening tools to identify patients with mild cognitive impairment. Preference given to computerised tests. Excluding imaging, cerebral spinal fluid (CSF) and blood testing.
Comparator	Clinical assessment, no assessment, other tests (including reference standards).
Outcome	Internal validity of test, ease of use of test, test accuracy, costs
Study design	Systematic reviews that have undertaken a wide search of the literature to identify test accuracy studies.

* reduced from 40 years to 35 years after consultation with the requester.

Diagnosis of MCI is also dependent on the definition of MCI. There does seem to be a plethora of diagnostic criteria which has evolved overtime. For the purposes of this report, the definition given by Luck et al 2010[6] has been utilised and consists of the following criteria: 1. A cognitive complaint (self and/or informant reported); 2. Preserved basic activities of daily living (ADL); 3. Cognitive impairment (not normal for age and education) or decline in cognition evidenced by performance on objective cognitive tasks; 4. Preserved general cognitive functioning; 5. Absence of dementia.

Results

Four reviews met the study selection criteria.[1-4] Greater weight has been given to the systematic review by Wild et al 2008,[3] as it specifically examined computerised cognitive testing. Full search results can be found in Appendix B.

Wild K, Howieson D, Webbe F, Seelye A, Kaye J. Status of computerized cognitive testing in aging: a systematic review. *Alzheimer's & Dementia*. 2008; 4(6):428-37.

The objective of this systematic review was to examine the utility of computer-based cognitive testing, aimed at identifying elderly people with age related changes in cognition, MCI or early dementia. No definition of 'elderly' was given. The review was conducted using appropriate systematic review methodology. The review sought to find and assess widely used and researched computer tests and to assess them according to a set of rating criteria (see table 1). Effectiveness studies that had compared computer testing to standard cognitive testing were excluded, as were studies related to patients with multiple sclerosis or for testing in specific applications e.g. driving safety evaluations. It is reasonably up to date, with searches up to 2007 although EMBASE was not searched which may have introduced some publication bias.

Utility was assessed using a uniform set of rating criteria (see table 1 below).

Table 1. Rating criteria.

Rating criteria	Definition	Scores
Subtests	Comprehensiveness of domains and depth of coverage within domains.	1 = narrow focus, lack of depth 2 = comprehensive but not in depth or narrow focus 3 = comprehensive and in depth
Normative data	Explanation not given	1 = no data 2 = small sample size of elderly, otherwise OK 3 = adequate sample of elderly
Reliability	Inter-rater, test-retest, internal consistency	1 = no data 2 = adequate data, 1 type of reliability 3 = >1 type of reliability reported
Validity	Content, construct, criterion	1 = no data 2 = adequate data, 1 type of validity 3 = >1 type of validity reported

Rating criteria	Definition	Scores
Factor analysis	Explanation not given	1 = no data 2 = no comment given 3= any factor analysis reported
Administration/interface	Resources required e.g. administrator and ease of use.	1 = poorly designed or described interface 2 = reliance on administrator, but good interface 3 = independent administration, self-explanatory with good interface

Redrawn from Wild et al 2008[3]

Eleven tests were identified. Table 2 details the names of each test and the domains that they cover. Whilst all of the tests include some type of memory evaluation, there is variability regarding the other domains tested within each tool. This seems to reflect the uncertainty regarding different diagnostic criteria in the literature.[3]

Table 2. Names and domains of tests.

	Name of test (abbreviation)	Domains
1	Automated Neuropsychological Assessment Metrics (ANAM)	Memory, attention, psychomotor speed, language, reaction time
2	Computer Administered Neuropsychological Screen for MCI (CANS-MCI)	Memory, language, executive function
3	Cambridge Neuropsychological Test Automated Battery (CANTAB)	Working memory, attention, visuospatial memory
4	CNS Vital Signs	Memory, psychomotor speed, processing speed, cognitive flexibility, sustained attention
5	Computerized Neuropsychological Test Battery (CNTB)	Memory , language, information processing, motor speed, attention, spatial,
6	Cognitive Drug Research Computerized Assessment System (COGDRAS-D)	Memory, attention, reaction time
7	CogState	Working memory, executive function, attention, reaction time
8	Cognitive Stability Index (CSI), also Cognitive Screening Test	Memory, attention, response speed, processing speed
9	MCI screen (based on CERAD)	Memory, executive function, language
10	MicroCog (formerly Assessment of Cognitive Skills)	Memory, attention, reaction time, spatial ability, reasoning/ calculation
11	Mindstreams (Neurotrax)	Memory, executive function, visuospatial, verbal fluency, attention, motor skills, information processing.

Seven tests were able to discriminate MCI from healthy controls, with three discriminating MCI from dementia. In total 43 studies contributed to the data. Sample sizes seem reasonable, the largest was 1069, the smallest 113. There was a wide span of age ranges studied with five concentrating on middle to old age.

Table 3. Study characteristics.

	Name	Discrimination potential*	Number of studies contributing to the data* Largest sample**	Age ranges**
1	ANAM	Cognitively impaired elderly	6 studies 191	22-77
2	CANS-MCI	Healthy controls & MCI	1 study [Tornatore JB et al 2005] 310	51-93
3	CANTAB	Healthy controls & early stage Alzheimer's disease & Parkinson's disease, healthy elderly subjects & early detection of memory deficits.	9 studies 771	8-80
4	CNS Vital Signs	Healthy controls & MCI, MCI & mild dementia.	2 studies 1069	7-90
5	CNTB	Aimed at distinguishing Alzheimer's disease.	3 studies 209	21-87
6	COGDRAS-D	Healthy controls & mild dementia, Alzheimer's disease & Huntington disease, Alzheimer's disease & Lewy Body dementia.	4 studies 190	67-103
7	CogState	Healthy controls & MCI – particularly long term changes in memory.	5 studies 113	18-40 & 46-62
8	CSI	Healthy controls & MCI, also dementia.	2 studies 284	18-89
9	MCI screen	Healthy controls & MCI especially in primary care setting.	3 studies 215	>65
10	MicroCog	Healthy controls & MCI	4 studies 810	18-89
11	Mindstreams	Healthy controls & MCI & mild dementia.	4 studies 213	>50

* Data taken from text, data taken from Table 2 of publication (page 430).
** Data taken from results text (page 430 – 434)

Table 4. Results of rating criteria (limited to tests able to discriminate MCI)

		Subtests	Normative data	Reliability	Validity	Factor analysis	Admin/ Interface	Total no. at level 3/best tests?
2	CANS-MCI	2	3	3	3	3	3	5✓
4	CNS Vital Signs	3	3	2	3	1	2	3
7	CogState	3	2	2	2	1	2	1
8	CSI	2	2	3	3	3	2	3
9	MCI screen	1	3	2	2	3	2	2
10	MicroCog	3	3	2	3	1	3	4✓
11	Mindstreams	3	2	1	2	1	2	1
	Total	1 = 1 2 = 2 3 = 4	1 = 0 2 = 3 3 = 4	1 = 1 2 = 4 3 = 2	1 = 0 2 = 2 3 = 4	1 = 4 2 = 0 3 = 3	1 = 0 2 = 5 3 = 2	

where 1 = failure to address component; 2 = partial consideration and/or presentation of the variable; 3 = comprehensive.

Overall, most of the tests scored reasonably well according to the rating criteria (see table 4).

One test (CANS-MCI) met five out of six of the criteria and could distinguish healthy people from people with MCI. Completion of this test took on average 30 minutes. Data from a single study [Tornatore 2005] with a sample size of 310 participants was used as evidence to assess the tool. The test was undertaken on patients between 51 and 93 years old. The test development was based in the USA but there is a UK version on their website.[7]

The website also gives the following test accuracy data. For patients with less than 13 years education, sensitivity was 100% and specificity was 100%. For patients with more than 13 years education, sensitivity was 100%, with specificity at 84.8%. The website says this is based on a study by Winter 2005, but searches have been unable to find the full reference, therefore it is unclear how this data was arrived at and therefore should be used with caution.

The next 'best' test (MicroCog) met four of the six criteria (see table 4). The test was formerly known as the Assessment of Cognitive Skills (ACS) test and is marketed by Psych Corp. Completion of the test takes around 1 hour, although it is acknowledged that for impaired subjects this might be longer. Data from four studies were used as evidence to assess the tool [Green RC 1994, Elwood RW 2001, Johnson JA 2003 and Helmes E 2006] using a combined sample size of 810. The test was undertaken on patients aged 18-89 and can be undertaken in a variety of settings. Test accuracy data was not identified.[8]

Other reviews.

Further details regarding the other reviews can be found in Appendices C, D, and E. None of the tests were computerised but are given here to alert the reader as to the existence of other tests. The tests that they recommended are given in table 5 below:

Table 5. Reviews that had sought to identify screening tools.

	Review recommended tests for MCI
Cullen B *et al 2007*[2] Aim: to identify screening tools for cognitive impairment, that could be administered by a GP or in the wider community. Tests self administered or by proxy.	- Modified mini mental state examination (3MS). - Cognitive abilities screening instrument (CASI).
Holsinger T *et al 2007* [1] Aim: to identify brief cognitive screening tools for patients 60 years or over.	- Hopkins verbal learning test. - Word list acquisition test.

	Review recommended tests for MCI
Howe E *et al 2007* [4] Aim: to describe screening tools for patients who have concerns about memory lost.	- The 'WORLD' test. - The one minute naming game. - The Mini-Cog test. - Montreal cognitive assessment test (MoCA) with this being described as being the most effective & developed specifically for MCI.

Discussion.

When considering which is the 'best' test to use for identifying people who have MCI several factors have to be taken into account:

The internal validity of the test –does the test measure what it is supposed to measure.	Consider – • Reliability • Validity • Comprehensiveness	*How are these scored, what are the cut off points that differentiate diseased & non diseased. How well does the pathology identified match the case definition and has the case definition changed through time.*
The diagnostic test accuracy – How does it compare to other tests available.	Consider test – • Sensitivity • Specificity • Positive predictive value (PPV) • Negative predictive value (NPV) • Likelihood ratio (LR) • Receiver operating curves.[9] • Measures of uncertainty around test accuracy measures.	*Is the incidence/prevalence of the disease in the clinical setting the same as the study/trial setting. If lower, this can adversely affect test accuracy.*
The external validity of the test – where does it sit in the patient care pathway.	Consider - • Is it a replacement test • A triage test • An addition (add on) test[10] • Is there an effective treatment for the disease the test has diagnosed.	*Will the test improve patient outcomes, what is the treatment of the disease the test has identified & are there any adverse effects about using the test. For example:* ▪ *Does it matter if the test has a low sensitivity i.e. if patients with true disease are missed are there are there opportunities for the disease to be identified by other means and how does delay change their disease course.* ▪ *Does it matter if there is a low specificity i.e. patients without disease (false positives) are identified as having the disease, depends upon how quickly they are recognised, in a triage test this may be sooner down the patient pathway and hopefully before any invasive treatment has taken place.*

The data from the review by Wild et al, [3] which looked at computer-based tests, did provide data relating to the internal validity of the tests, using their test rating criteria. From this it could be seen

that the best of the tests identified were CANS-MCI and MicroCog. Upon investigation of the CANS-MCI website, data regarding the sensitivity and specificity and ROC curves are also given, which suggest that the test is perfect in patients with less than 13 years of education (ROC = 1, Sensitivity = 100%, Specificity = 100%). Unfortunately, no data regarding the setting of this test that gives the test accuracy data is described, which makes it difficult to tell if the test would be as accurate in the setting where it will be applied and also how valid the test is over the disease spectrum. The same problem also occurs with applying the MicroCog (although no test accuracy data has been identified) therefore to apply these tests with such little data is not advisable.

Regarding data from the other reviews, the review by Holsinger et al[1] only included studies in which the patients were 60 years or older, which is substantially older than that stated in the target question of this request. Age in MCI is an important determination of disease prevalence. This causes a fundamental problem in that patients that are younger are almost certainly likely to have a lower disease prevalence, which reduces accuracy estimates resulting in lower predictive values and lower sensitivity and specificity.

Whilst the reviews have identified several tests that could be used to detect patients with MCI, none of them stated whether these tests could recognise patients who were likely to progress to AD. If the test does not discriminate between people who have MCI who will or will not progress to AD, then any subsequent evaluations of interventions that aim to reduce progression will suffer with lead time bias.[1] Such bias can result in a test appearing to slow down disease progression when all that has happened is that the patient has been diagnosed earlier. The consequence of this is that an ineffective treatment may appear to be effective i.e. lengthens the time to progression.[12;13] This is a common problem of most screening programs which detect pre-disease states, for example the cervical screening program. When considering which test to use, one must also consider how many false positives it identifies (measured by specificity). If there are many, this may give rise to harm (e.g. anxiety) in people who take the test and do not have the disease, and an additional cost without benefit, as healthy patients may get unnecessary treatments. Further information regarding these issues and a discussion regarding the pros and cons of early detection can be found in recently published NICE guidelines[12] particularly pages 143 to 144.

[1] Which may be a reason why some studies report that early screening for AD is “cost effective”. Relkin 2002[11]

Conclusions

In summary, four reviews were identified that describe a number of tests that could be used to detect people with MCI. However, to identify the 'best' test for use in clinical practice, a more detailed assessment of each test to determine test accuracy and external validity is required, therefore the information contained in the reviews can only act as a starting point in searching for the best test for identifying MCI in patients presenting with SCI.

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3. Wild K, Howieson D, Webbe F, Seelye A, Kaye J. Status of computerized cognitive testing in aging: a systematic review. Alzheimers Dement 2008; 4(6):428-437.

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12. National Institute for Health and Clinical Excellence London: NICE. CG42 Dementia: full guideline including appendices 1 - 7. Internet [2006 Available from: URL:http://guidance.nice.org.uk/CG42/Guidance/pdf/English [accessed 5-7-10]

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Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 subjective cognitive impairment.mp.
2 mild cognitive impairment.mp.
3 sci.mp.
4 mci.mp.
5 ((pre cursor$ or pre-cursor$ or early or sign$ or predictor$ or indicator$) adj2 (dementia or cognition or cognitive or Alzheimer$)).
6 or/1-5
7 (diagnosis or diagnostic or diagnos$).mp.
8 screen$.mp.
9 exp Diagnosis/
10 exp Mass Screening/
11 accuracy.mp.
12 exp "Sensitivity and Specificity"/
13 or/7-12
14 6 and 13
15 limit 14 to "reviews (specificity)"
16 from 15 keep 1-18

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Appendix B – Literature search results

Source – Cochrane Library 2010 Issue 2 (DARE)

Holsinger T, Deveau J, Boustani M, Williams J W Does this patient have dementia? JAMA 2007; 297(21): 2391-2404 http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12007008160/frame.html

Castilla-Rilo J, Lopez-Arrieta J, Bermejo-Pareja F, Ruiz M, Sanchez-Sanchez F, Trincado R Instrumental activities of daily living in the screening of dementia in population studies: a systematic review and meta-analysis (Provisional abstract) International Journal of Geriatric Psychiatry 2007; 22(9)**:** 829-836
http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12007007325/frame.html

Jorm A F Methods of screening for dementia: a meta-analysis of studies comparing an informant questionnaire with a brief cognitive test (Structured abstract) Alzheimer Disease and Associated Disorders 1997; 11(3): 158-162
http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-11997001155/frame.html

Petersen R C, Stevens J C, Ganguli M, Tangalos E G, Cummings J L, DeKosky S T Practice parameter: early detection of dementia. Mild cognitive impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology (Structured abstract) Neurology 2001; 56(9): 1133-1142
http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12001001239/frame.html

Dougall N J, Bruggink S, Ebmeier K P Systematic review of the diagnostic accuracy of 99mTc-HMPAO-SPECT in dementia (Structured abstract) American Journal of Geriatric Psychiatry 2004; 12(6): 554-570 http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12004002046/frame.html

Source – Cochrane Library (Wiley) 2010 Issue 2 (HTA)

Swedish Council on Technology Assessment in Health Care Dementia - diagnostic and therapeutic interventions (Vol 2) (Structured abstract) Stockholm: Swedish Council on Technology Assessment in Health Care (SBU) 2008: 552
http://www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-32008100076/frame.html

National Horizon Scanning Centre New tests for Alzheimer's disease - horizon scanning review (Structured abstract) Birmingham: National Horizon Scanning Centre (NHSC) 2002: 5
http://www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-32002000541/frame.html

Matchar D B, Kulasingam S L, Huntington A, Patwardhan M, Mann L O Positron emission tomography, single photon emission computed tomography, computed tomography, functional magnetic resonance imaging, and magnetic resonance spectroscopy and for the diagnosis and management of Alzheimer's dementia (Structured abstract): Rockville: Agency for Healthcare Research and Quality (AHRQ): 2004: 93
http://www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-32005000065/frame.html

Source – MEDLINE (Ovid) 1950 to May Week 2 2010

Ehreke L, Luppa M, Konig HH, Riedel-Heller SG Is the Clock Drawing Test a screening tool for the diagnosis of mild cognitive impairment? A systematic review. International Psychogeriatrics. 2010; 22(1):56-63
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Schroeter ML, Stein T, Maslowski N, Neumann J. Neural correlates of Alzheimer's disease and mild cognitive impairment: a systematic and quantitative meta-analysis involving 1351 patients. Neuroimage. 2009; 47(4):1196-206

Yuan Y, Gu ZX, Wei WS. Fluorodeoxyglucose-positron-emission tomography, single-photon emission tomography, and structural MR imaging for prediction of rapid conversion to Alzheimer disease in patients with mild cognitive impairment: a meta-analysis. American Journal of Neuroradiology.2009; 30(2):404-10, 2009 Feb.

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Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. International Journal of Geriatric Psychiatry. 2000; 15(11):983-91

Guidelines

Source – NICE

Memory assessment service for the early identification and care of people with dementia Commissioning Guidance National Institute for Health and Clinical Excellence London: NICE; December 2007
http://www.nice.org.uk/media/4F1/D6/Memory_assessment_service_commissioning_guide.pdf

CG42 Dementia: full guideline including appendices 1 – 7. National Institute for Health and Clinical Excellence London: NICE; November 2006
http://guidance.nice.org.uk/CG42/Guidance/pdf/English

Source – National Guidelines ClearingHouse

Management of patients with dementia A national clinical guideline Guideline 86 Scottish Intercollegiate Guidelines Network Edinburgh : SIGN ; February 2006
http://www.sign.ac.uk/pdf/sign86.pdf

Cognitive impairment in the elderly – recognition, diagnosis and management Clinical Practice Guidelines in British Columbia 15 July 2007 http://www.bcguidelines.ca/gpac/pdf/cognitive.pdf

Economic evaluations

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http://www.mrw.interscience.wiley.com/cochrane/cleed/articles/NHSEED-21999008259/frame.html

Background information

Source – Merck Manual

Dementia
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Source – Internet

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Background – Diagnosis

Source - Internet

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http://www.neurowissenschaft.ch/oldNeuro/Lehre/WS0607/Spezialfaelle/Demenz/Petersen-2004-MCI.pdf

Background – predictors

Source - Internet

Dartiques J-F, Commenges D, Letenneur L, Barberger-Gateau P, Gilleron V, Fabrigoule C et al Cognitive Predictors of Dementia in Elderly Community Residents Neuroepidemiology 1997; 16(1): 29-39
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Oulhaj A, Wilcock GK, Smith AD, de Jager CA Predicting the time of conversion to MCI in the elderly. Role of verbal expression and learning, Neurology, 3rd Nov. 2009, 73 (18) ;436-1442 http://www.neurology.org/cgi/content/abstract/73/18/1436

Anderson P Subjective Cognitive Impairment Early Indicator of Further Cognitive Deficits Medscape Today 14 January 2010

http://www.medscape.com/viewarticle/715237

Reisberg B, Gauthier S Current evidence for subjective cognitive impairment (SCI) as the pre-mild cognitive impairment (MCI) stage of subsequently manifest Alzheimer's disease. Int Psychogeriatr 2008; 20(1): 1-16

Jessen F, Wiese B, Bachmann C, Eifflaender-Gorfer C, Haller F, Kolsch H et al Prediction of dementia by subjective memory impairment: effects of severity and temporal association`n with cognitive impairment. Arch Gen Psychiatry 2010 ; 67(4): 414-422
http://www.ncbi.nlm.nih.gov/pubmed/20368517?dopt=AbstractPlus

Background – papers provided by requestor

Reisberg B, Schulman MB, Torossian C, Leng L, Zhu W. Outcome over seven years of healthy adults with and without subjective cognitive impairment Alzheimer's and Dementia 2010 ; 6(1) : 11-24 (pdf available)

Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) Wikipedia accessed 27 May 2010 http://en.wikipedia.org/wiki/Informant_Questionnaire_on_Cognitive_Decline_in_the_Elderly

Brodaty H, Draper BM , Low L-F Behavioural and psychological symptoms of dementia: a seven-tiered model of service delivery MJA 2003 ; 178 (5): 231-234

Is there hope for the prevention of dementia? Science Daily 4 September 2008
http://www.sciencedaily.com/releases/2008/09/080902112259.htm

Purandree N Prevention of dementia : role of vascular risk factors and cerebral emboli Indian Jnl Psychiatry 2009; 51(5): 39-43 http://www.indianjpsychiatry.org/article.asp?issn=0019-

Screening cognitive decline in dementia: preliminary data on the Italian version of the IQCODE Neurological Sciences 2002; 23(2): s79-s80
http://www.springerlink.com/content/bv2gv972pm9e66xb/

Worsening Memory Associated With Later Alzheimer's Disease Science Daily April 7 2010
http://www.sciencedaily.com/releases/2010/04/100406205315.htm

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Appendix C – Critical appraisal of:

Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA. A review of screening tests for cognitive impairment. J Neurol Neurosurg Psychiatry 2007; 78:790-799.

The aim of this review "intended to serve as a resource and starting point" to identify screening tools for cognitive impairment. The age of the population of interest was not specified, however how the test and how it would be administered was defined as either in primary care administered by a GP or in the wider community, generally self administered or administered by proxy. The screening tool also had to be brief with administration time no longer than 20 minutes. Systematic review methodology was generally poor with no search dates stated and inconsistent reporting of results. As regards test accuracy assessment, this was a little better with the reference standard defined as that based on international diagnostic guidelines or clinical judgement following a full assessment battery. Data was presented on tables, only data relating to mild cognitive impairment is reported here.

1. Brief assessment in the doctor's office:
See table 2 of paper – tests that performed well in this context were the modified mini mental state examination (3MS) and the cognitive abilities screening instrument (CASI).

Both tests examined mild cognitive impairment.

Test name	Population	Result.
Modified mini mental state exam (3MS)	Unselected community 5 studies	Sens 78
Cognitive abilities screening instrument (CASI)	Unselected community x 1 Unselected primary care x1 Selected geri/psy/mem clin x1	Spec 76
Short test of mental status	Selected geri/psy/mem clin x2 Other x 1	AUC 82
Mini cog	Unselected community x 1 Other x 1	Sens 55 Sens 74-84
Six item screener	Unselected commun x 1 Selected geri/psy/mem clin x1	Spec 80 – 85
DemTect	Selected geri/psy/mem clin x1	Sens 80 Spec 92

Red = recommended by review authors

The review authors noted that the CASI has been criticised for having low specificity in some unselected samples, and that 3MS has been found to have a wide variation in scores without any accompanying clinical change.

2. Large scale screening programmes in the community. Just one test examined mild cognitive impairment.

Test name	Population	Result.
Informant Questionnaire on Cognitive Decline in the Elderly – Short Form IQCODE-SF	Unselected commun x 2 Selected geri/psy/mem clin x1	PPV 50%

The review authors noted that were shortcomings in this tests evaluation i.e. that it had been evaluated using variable test-retest reliability across individual items.

The review authors also noted that one test the AB Cognitive Screen (ABSC) had been specifically developed to assess mild cognitive impairment, however, no further information was given regarding this test.

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Appendix D – Critical appraisal of:

Holsinger T, Deveau J, Boustani M, Williams J W. Does this patient have dementia? *JAMA* 2007; 297(21): 2391-2404

The aim of this review was to identify and assess the "practicality and accuracy of brief cognitive screening instruments in primary care to detect dementia before it becomes clinically obvious". It was concerned with patients aged 60 years or older. Searches were from 2000 to 2006 and the systematic review methodology was generally good. Data was collected so that 2x2 tables could be constructed and the sensitivity, specificity and likelihood ratios calculated. Tests were categorised as: standard instruments, brief instruments, more comprehensive instruments and instruments for special situations.

Twenty nine studies were identified, yielding a total of 38 unique screening tools.

Type of tool	Number of studies	Test name
1. Standard instruments	n = 11	10 = Mini mental state examination (MMSE) 1 = MMSE + informant questionnaire for cognitive decline in the elderly
2. Brief instruments	n = 15	1 = memory impairment screen 2 = abbreviated mental test 3 = clock drawing 1 = 7 minute screen 1 = short cognitive evaluation battery 1 = GP assessment of cognition 1 = 3 word recall 1 = subjective complaints 1 = 6 item screener 1 = mini cog 1 = short and sweet screening instrument 1 = brief Alzheimer screen
3. More comprehensive instruments	n = 7	1 = community screening interview for dementia 1 = Cambridge cognitive exam 1 = Community screening interview for dementia 2 = Modified MMSE 1 = Modified MMSE + dementia questionnaire.
4. Instruments for special situations	n = 8	1 = memory impairment screen – telephone version 1 = telephone interview for cognitive status 1 = cognitive assessment screening test 3 = **Hopkins verbal learning test** 1 = Montreal cognitive assessment 1 = AD8 1 = psychogeriatric assessment scales.

The review authors recommended that for patients with the suspicion of mild impairment, the Hopkins Verbal Learning Test or the Word List Acquisition Test were the most practical screening tools for general practitioners. The Verbal Learning Test was assessed in three studies (Hogervorst 2002, Frank & Byrne 2000, and Kuslansky 2004).

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Appendix E – Critical appraisal of:

Howe E Update on Alzheimer's: Initial screening of patients for Alzheimer's Disease and Minimal Cognitive Impairment *Psychiatry* 2007 http://www.psychiatrymmc.com/initial-screening-of-patients-for-alzheimer%E2%80%99s-disease-and-minimal-cognitive-impairment/

This is a narrative review but for the purposes of this request – to identify tests - is probably as useful as a systematic review. In addition the author does identify tools specifically aimed at identifying mild cognitive impairment. The author describes four tools: The WORLD test; the one minute naming game; the Mini-Cog test, and the Montreal Cognitive Assessment Test. (MoCA). The MoCA is described as being the most effective and the author states that it was developed specifically to detect mild cognitive impairment.

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Archived ARIF Request

Elderly Mentally Infirm Dementia

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in February 1996.

The Problem Submitted for ARIF to Advise Upon:

What is the evidence concerning treatment of the elderly mentally infirm, in particular with regard to dementia?

Question Reformulated

The objective of the question stated was to develop a district-wide pattern of services. An initial search revealed no reviews of research on such constellations of services. Subsequent searches were refocussed to give an indication of the range and effectiveness of elements of care of the elderly mentally infirm which should be included.

Reviews Identified

- Melzer D et al. Dementia. In: Health care needs assessment: the epidemiologically based needs assessment reviews. Vol 2. Oxford: Radcliffe Medical Press, 1994. pp305-340
- Yeager BF. Management of the behavioural manifestations of dementia. Archives of Internal Medicine 1995; 155: 250-260

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Comments

Although, neither review suggested is systematic, both provide well-structured considerations of various aspects of the management of the elderly mentally infirm together with indications of their likely effectiveness. The references cited in the reviews would be the starting point for a more detailed consideration of the effectiveness of any individual elements of particular interest in a wider programme of care.

This is an area prone to the need for regular updated as new information is continually becoming available. The advent of new anti-dementia drugs is particularly relevant on this respect.

Request Carried Out: February 1996

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Archived ARIF Request

Memory Clinics
Dementia

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in December 1998 and update in March 2001.

The Problem Submitted for ARIF to Advise Upon:

Is there any evidence that memory clinics are more effective than routine OPD appointments in the management of people with dementia?

Question Reformulated:

Clarification that a memory clinic is an out-patient based service which takes a multi-specialty approach to the assessment and diagnosis of people with memory impairment, and that it should be distinguished from other multi-disciplinary approaches to the co-ordination and management of the care of people with dementia.

Reviews Identified

None.

Other Literature Identified

Observational study

- Verhey FRJ, Jolles J, Ponds RWHM et al. Diagnosing dementia: a comparison between a monodisciplinary and a multidisciplinary approach. The Journal of Neuropsychiatry and Clinical Neurosciences 1993;5:78-85

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Comments

There are no reviews or other strong evidence on the effectiveness of memory clinics per se, but existing evidence from good systematic reviews on different pharmacological interventions for dementia points to the importance of early identification of people who are likely to benefit from this treatment. The importance of early diagnosis and treatment is also stressed in reviews of non-pharmacological interventions. The study by Verhey et al, while it does have significant methodological limitations, indicates that memory clinics may be more effective than routine appointments at least in this respect.

Information from reviews which have addressed issues around the co-ordination and concentrated delivery of care in other areas are also helpful as it is possible that some of the same basic principles may apply. These might include:

- Stroke Unit Triallists Collaboration. Collaborative systematic review of randomised trials of organised inpatient (stroke unit) care after stroke. BMJ 1997;314:1151-59
- Place M. The relationship between concentration, patient accessibility and utilisation of services. The University of York. Centre for Health Economics. York Health Economics Consortium. NHS Centre for Reviews and Dissemination. 1997 CRD Report 8, Part III.

Request Carried Out: December 1998

Update: March 2001 - In light of recent guidance by NICE on the use of donepezil, rivastigmine and galantamine for patients with Alzheimer's disease, we were asked to revisit our previous work on the effectiveness of memory clinics for the diagnosis and assessment of patients with memory impairment. We re-ran our previous searches but identified no systematic reviews. We did identify a randomised control trial on the effects of attendance at a memory clinic on the psychosocial health of carers of community-dwelling patients diagnosed with mild to moderate dementia:

- Logiudice D; Waltrowicz W; Brown K; Burrows C; Ames D; Flicker L. Do memory clinics improve the quality of life of carers? A randomized pilot trial. International Journal of Geriatric Psychiatry 1999; 14 (8): 626-32

There continues to be no robust evaluation of the use of memory clinics for the diagnosis and treatment of dementia. Although there is no strong data evaluating the effectiveness of memory clinics on patients, it is possible the memory clinic may be of some benefit to carers of those already diagnosed with mild to moderate dementia.

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Archived ARIF Request

Professions Complimentary to Dentistry Dental Care

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in July 2004.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness and cost-effectiveness of providing dental care by people from professions complimentary to dentistry (PCD's)?

Question Reformulated

PCD's include dental nurses, dental hygienists and dental therapists.

Reviews Identified

- Galloway J, Gorham J, Lambert M, Richards D, Russell D, Russell I, Welshman J. The professionals complimentary to dentistry: systematic review and synthesis. Oxford: Centre for Evidence Based Dentistry, 2002 (revised 2003). Pp153

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Comments

Although the review identified has some shortcomings (detailed appraisal available on request), the conclusions appear valid. The results of the meta-analyses need to be treated with considerable caution.

The recommendation of the review to increase the numbers of PCD's seems reasonable as does the call to conduct further better quality research on the effectiveness and cost-effectiveness of PCD's.

Request Carried Out: July 2004

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Physical activity for depression

Synopsis

Question:	What is the evidence that increased physical activity improves depression in adults?
Evidence Identified:	Mead GE, Morley W, Campbell P, Greig CA, McMurdo M. Lawlor DA. Exercise for depression. Cochrane Database of Systematic Reviews. (3):CD004366, 2009. Daley A, Jolly K, MacArthur C. The effectiveness of exercise in the management of post-natal depression: systematic review and meta-analysis. Family Practice 2009; 26:154–162.
Comments:	Of the two systematic reviews on which this report was based, one assessed the evidence on the effect of exercise in depressed adults and the other the effect on past-natal depression. Exercise seems to reduce symptom severity of depression in adults compared to no treatment or placebo when based on all available RCT data, but no significant effect is seen when based on the more methodologically sound trials only, although this might be due to lack of power. Of the findings, measured as standardised mean differences, it is unclear how clinically meaningful the changes in the overall effect sizes are. Furthermore, most of the primary studies had low methodological quality, and between the trials there was wide variation in terms of the severity of depression, type, level and duration of exercise intervention, type of comparator and outcome measurement. The data come from outcome measured close to the end of the treatment period. Although there is data from studies that measured outcome several months after the end of the intervention and also indicated a significant benefit of exercise, the review, however did not indicate if there was any modulation in the effect of exercise on depression the longer the follow-up. The effect of exercise on symptom score of post-natal depression is unclear. Overall, there is some uncertainty in the effect of physical activity for the treatment of depression in adults or post-natal depression.
Date Completed:	September 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Physical activity for depression

Request completed: September 2010

Question

What is the evidence that increased physical activity improves depression in adults?

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol (www.arif.bham.ac.uk/strategy.shtml). Text and index terms were used to represent the population and the intervention. Sources were searched from their inception to August in 2010. No language restriction was applied to the searches. As an example the MEDLINE search can be found in Appendix A. The following inclusion criteria were used for study selection:

Population	Adults who were diagnosed with depression
Intervention	Physical activity
Comparator	Any treatment other than exercise
Outcome	Measure of depression
Study design	Systematic reviews and health technology assessments

Results

Although many systematic reviews were identified, two systematic reviews were selected as being the most recent and relevant to the question posed: one, by Mead et al,[1] focused on the effectiveness of exercise in the treatment of depression for adults but excluded post-natal depression, the other, by Daley et al,[2] focused solely on exercise for post-natal depression. Full search results can be found in Appendix B, and the selected reviews are documented below.

Mead et al, 2009[1] – exercise for the treatment of depression for adults

Characteristics of the review

This was a generally well-conducted Cochrane systematic review. Published in 2009, it was an update of a previous review on the same topic which was published in 2001.[3] Searches were conducted up to 2007. Studies included were randomised controlled trials (RCTs). The population was adults aged 18 years or over with a diagnosis of depression, excluding post-natal depression. The intervention was any type of exercise and the comparator was no treatment, placebo or any

other type of intervention. Studies comparing exercise plus another intervention versus the other intervention alone were also included. The primary outcome was a measure of depression or mood. Secondary outcome measures included the number of people who were screened for inclusion, the number recruited, attendance at the exercise interventions, and the number completing the interventions.

Characteristics of included studies

A total of 28 trials met the review's inclusion criteria. They were published between 1979 and 2007, with 17 trials being published more than a decade ago. Six of the trials were from Europe including three from the UK, one was from Canada, one from Australia, two from Hong Kong, and one from Thailand. The remaining trials were all from the US.

There was wide variation in the participants across the trials. In 21 trials participants were recruited from non-clinical populations including community volunteers, in six trials they were recruited from clinical populations i.e. hospital inpatients or outpatients, and in the remaining trial participants comprised both clinical and non-clinical populations. Different methods and various scales were used for diagnosis of depression. Severity of depression of the participants was not reported for most of the trials, and, where reported, some trials included mild to moderate depression, some included major depression or dysthymia, while the others included major depression only. The sample size of the trials ranged from 11 to 202 patients and number of comparison groups ranged from two to six. There was also wide variation in the type, level and duration (1 - 16 weeks) of the exercise intervention. The comparator also varied. All the trials assessed outcomes at the end of the interventions; five trials also reported long-term follow-up (4 - 26 months) data beyond the end of the interventions. To measure the outcome of depression, various scales were used.

Of the 28 trials, only eight were judged to have adequate allocation concealment, seven had blinding of outcome assessor, and seven had intention to treat (ITT) analyses. Only three trials fulfilled all three methodological criteria.

Effectiveness results

Twenty-five of the trials were included in meta-analyses. The authors stated that of the remaining three trials, two were unsuitable for statistical pooling, and one was published in abstract form and the data were not available for meta-analysis. As the primary outcome was recorded using a variety of continuous outcome scales, pooled effect measures were presented as standardised mean difference (SMD).

Table 1 below presents the effects of the interventions when pooling all the available data. Meta-analysis of 23 trials (n = 907) comparing exercise with no treatment or placebo showed a large significant effect in favour of exercise in reducing symptom severity at post-treatment, with a SMD of -0.82 (95%CI -1.12 to -0.51). However, there was significant heterogeneity between trials. The effect was consistently significant when analysed according to exercise type, of which most being aerobic exercise. Meta-analysis at a longer but widely ranged follow-up (4 – 26 months), included only the five trials where data was available, still showed a significant reduction in symptom severity in favour of exercise compared with no treatment or placebo (SMD = -0.44; 95%CI -0.71 to -0.18). However, an analysis of pooled effect size of the five trials at post-treatment was not conducted, and as such, the longer term effect of exercise is not totally clear. Turing to other comparators, pooled estimates at post-treatment showed that the reduction in symptom severity with exercise was not significant compared with either cognitive therapy (six trials) or antidepressants (two trials). Based on only one small trial, exercise reduced significantly symptom severity at post-treatment compared with bright light therapy. As all the trials had small sample sizes and no power calculation was mentioned, it was unclear whether any of the inefficacy of the pooled effect sizes was due to lack of power. See Table 1 for details. No subgroup analyses according to exercise levels were conducted. The authors stated that attendance rates for exercise was reported in nine trials and ranged from 59% to 100%. The authors also stated that as with intensity of exercise, it is difficult to attribute any differences in outcome to differences in attendance rates, due to sources of variation in the type of interventions and differences in the methodological quality between trials which might account for differences in outcome.

Table 1 Effects of interventions – meta-analysis of available data (SMD and 95% CI)

Comparison	Symptom severity reduction at post-treatment	Symptom severity reduction at follow-up	Secondary outcome
Exercise vs. control*	**SMD = -0.82 (-1.12, -0.51)**; I^2 = 77% (23 trials; number of patients: 476 vs. 431)	**SMD = -0.44 (-0.71, -0.18)**; no statistical heterogeneity (5 trials; number of patients: 108 vs. 110)	Insufficient data for meta-analyses. Four trials reported a lack of difference in adverse events between groups
Sub-group exercise vs. control*			
• **aerobic exercise**	**SMD = -0.63 (-0.95, -0.30)** (17 trials; number of patients: 334 vs. 306)		
• **mixed exercise**	**SMD = -1.47 (-2.56, -0.37)** (4 trials; number of patients: 107 vs. 91)		
• **resistance exercise**	**SMD = -1.34 (-2.07, -0.61)** (2 trials; number of patients: 35 vs. 34)		
Exercise vs. cognitive therapy	**SMD = -0.17 (-0.51, 0.18)**; no statistical heterogeneity indicated (6 trials; number of patients: 74 vs. 78)		Insufficient data for meta-analyses
Exercise vs. bright light therapy	**SMD = -6.40 (-10.20, -2.60)** (1 trial; number of patients: 9 vs. 9)		Insufficient data for meta-analyses
Exercise vs. anti-depressants	**SMD = -0.04 (-0.31, 0.24)** (2 trials; number of patients: 104 vs. 97)		One trial found significantly higher rates of diarrhoea and loose stool in the sertraline than the exercise group

*Control: waiting list or placebo

Table 2 below presents sensitivity analyses of the effects for exercise compared with placebo or no treatment. Based on studies that had only fulfilled one of three methodological criteria (adequate allocation concealment, intention to treat analysis and blinded outcome assessment), pooled effect sizes all favoured exercise significantly in reducing severity of depression symptom at post-treatment. When only the three trials that met all three quality criteria were pooled the standardised mean difference was moderate and non-significant (SMD = -0.42; 95%CI -0.83 to 0.33). However, given that the three good quality trials had a total sample size of only 216 participants, it is uncertain whether lack of statistical significance was due to lack of power. See Table 2 for details.

Table 2 Effects of exercise vs. control* – sensitivity analyses (SMD and 95% CI)

Data included in meta-analysis	Symptom severity reduction at post-treatment
Studies with adequate allocation concealment	**SMD = -0.77 (-1.12, -0.42)** (8 trials; number of patients: 226 vs. 204)
Studies using ITT analysis**	**SMD = -0.63 (-1.16, -0.10)** (9 trials; number of patients: 210 vs. 193)
Studies with blinded outcome assessment	**SMD = -0.39 (-0.75, -0.03)** (7 trials; number of patients: 220 vs. 198)
Studies with allocation concealment, ITT, blinded outcome assessment	**SMD = -0.42 (-0.88, 0.03)** (3 trials; number of patients: 111 vs. 105)

*Control: waiting list or placebo.
** Two trials reported data for individual patients; the review authors included the two trials in the meta-analysis using last observation carried forward (LOCF) method to replace data from the patients who did not complete the trial.

Summary

Overall, pooled estimates, when all the trials where data was available were included, suggested that exercise improved depressive symptoms in adults with a diagnosis of depression, compared with no treatment or placebo. However, this was based on trials most of which had low methodological quality, and between which there was wide variation in terms of the severity of depression, type, level and duration of exercise intervention, type of comparator and outcome measurement. When sensitivity analysis included only good quality trials, the effect sizes were only moderate and not statistically significant. However, it was uncertain whether the inefficacy of the pooled effect sizes was due to lack of power. Exercise also seemed to have a significant reduction in symptom severity at a longer time follow-up compared with no treatment or placebo; it was unclear whether this effect size was sustained over time. Across the primary studies depression was measured in various scales and as such standard mean difference was used to derive pooled estimates of effect. Due to this, it was unclear how clinically meaningful any of the changes in the standard mean differences were.

Daley et al, 2009[3] – exercise for the treatment of post-natal depression

Characteristics of the review

The review aimed to evaluate the effectiveness of exercise in the management of post-natal depression (PND). It was generally well-conducted and published in 2009. The searches were conducted up to 2008. The review included RCTs and quasi-RCTs. The population was women who were between four weeks and 18 months post-partum and had been diagnosed with post-natal depression. Exercise was defined as any planned, structured and repetitive bodily movement. Trials involving exercise with additional interventions were also included but those comparing different types of exercise interventions were excluded. Inclusion criteria regarding comparators and outcome measures were not clearly stated.

Characteristics of included studies

Four RCTs and one quasi-RCT met the inclusion criteria. They were published between 2003 and 2008. Sample sizes were all small, ranging from 22 to 88 participants and giving a total of 238 participants. There was variation in the participants across the trials, as in three trials many participants were taking medication and/or receiving counselling, while one trial excluded such patients and in the other trials this information was not reported. A range of types and levels of exercise intervention, including pram walking, gentle stretching etc., were used in the trials; for one study the intervention was not actual exercise but exercise consultations that promoted regular exercise/pram walking and follow-up phone calls that encouraged regular exercise. The comparators were either social support or standard care, but for one study the control was not clearly stated. All the trials used the Edinburgh Post-natal Depression Scale (EPDS) to measure depression and one trial also used Hamilton Rating for Depression (HAM-D) scores. In all the trials the duration of the exercise intervention was 12 weeks while the follow-up duration ranged from 12 weeks to six months.

Methodological quality of the studies was rated as a seven point scale, with high score indicating good quality. Three trials were rated a 4/7, one 5/7 and one 6/7. Despite the relatively good quality scores, there were some notable methodological issues with the included studies. Blinded assessment of outcomes was reported only in one trial and in the others it was unclear. Given that the outcome measures were subjective, un-blinded outcome assessment might leave the studies open to measurement bias. Allocation concealment was judged as adequate in one trial and inadequate in another, while in the other three this information was unclear. The drop-out rate in the trials ranged from 18% to 28%, except one trial where no drop-out was reported. The trial with the highest drop-out rate did not use ITT analysis.

Effectiveness results

The review conducted a meta-analysis including the five trials with a total of 221 participants. A SMD and a weighted mean difference (WMD) were used respectively for the overall pooled EPDS score immediately post-treatment. Exercise reduced symptoms of PND significantly compared with no exercise (SMD = -0.81, 95%CI -1.53 to -0.10; WMD = -4.00, 95%CI -7.64 to -0.35). However, there was significant heterogeneity between trials. When excluding the trial that included exercise as a co-intervention with social support, the effect sizes were reduced and not significant (SMD = -0.42, 95%CI -0.90 to 0.05; WMD = -2.03, 95%CI -4.34 to 0.29), and significant heterogeneity between trials was no longer found. The review authors stated that all the trials reported very good attendance at exercise classes or adherence to exercise intervention guidelines.

Summary

Overall, based on all available data from small studies with limited methodological quality, the pooled estimate suggested that exercise reduced post-natal depression scores measured immediately post-intervention compared with social support or standard care. This pooled overall effect had high variance and was contingent on the inclusion of data from a trial which was significantly heterogeneous from the others and in which exercise was used as a co-intervention. Exercise also seemed to have good compliance in PND, however, the reliability of this finding was also hampered by the weakness of the quality of evidence. The effect of exercise beyond the completion of the intervention was unclear.

Conclusions

Exercise seems to reduce symptom severity of depression in adults, when based on all available data compared to no treatment or placebo at post-treatment or a longer follow up duration, however, no effect is seen when based on a small number of methodologically sound trials only, although this could be due to insufficient power. Of the findings, measured as standardised mean differences, it is unclear how clinically meaningful the changes in the overall effect sizes are.

Due to heterogeneity and small sample sizes the effect of exercise on symptom score of post-natal depression is unclear.

Overall, there is some uncertainty in the effect of physical activity for the treatment of depression in adults or post-natal depression.

References

1. Mead GE, Morley W, Campbell P, Greig CA, McMurdo M. Lawlor DA. Exercise for depression. Cochrane Database of Systematic Reviews. (3):CD004366, 2009.

2. Daley A, Jolly K, MacArthur C. The effectiveness of exercise in the management of post-natal depression: systematic review and meta-analysis. Family Practice 2009; 26: 154–162.

3. Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: Systematic review and meta-regression analysis of randomised controlled trials. BMJ 2001;322 (7289):763–67

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 exercise.mp. or exp Exercise/
2 exercising.mp.
3 physical activity.mp.
4 sport$.mp. or exp Sports/
5 fitness.mp. or exp Physical Fitness/
6 gym$.mp.
7 exp Exercise Therapy/
8 or/1-7
9 exp Depression/ or depression.mp.
10 depressed.mp.
11 or/9-10
12 8 and 11
13 limit 12 to "reviews (specificity)"

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Appendix B – Literature search results

Systematic reviews

Source – Cochrane Library (Wiley) 2010 Issue 8 (CDSR)

Mead GE, Morley W, Campbell P, Greig CA, McMurdo M, Lawlor DA Exercise for depression Cochrane Database of Systematic Reviews: Reviews 2009 Issue 3 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD004366.pub4; 2009: 3: John Wiley & Sons, Ltd http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004366/frame.html

Dong BR, He P, Lu Z, Wu T, Liu GJ, Huang CQ. Exercise for older depressed people (protocol). Cochrane Database of Systematic Reviews: Protocols 2008 Issue 3 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD007317; 2008; 3 John Wiley & Sons, Ltd http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD007317/frame.html

Mirza I, Pit SW. Exercise for positive mental health outcomes in adults (protocol). Cochrane Database of Systematic Reviews: Protocols 2006 Issue 1 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD005615; 2006: 1 John Wiley & Sons, Ltd http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD005615/frame.html

Dennis CL, Allen K. Interventions (other than pharmacological, psychosocial or psychological) for treating antenatal depression. Cochrane Database of Systematic Reviews: Reviews 2008 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD006795.pub2; 2008: 4 John Wiley & Sons, Ltd http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD006795/frame.html

Chi I , Jordan-Marsh M, Guo M , Xie B, Zhang M. Tai Chi for depression. Cochrane Database of Systematic Reviews: Protocols 2008 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD007143; 2008: 2 John Wiley & Sons, Ltd http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD007143/frame.html

Source – Cochrane Library (Wiley) 2010 Issue 3 (DARE)

Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials (Structured abstract). BMJ 2001; 322: 763-767 http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12001001020/frame.html

Daley A, Jolly K, MacArthur C. The effectiveness of exercise in the management of post-natal depression: systematic review and meta-analysis (Structured abstract). Family Practice 2009; 26(2): 154-162 http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12009104133/frame.html

Tsang HW, Chan EP, Cheung WM. Effects of mindful and non-mindful exercises on people with depression: a systematic review (Structured abstract). British Journal of Clinical Psychology 2008; 47(3): 303-322 http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12008105668/frame.html

Sjosten N, Kivela S L. The effects of physical exercise on depressive symptoms among the aged: a systematic review (Structured abstract) International Journal of Geriatric Psychiatry 2006; 21(5): 410-418 http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12006002327/frame.html

Kugler J, Seelbach H, Kruskemper GM. Effects of rehabilitation exercise programmes on anxiety and depression in coronary patients: a meta-analysis (Structured abstract) British Journal of Clinical Psychology 1994; 33(3): 401-10
http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-11995005057/frame.html

Stathopoulou G, Powers M B, Berry AC, Smits JA, Otto MW. Exercise interventions for mental health: a quantitative and qualitative review (Structured abstract) Clinical Psychology: Science and Practice 2006; 13(2): 179-193
http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12006002281/frame.html

Coventry PA, Gellatly JL. Improving outcomes for COPD patients with mild-to-moderate anxiety and depression: a systematic review of cognitive behavioural therapy (Structured abstract). British Journal of Health Psychology 2008; 13(3): 381-400
http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12009100320/frame.html

Dunn AL, Trivedi MH, O'Neal HA. Physical activity dose-response effects on outcomes of depression and anxiety (Structured abstract). Medicine and Science in Sports and Exercise 2001; 33(Supplement 6): S587-S597
http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12001004385/frame.html

Pilkington K, Kirkwood G, Rampes H, Richardson J. Yoga for depression: the research evidence (Structured abstract) Journal of Affective Disorders 2005; 89(1-3): 13-24
http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12006006064/frame.html

Source - Ovid MEDLINE(R) 1950 to July Week 4 2010

Blake H, Mo P, Malik S, Thomas S. How effective are physical activity interventions for alleviating depressive symptoms in older people? A systematic review. Clinical Rehabilitation. 2009; 23(10):873-87.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=fulltext&D=medl&AN=19675114

Rethorst CD, Wipfli BM, Landers DM. The antidepressive effects of exercise: a meta-analysis of randomized trials. Sports Medicine. 2009; 39(6):491-511.

Daley A. Exercise and depression: a review of reviews. [Review] [59 refs] Journal of Clinical Psychology in Medical Settings. 15(2):140-7, 2008 Jun.

Karmisholt K, Gotzsche PC. Physical activity for secondary prevention of disease. Systematic reviews of randomised clinical trials. [Review] [44 refs] Danish Medical Bulletin.2005; 52(2):90-4
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=fulltext&D=med4&AN=16009053

Frazer CJ, Christensen H, Griffiths KM. Effectiveness of treatments for depression in older people. [Review] [64 refs] Medical Journal of Australia. 2005; 182(12):627-32.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=fulltext&D=med4&AN=15963019

Dennis CL. Treatment of postpartum depression, part 2: a critical review of nonbiological interventions. Journal of Clinical Psychiatry. 2004; 65(9):1252-65.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=fulltext&D=med4&AN=15367054

North TC, McCullagh P, Tran ZV. Effect of exercise on depression. Exercise & Sport Sciences Reviews. 1990;18:379-415. Link to the Ovid Full Text or citation
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=fulltext&D=med3&AN=2141567

Other reviews

Source - Trip database

Teychenne M, Ball K, Salmon J. Physical activity and likelihood of depression in adults: a review. Prev Med 2008; 46(5): 397-411 http://www.ncbi.nlm.nih.gov/pubmed/18289655?dopt=Abstract

Guidance

Source – NICE website

The treatment and management of depression in adults NICE Clinical Guideline 90 CG90 National Institute of Health and Clinical Excellence London: NICE Guidance; 2009 (partially replaces Clinical Guideline 23) http://www.nice.org.uk/nicemedia/live/12329/45888/45888.pdf

Depression: the treatment and management of depression in adults. Final draft. National Collaborating Centre for Mental Health for NICE; 2009 CG90 http://www.nice.org.uk/nicemedia/live/12329/45896/45896.pdf See section 7.3 Physical activity programmes

Source - National Library of Guidelines

Non-pharmaceutical management of depression in adults. A national clinical guideline. Scottish Intercollegiate Guidelines Network Edinburgh: SIGN; 2010 http://www.sign.ac.uk/pdf/sign114.pdf See section 5 Exercise and lifestyle modification and Annex 3.

Source - Trip database

Exercise referral systems: A National Quality Assurance Framework Department of Health London: DOH; 2001 http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4079009.pdf

Primary studies

Source – Cochrane Library (Wiley) 2010 Issue 3 (HTA)

Health Technology Assessment. A pragmatic randomised controlled trial to evaluate exercise prescription as a treatment for depression (TREAD) (Project record) Health Technology Assessment 2006 Southampton: NCCHTA http://www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-32006001314/frame.html

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Archived ARIF Request

Prevention
Depression in Adults

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in August 2005.

The Problem Submitted for ARIF to Advise Upon:

Can depression be prevented in adults?

See related requests: Can mental illness be prevented?, Can depression be prevented in children and adolescents?, Can postnatal depression be prevented?, Can eating disorders be prevented?

Reviews Identified

- Cole MG, Dendukuri N. The feasibility and effectiveness of brief interventions to prevent depression in older subjects: a systematic review. International Journal of Geriatric Psychiatry. 2004; 19(11):1019-25

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Comments

This review by Cole aimed to explore brief (less than 12 weeks) interventions to prevent depression in older adults with a mean age of 50 years or more. The review was conducted systematically and was of reasonable quality.

The review included 10 trials, with a total of 1,075 subjects. The authors report the results simply, using tables to describe the trials individually.

Three trials found that the intervention reduced depression incidence with cognitive behavioural techniques being a common element. There was one trial in which the incidence of depression was increased in the intervention group. This was a weekly bereavement support group where the incidence of depression was 45% in the intervention group and 28% in the control. This was a relatively small trial with 127 participants.

This review suggests that some brief interventions to prevent depression in older people are feasible. However, the evidence base is weak, with a limited number of trials many of which were thought to be

of poor quality by the systematic review identified.

Request Carried Out: August 2005

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Archived ARIF Request

Prevention
Depression in Children and Adolescents

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in August 2005.

The Problem Submitted for ARIF to Advise Upon:

Can depression be prevented in children and adolescents?

See related requests: Can mental illness be prevented?, Can postnatal depression be prevented?, Can depression be prevented in adults?, Can eating disorders be prevented?

Reviews Identified

- Merry S, McDowell H, Hetrick S, Bir J, Muller N. Psychological and/or educational interventions for the prevention of depression in children and adolescents. The Cochrane Database of Systematic Reviews: Reviews 2004 Issue 2 John Wiley & Sons, Ltd Chichester , UK

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Comments

This was a Cochrane review with the aim to determine whether psychological and/or educational interventions (both universal and targeted) were effective in reducing the risk of a depressive disorder and whether an effective intervention could prevent depression up to 3 years post intervention. It is a well conducted systematic review.

A total of 21 RCTs met the inclusion criteria, with a population age range from 5 to 19 years old. The main outcome sought was a reduction in depressive symptoms on pre-post assessment or a reduction in the onset of depressive symptoms.

The review authors state “ the results of this review are encouraging but the implementation of depression prevention programmes would be premature until further data are available which compare intervention to a placebo group and until a lasting effect for the programmes is demonstrated”.

Request Carried Out: August 2005

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Archived ARIF Request

Dextropopoxyphene Detoxification Opiate Addiction

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in November 1998.

The Problem Submitted for ARIF to Advise Upon:

Is there any evidence on the effectiveness of dextropopoxyphene in the management of detoxification for opiate addiction?

Reviews Identified

None identified.

Trials Identified

- Janinski DR, Pevnick JS, Clark CC, Griffith JD. Therapeutic usefulness of propoxyphene napsylate in narcotic addiction. Archives of General Psychiatry 1977; 34: 227-233
- Wang RI, Kochar C, Hasegawa AT, Byung LR. Propoxyphene napsylate compared to methadone for opiate dependence. Psychopharmacology 1981; 75: 335-338
- Woody GE, Mintz J, Tennant F et al. Propoxyphene for maintenance treatment of narcotic addiction.Archives of General Psychiatry 1981; 38: 898-900
- Tennant FS, Russell BA, Casas SK, Bleich RN. Heroin detoxification. A comparison of propoxyphene and methadone. JAMA 1975; 232 (10): 1019-1022

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Comments

No reviews were identified. However, we identified a substantial body of potentially relevant primary studies which ranged from case series to randomised controlled trials, dating from the mid 1970s to the mid 1980s. No recent trials or other studies appear to have been published.

The first two trials cited look specifically at the safety and efficacy of dextropopoxyphene in this context. Both are very small and their results should be interpreted cautiously. Their findings suggest that oral dextropopoxyphene does represent an effective option for detoxification when given in high doses, but adverse effects are common.The latter two trials cited consider the effectiveness of dextropopoxyphene relative to that of methadone. Both trials are somewhat dated but are of good size, and are reasonably

well-conducted, double blind randomised controlled trials. Together they demonstrate that dextropopoxyphene is probably less effective than methadone in the prevention of withdrawal symptoms and is associated with higher dropout rates. No significant differences were observed between the groups for adverse effects, nor for abstinence levels at one and six months after treatment.

In summary, at this time there does not appear to be a solid evidence base to support the use of dextropopoxyphene over methadone in the management of detoxification.

Additional information relevant to this request is available in the request entitled "Buprenorphine - Detoxification/Opiate Addiction"

Request Carried Out: November 1998

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Archived ARIF Request

Population Registers
Diabetes Mellitus

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in November 1997.

The Problem Submitted for ARIF to Advise Upon:

What is the evidence that population registers for diabetes at a district level are effective in improving patient care and disease outcomes?

Question Reformulated

This is a complex question. With knowledge of the specific population register being proposed and on the basis that there is increasing evidence confirming that good diabetic control and early identification of complications is effective, it was simplified thus:

- Population/condition: Any person resident in a particular health authority area with a diagnosis of diabetes mellitus (IDDM + NIDDM)
- Intervention: Ascertainment and updating a central record with the identities and locations of all individuals with diabetes mellitus (particularly through aggregation of individual GP registers of patients with diabetes mellitus) to facilitate systematic recall and examination
- Outcomes:
  - Coverage: proportion of all known diabetics being regularly examined in key respects e.g.
    - Glycaemic control
    - Blood Pressure
    - State of Retina
  - Cost to achieve above

Reviews Identified

- Griffin S, Kinmonth AL. Diabetes care: the effectiveness of systems for routine surveillance for people with diabetes. In: Williams R, Bennett P, Nicolucci A, Krans HMJ, Ramirez G (eds) Diabetes Module of The Cochrane Database of Systematic Reviews, [updated 01 September 1997]. Available in The Cochrane Library [database on disk and CD-ROM]. The Cochrane Collaboration; Issue 4. Oxford: Update Software; 1997. Updated quarterly.
- Greenhalgh PM. Shared care for diabetes: a systematic review. London: Royal College of General Practitioners, 1994. Pp 35
- Dawson A, Ferrero M (eds). Chronic disease management registers. Proceedings of a conference. London: HMSO, 1996, pp 157

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Comments

No directly relevant systematic reviews were identified.

The first two reviews, which are systematic in approach, provide some indirect support for a hypothesis that structured care, including organised recall, does lead to more complete follow-up of patients with diabetes. The third review provides useful general background.

The bottom line is that it is not true to say that population registers for diabetes have no evidence base. However, it is weak, suggesting the need for further direct evaluations of the ability of population registers to better identify individuals who would benefit from surveillance and increase the length of time these individuals are actually kept under observation.

Request Carried Out: November 1997

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Effectiveness of Pioglitazone versus Incretin enhancers or Incretin mimics

Synopsis

Question:	Is there evidence that pioglitazone (a glitazone) is a more effective second line therapy than newer drugs e.g. Incretin enhancers (DPP-4 inhibitors) and Incretin mimics (GLP-1 analogues) in controlling HbA1c in adults with type 2 diabetes?
Evidence Identified:	National Collaborating Centre for Chronic Conditions. Type 2 diabetes: national clinical guideline for management in primary and secondary care (update). London: Royal College of Physicians, 2008
Comments:	The NICE review that informed the NICE guideline 87 regarding the use of these drugs in the patient pathway is probably the most recent and relevant review at the present time. Of the two trials that were identified that compared a thiazolidinedione against the more recent drugs incretin enhancers and incretin mimics, only one trial involved pioglitazone. Powered to detect non-inferiority the mean change difference of HbA1c between the groups was -0.10% (95%CI-0.05, -0.26). More head to head comparisons are required to give a more accurate assessment of the place of pioglitazone in the patient pathway of type 2 diabetes compared to incretin enhancers and incretin mimics.
Date Completed:	September 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Effectiveness of Pioglitazone versus incretin enhancers or incretin mimics

Request completed: September 2010

Question

Is there evidence that pioglitazone (a glitazone) is a more effective second line therapy than newer drugs e.g. incretin mimics and incretin enhancers in controlling HbA1c in adults with type 2 diabetes.

Question clarification

This report focuses specifically on the effectiveness of pioglitazone in blood glucose control (measured by HbA1c) compared to either an incretin mimic or incretin enhancer. It does not consider the cost effectiveness of the drugs, neither has it investigated safety data.

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol (www.arif.bham.ac.uk/strategy.shtml). Text and index terms were used to represent the population and the intervention. Sources were searched from their inception to September 2010. No language restriction was applied to the searches. As an example, the MEDLINE search can be found in Appendix A. The following criteria were used for study selection:

Population/ setting	Adult patients with type 2 diabetes, uncontrolled on metformin, a sulphonylurea or a combination of both.
Intervention	*Pioglitazone (Actos®)* a thiazolidinedione (glitazone).
Comparator	• Incretin mimics (GLP-1 analogues) [*Exenatide - Byetta® Liraglutide® NN2211 not licensed in the UK*]. • Incretin enhancers (DPP-4 inhibitors, gliptins). [*Sitagliptin - Januvia® and Vildagliptin - Galvus®*].
Outcome	HbA1c (treatment aim 6.5% to 7.5%)[1]
Study design	Systematic reviews and health technology assessments.

Results

Full search results can be found in Appendix B.

The most relevant review identified[2] was undertaken under the auspices of the NICE guideline development group. It informed recommendations given in Guideline 87[1], which was a partial update of Guideline 66.[3] The review and guideline consider how thiazolidines, incretin mimics and

incretin enhancers should be used in the patient treatment pathway, particularly focusing on these drugs as second and third line therapies. The review is divided into chapters, which each class of drug afforded a separate chapter. The review also considered cost effectiveness and has incorporated a de novo economic model, however, this report has not appraised this part of the review.

The review of clinical effectiveness data was reasonably well conducted, using appropriate systematic review methodology. Searches were up to April 2008. Patients of interest were adults, diagnosed with type 2 diabetes, excluding women with gestational diabetes.

Studies were included if they compared either:

- long-acting insulin analogues (insulin glargine and insulin detemir),
- incretin mimics (exenatide and liraglutide),
- incretin enhancers (sitagliptin and vildagliptin),
- and thiazolidinediones (rosiglitazone and pioglitazone),

with oral glucose lowering medications (metformin or sulphonylurea) used alone or in combination and/or intermediate acting, long acting or biphasic (premix) insulins.

Outcomes assessed were blood glucose control (changes in blood glucose control, changes in HbA1c levels and the frequency and severity of hypoglycaemic episodes), weight control, long term diabetic complications (microvascular e.g. retinopathy, nephropathy, macrovascular e.g. heart disease, stroke), adverse events, health related quality of life, mortality and economic aspects.

Review results

The review identified two trials that were head to head comparisons. Both compared an incretin enhancer to a thiazolidinedione adjunct to metformin. No head to head trials were identified that compared a thiazolidinedione with an incretin mimic.

The first trial (Bolli 2008) was a 24 week non-inferiority trial and included 567 patients whose control on metformin monotherapy was inadequate (HbA1c 7.5% to 11%). Patients were aged between 18 and 75 years and had had diabetes for an average of 6.4 years. The comparisons were:

- Incretin enhancer (vildagliptin) + metformin vs. glitazone (pioglitazone) + metformin.

The mean change of HbA1c from baseline of vildagliptin + metformin was -0.88% compared to a change of -0.98% for the pioglitazone + metformin group. The mean change difference of HbA1c between the groups was -0.10% (95%CI-0.05, -0.26). As the trial was powered to detect a non-inferiority result, it can be concluded that vildagliptin was not inferior to pioglitazone.

The second trial (Scott 2007) was an 18 week trial and included 273 patients, again whose HbA1c was inadequately controlled on metformin monotherapy (HbA1c between 7% to 11%). Patients were aged between 18 and 77 years and had had diabetes for an average of 5 years. Three comparisons were made:

- Incretin enhancer (sitagliptin) + metformin vs. glitazone (rosiglitazone) + metformin vs. placebo + metformin.

The mean change of HbA1c from baseline of sitagliptin + metformin was -0.76% compared with -0.76% for the rosiglitazone + metformin group. Mean change in the placebo + metformin group was -0.22%. No variance statistics are reported by the review authors.

In both trials, quality assessment was judged as good by the review authors but both trials failed to report methods of randomisation and allocation concealment, leaving both trials potentially at risk from selection bias. In addition the review authors felt that the variance figures for mean change in the Bolli trial were erroneous

Overall, the two trials show that there is very little difference in control of blood glucose between a thiazolidinedione compared to an incretin enhancer. No head to head comparisons were assessed for comparisons with an incretin mimic.

Discussion.

Guideline recommendations.

NICE recommendations regarding the use of these three drug classes are given in Guideline 87.[1] As well as HbA1c results the guideline group recommendations took into account the effect on hypoglycaemic episodes and weight management issues.

The recommendations[1] are not summarised in this report as it was felt that the wording (in the recommendations) was carefully chosen to reflect the nuances in the data, therefore a summary may oversimplify and may misinterpret the recommendations. Recommendations for incretin enhancers can be found on pages 20 to 21 and page 33 for incretin mimics.

Recommendations for the thiazolidinediones can be found on page 28 to 29 of Guideline 87.[1] However, on the 24th September 2010 NICE issued a partial update[4] temporarily withdrawing its recommendations on the use of rosiglitazone. This was due to the decision from the European Medicines Agency(EMA)[5] to suspend the market authorisation of rosiglitazone due to a poor risk/benefit profile of this drug. Further information can be found at the EMA website[5] and also on the UK Medicines and Healthcare products Regulatory Agency (MHRA).[6]

Review limitations.

The NICE review[2] searches were undertaken in 2008, which may mean that there are more recent studies that have investigated head to head comparisons between thiazolidinediones and the incretin enhancers and incretin mimics. The ARIF search identified a systematic review by Phung et al (2010)[7] who had searched for similar studies to those of the NICE review in January 2010, but did not identify any new relevant head to head trials.

Conclusions

The NICE review[2] that informed the NICE guideline 87[1] regarding the use of these drugs in the patient pathway is probably the most recent and relevant review at the present time. Of the two trials that were identified that compared a thiazolidinedione against the more recent drugs incretin enhancers and incretin mimics, only one trial involved pioglitazone. Powered to detect non-inferiority the mean change difference of HbA1c between the groups was -0.10% (95%CI-0.05, -0.26). More head to head comparisons are required to give a more accurate assessment of the place of pioglitazone in the patient pathway of type 2 diabetes compared to incretin enhancers and incretin mimics.

References

1. Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes. NICE short clinical guideline 87. London: NICE; 2009. http://www.nice.org.uk/nicemedia/live/12165/44318/44318.pdf [accessed 6-9-10]

2. National Collaborating Centre for Chronic Conditions. Type 2 diabetes: national clinical guideline for management in primary and secondary care (update). London: Royal College of Physicians, 2008. (see comment below*) http://www.nice.org.uk/nicemedia/live/11983/40803/40803.pdf [accessed 6-9-10]

3. Type 2 diabetes: the management of type 2 diabetes. NICE clinical guideline 66. London: NICE; 2009. http://www.nice.org.uk/nicemedia/pdf/CG66NICEGuideline.pdf [accessed 6-9-10]

4. Type 2 diabetes: newer agents (partial update of CG66). London: NICE; 2010 http://www.nice.org.uk/CG87 [accessed 27-9-10]

5. European Medicines Agency. Recommends suspension of Avandia, Avandamet and Avaglim. Press release. 23 September 2010 EMA/585784. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/09/WC500096996.pdf [accessed 27-9-10]

6. MHRA Press statement: Europe-wide suspension of marketing authorisation for Avanda, Avandamet and Avaglim (rosiglitazone). 23rd September 2010. http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON094121 [accessed 27-9-10]

7. Phung OJ, Scholle JM, Talwar M, Coleman CI. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycaemia in Type 2 diabetes. JAMA Vol. 303. No. 14 2010.

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*This review has now been published and is indexed on Medline as:
Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, *et al.* Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. *Health Technol Assess* 2010;**14**(36).

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 (pioglitazone or actos).mp.
2 diabetes.mp.
3 Diabetes Mellitus, Type 2/
4 2 or 3
5 1 and 4
6 limit 5 to (humans and "reviews (specificity)")

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Appendix B – Literature search results

Literature search results

Systematic reviews

Source – Cochrane Library (CDR) 2010 Issue 8

Richter Bernd, Bandeira-Echtler Elizabeth, Bergerhoff Karla, Lerch Christian. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews: Reviews 2008 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD006739.pub2 http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD006739/frame.html

Richter Bernd, Bandeira-Echtler Elizabeth, Bergerhoff Karla, Clar Christine, Ebrahim Susanne H. Pioglitazone for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews: Reviews 2006 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD006060.pub2 http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD006060/frame.html

Richter Bernd, Bandeira-Echtler Elizabeth, Bergerhoff Karla, Clar Christine, Ebrahim Susanne H. Rosiglitazone for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews: Reviews 2007 Issue 3 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD006063.pub2 http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD006063/frame.html

Source – Cochrane Library (DARE) 2010 Issue 3

Selvin E, Bolen S, Yeh H C, Wiley C, Wilson L M, Marinopoulos S S et al
Cardiovascular outcomes in trials of oral diabetes medications: a systematic review (Structured abstract)
Archives of Internal Medicine 2008; 168 (19): 2070-80

Czoski-Murray C, Warren E, Chilcott J, Beverley C, Psyllaki M A, Cowan J
Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation (Provisional abstract)
Health Technology Assessment 2004; 8 (13): 1-104

Chilcott J, Wight J, Lloyd Jones M, Tappenden P.
The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review (Structured abstract)
Health Technology Assessment 2001; 5 (19): 1-71

Boucher M, McAuley L, Brown A, Keely E, Skidmore B.
Comparative clinical and budget evaluations of rosiglitazone and pioglitazone with other anti-diabetic agents (Provisional abstract)
Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
2003: 1-17

Boucher M, McAuley L, Brown A, Keely E, Skidmore B
Efficacy of rosiglitazone and pioglitazone compared to other anti-diabetic agents: systematic review and budget impact analysis (Structured abstract)
Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
2002: 1-76

Mannucci E, Monami M, Lamanna C, Gensini G F, Marchionni N
Pioglitazone and cardiovascular risk: a comprehensive meta-analysis of randomized clinical trials (Structured abstract)
Diabetes Obesity and Metabolism 2008; 10 (12); 1221-38

Nagajothi N, Adigopula S, Balamuthusamy S, Velazquez-Cecena J L, Raghunathan K, Khraisat A et al.
Pioglitazone and the risk of myocardial infarction and other major adverse cardiac events: a meta-analysis of randomized, controlled trials (Structured abstract)
American Journal of Therapeutics 2008; 15 (6): 506-511

Source – Cochrane Library (HTA database) 2010 Issue 3

National Institute for Clinical Excellence
Guidance on the use of pioglitazone for type 2 diabetes mellitus. London: National Institute for Clinical Excellence (NICE); 2001

Source – MEDLINE (Ovid) 1950 – August week 2 2010

Sarafidis PA, Stafylas PC, Georgianos P, Saratzis AN, Lasaridis AN.
Effect of thiazolidinediones on albuminuria and proteinuria in diabetes: a meta-analysis. [Review] [54 refs]
American Journal of Kidney Diseases. 55(5):835-47, 2010 May.

Clar C, Royle P, Waugh N.
Adding pioglitazone to insulin containing regimens in type 2 diabetes: systematic review and meta-analysis. [Review] [87 refs]
PLoS ONE [Electronic Resource]. 4(7):e6112, 2009.

Loke YK, Singh S, Furberg CD.
Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis.
Comment in: CMAJ. 2009 Apr 14;180(8):841; PMID: 19364797], Comment in: CMAJ. 2009 Jan 6;180(1):16-7; PMID: 19073650]
CMAJ Canadian Medical Association Journal. 180(1):32-9, 2009 Jan 6.

Petrazzi L, Grassi D, Polidoro L, D'Aurelio A, Croce G, Properzi G et al. Cardiovascular risk and cardiometabolic protection: role of glitazones. [Review] [100 refs]
Journal of Nephrology. 21(6):826-35, 2008 Nov-Dec.

Eleftheriadou I, Grigoropoulou P, Katsilambros N, Tentolouris N.
The effects of medications used for the management of diabetes and obesity on postprandial lipid metabolism. [Review] [127 refs]
Current Diabetes Reviews. 4(4):340-56, 2008 Nov.

Pinelli NR, Cha R, Brown MB, Jaber LA.
Addition of thiazolidinedione or exenatide to oral agents in type 2 diabetes: a meta-analysis.
Annals of Pharmacotherapy. 42(11):1541-51, 2008 Nov.

Khanderia U, Pop-Busui R, Eagle KA.
Thiazolidinediones in type 2 diabetes: a cardiology perspective. [Review] [64 refs]
Comment in: Ann Pharmacother. 2009 Feb;43(2):391-2; author reply 392-3; PMID: 19193598]
Annals of Pharmacotherapy. 42(10):1466-74, 2008 Oct.

Gagliardino JJ, Santoro S, Arellano S, Di Girolamo G.
New treatments for type 2 diabetes mellitus: combined therapy with sitagliptin. [Review] [81 refs]

Expert Opinion on Pharmacotherapy. 9(9):1495-507, 2008 Jun.
Betteridge DJ, DeFronzo RA, Chilton RJ.
PROactive: time for a critical appraisal. [Review] [97 refs]
European Heart Journal. 29(8):969-83, 2008 Apr.

Norris SL, Carson S, Roberts C.
Comparative effectiveness of pioglitazone and rosiglitazone in type 2 diabetes, prediabetes, and the metabolic syndrome: a meta-analysis.
Current Diabetes Reviews. 3(2):127-40, 2007 May.

Zerilli T, Pyon EY.
Sitagliptin phosphate: a DPP-4 inhibitor for the treatment of type 2 diabetes mellitus. [Review] [48 refs]
Comment in: Clin Ther. 2008 Apr;30(4):785-6; author reply 786; PMID: 18498926]
Clinical Therapeutics. 29(12):2614-34, 2007 Dec.

Lago RM, Singh PP, Nesto RW.
Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. [Review] [49 refs]
Comment in: Lancet. 2007 Sep 29;370(9593):1101; PMID: 17905143], Comment in: ACP J Club. 2008 Mar-Apr;148(2):39; PMID: 18311869], Comment in: Lancet. 2007 Sep 29;370(9593):1103-4; PMID: 17905146]
Lancet. 370(9593):1129-36, 2007 Sep 29.

Lincoff AM, Wolski K, Nicholls SJ, Nissen SE.
Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials.
Comment in: JAMA. 2007 Sep 12;298(10):1216-8; PMID: 17848659]
JAMA. 298(10):1180-8, 2007 Sep 12.

Schneider CA.
Improving macrovascular outcomes in type 2 diabetes: Outcome studies in cardiovascular risk and metabolic control. [Review] [94 refs]
Current Medical Research & Opinion. 22 Suppl 2:S15-26, 2006.

Goldberg RB.
Impact of thiazolidenediones on serum lipoprotein levels. [Review] [54 refs]
Current Atherosclerosis Reports. 8(5):397-404, 2006 Sep.

Sarafidis PA, Nilsson PM.
The effects of thiazolidinediones on blood pressure levels - a systematic review. [Review] [127 refs]
Blood Pressure. 15(3):135-50, 2006.

Rajagopalan R, Xu Y, Abbadessa M. Quartet Study Group.
The effect of pioglitazone on glycemic and lipid parameters and adverse events in elderly patients with type 2 diabetes mellitus: a post hoc analysis of four randomized trials.
American Journal of Geriatric Pharmacotherapy. 4(2):123-33, 2006 Jun.

Lester JW, Fernandes AW.
Pioglitazone in a subgroup of patients with type 2 diabetes meeting the criteria for metabolic syndrome.
International Journal of Clinical Practice. 59(2):134-42, 2005 Feb.

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Diabetologia. 48(3):553-60, 2005 Mar.

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Cardiovascular effects of treatment of type 2 diabetes with pioglitazone, metformin and gliclazide.
International Journal of Clinical Practice. 58(9):833-7, 2004 Sep.

Chiquette E, Ramirez G, Defronzo R.
A meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors.
Archives of Internal Medicine. 164(19):2097-104, 2004 Oct 25.

Buse JB, Tan MH, Prince MJ, Erickson PP.
The effects of oral anti-hyperglycaemic medications on serum lipid profiles in patients with type 2 diabetes. [Review] [90 refs]
Diabetes, Obesity & Metabolism. 6(2):133-56, 2004 Mar.

Source – EMBASE (Ovid) 1980 – week 32 2010

Diener H.C.
Diabetes mellitus type 2: Aggressive reduction of blood glucose levels - A meta-analysis of randomized studies. [German]
Arzneimitteltherapie 2010; 28 (1) : 25-26.

Meta-analysis finds antidiabetic drugs lower glucose similarly when added to metformin in type 2 diabetes mellitus.
Formulary 2010; 45 (5): 146

Guidelines

Source – NICE web site

Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes. NICE short clinical guideline 87. London: NICE; 2009. http://www.nice.org.uk/nicemedia/live/12165/44318/44318.pdf

National Collaborating Centre for Chronic Conditions. Type 2 diabetes: national clinical guideline for management in primary and secondary care (update). London: Royal College of Physicians, 2008.
http://www.nice.org.uk/nicemedia/live/11983/40803/40803.pdf

Economic evaluations

Source – Cochrane Library (EED) 2010 Issue 3

Neeser K, Lubben G, Siebert U, Schramm W
Cost effectiveness of combination therapy with pioglitazone for type 2 diabetes mellitus from a German statutory healthcare perspective
Pharmacoeconomics 2004; 22 (5): 321-41

Brandle M, Goodall G, Erny-Albrecht K M, Erdmann E, Valentine W F
Cost-effectiveness of pioglitazone in patients with type 2 diabetes and a history of macrovascular disease in a Swiss setting
Swiss Medical Weekly 2009; 139 (11-12): 173-84

Scherbaum W A, Goodall G, Erny-Albrecht K M, Massi-Benedetti M, Erdmann E
Valentine W J.
Cost-effectiveness of pioglitazone in type 2 diabetes patients with a history of macrovascular disease: a German perspective
Cost Effectiveness and Resource Allocation 2009; 7: article 9

Shearer A T, Bagust A, Liebl A, Schoeffski O, Goertz A
Cost-effectiveness of rosiglitazone oral combination for the treatment of type 2 diabetes in Germany
Pharmacoeconomics 2006; 24 (suppl 1)) 35-48

Grossman L D, Longo C J,
Economic benefits of pioglitazone for treating patients with Type 2 diabetes
Expert Review of Pharmacoeconomics and Outcomes Research 2004; 4 (2): 135-42

Umpierrez G, Issa M, Vlajnic A
Glimepiride versus pioglitazone combination therapy in subjects with type 2 diabetes inadequately controlled on metformin monotherapy: results of a randomized clinical trial (Structured abstract)
Current Medical Research and Opinion 2006; 22 (4): 751-59

Valentine W J, Tucker D, Palmer A J, Minshall M E, Foos V, Silberman C
Long-term cost-effectiveness of pioglitazone versus placebo in addition to existing diabetes treatment: a US analysis based on PROactive
Value in Health 2009; 12 (1): 1-9

Tunis SL, Minshall ME, St.Charles M, Pandya BJ, Baran RW
Pioglitazone versus rosiglitazone treatment in patients with type 2 diabetes and dyslipidemia: cost-effectiveness in the US (Provisional abstract)
Current Medical Research and Opinion 2008; 24 (11): 3085 - 96

Valentine W J, Bottomley J M, Palmer A J, Brandle M, Foos V, Williams R et al.
PROactive 06: cost-effectiveness of pioglitazone in Type 2 diabetes in the UK Diabetic Medicine 2007; 24 (9): 982-1002

Kalsekar I, Iyer S, Mody R, Rajagopalan R, Kavookjian J
Utilization and costs for compliant patients initiating therapy with pioglitazone or rosiglitazone versus insulin in a Medicaid fee-for-service population
Journal of Managed Care Pharmacy; 2006 12 (2): 121-129

Background information

Source NHS Clinical Knowledge Service

Evidence on gliptins
http://www.cks.nhs.uk/diabetes_type_2/evidence/supporting_evidence/antidiabetic_drugs/gliptins_dipeptidylpeptidase_dpp_4_inhibitors

Evidence on glitazones
http://www.cks.nhs.uk/diabetes_type_2/evidence/supporting_evidence/antidiabetic_drugs/glitazones

Source –NHS Evidence

Verdict and summary. Pioglitazone. (MTRAC) Midlands Therapeutics Review and Advisory Committee. Keele: Keele University; 2008.

http://195.62.199.219/pctsla/mtrac/productinfo/verdicts/P/Pioglitazone2.pdf

Scottish Medicines Consortium. Pioglitazone. 2007.
http://www.scottishmedicines.org.uk/files/pioglitazone%2015mg%2030mg%2045mg%20tablets%20(Actos)%20FINAL%20August%202007%20for%20website.pdf

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Archived ARIF Request

Screening Programme Diabetic Eye Disease

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in July 1997.

The Problem Submitted for ARIF to Advise Upon:

What are the effects/effectiveness of alternative arrangements for the screening (or early diagnosis) of diabetic retinopathy?

Question Reformulated

Clear account needs to be taken in considering this question of:

- Populations or groups of patients to which the interventions might be applied
- Precise nature of the interventions (consider variation in the operators of the screening/diagnostic equipment, their location and the equipment that will be used)
- Important outcomes to be achieved
- Coverage of the at risk population, measuring our ability to enrol individuals in the programme
- Yield of true positives, true negatives, false positives and false negatives, measuring the performance of our chosen test/operator/location combination/s
- Clinical outcomes, measuring the ability of the available treatment to improve outcome

Reviews Identified

- Bachmann M, Nelson S. Screening for diabetic retinopathy: a quantitative overview of the evidence applied to the populations of health authorities and boards. Bristol: Health Care Evaluation Unit, 1996. ppi-iii; 456

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Comments

An important point is that there are no trials of the effects of different screening programmes. In their absence, the likely effects of different approaches to screening for diabetic retinopathy needs to be built up from research evidence on coverage of different programmes; test performance of different diagnostic/screening tests; effects of treatment.

There are many reviews of research on this topic; however, at the time of this request the review above was, in ARIF's opinion, by far the best summary of the available research, judged by its systematic

approach.

How the available research evidence is applied requires care however. The implication of the finding that combinations of fundal photography and ophthalmoscopy appear to perform best in terms of accurate identification of disease state, is not necessarily that an existing screening strategy, such as use of optometrists, should be completely changed. Careful appraisal, interpretation and application to the local situation of the relevant research is required; other options to maximise accurate detection of diabetic retinopathy in those already involved in the screening process need to be considered; as will the impact of changes in test/operator/location combinations on coverage.

Coincidentally ARIF notes that a review on the effects of different screening programmes on coverage is in the process of preparation by members of the Cochrane Collaboration: Grimshaw G, Hood E, Baker R, Thompson J, Wilson A. Effective coverage in schemes for diabetic retinopathy screening. [Protocol]. In: Williams, R, Bennett, P, Nicolucci, A, Krans, HMJ, Ramirez,G (eds) Diabetes Module of The Cochrane Database of Systematic Reviews , [updated 05 March 1997]. Available in The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration; Issue 2. Oxford: Update Software; 1997. Updated quarterly.

This is an area prone to need for regular updating as new information is continually becoming available.

Request Carried Out: July 1997

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These pages are maintained by Ann Massey

Dietician advice and dietary change for symptomatic gallstones

Synopsis

Question:	Is dietician advice and dietary change for symptomatic gallstones effective in reducing or abolishing symptoms and in eliminating the need for surgery?
Reviews Identified:	No systematic reviews or health technology assessments were identified.
Comments:	Currently there is no reviewed evidence on the effectiveness of dietician advice and dietary change for symptomatic gallstones in reducing or abolishing symptoms and in eliminating the need for surgery.
Date Completed:	May 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Dietician advice and dietary change for symptomatic gallstones

Request completed: May 2010

Question

Is dietician advice and dietary change for symptomatic gallstones effective in reducing or abolishing symptoms and in eliminating the need for surgery?

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol http://www.arif.bham.ac.uk/strategy.shtml. Text and index terms were used to represent the population and the intervention. Sources were searched from their inception to May 2010. No language restriction was applied to the searches. The MEDLINE search can be found in Appendix A. The following inclusion criteria were used for study search and selection:

Population	Patients with symptomatic gallstones
Intervention	Dietician advice and dietary change without cholecystectomy
Comparator	Any treatments other than dietician advice and dietary change
Outcome	Remission or elimination of symptoms and complications of gallstones; need for cholecystectomy
Study design	Systematic reviews and health technology assessments

Results

No systematic reviews or health technology assessments that answered the question were identified. The search did however identify one review[1] and four primary studies[2-5], which might be somewhat informative to the question and thus are described below. Full search results can be found in Appendix B.

Review

The review was a piece of question-answering information published in August 2007 in TRIP Answers in the TRIP Database, which is an online repository of clinical questions and answers. The question was: '*Is there any evidence that gallstones can be encouraged to dissolve spontaneously providing the patient adheres to a strict diet. Have you any information on the changes of spontaneous remission of symptoms associated with gallstones?*' Five references were cited: an e-Medicine article, a patient information leaflet, an article from GPNotebook, a

primary study data and a MEDLINE abstract. The conclusion in the answer was: "*Although we found numerous studies examining diet as a risk factor for the development of gallstones, we found little information on diet therapy to treat patients with gallstones.*" (For details see www.tripanswers.org/answer.aspx?qid=2789). Given the nature of the TRIP Database no information was provided enabling an assessment of the review's methodology.

Primary studies

Three of the four primary studies were all small randomised controlled trials (RCTs) investigating the effect of dietary intervention on gallstones: one looked at the effect of diet on recurrence of treated gallstones,[3] and two looked at the effect of diet on bile acid kinetics in patients with gallstones.[4-5] The fourth was a Russian study with limited information about its study design, population, intervention and outcome in its English abstract.[2] As such, none of these appear to address the specific question of this report. Table 1 below outlines the intervention, population and outcome measure of the studies.

Table 1. Outline characteristics of the primary studies

Study	Study design	Population	Intervention/comparator	Outcome
Kurbanov, 2003[2]	?	Obese patients with gallstones and impaired glucose tolerance; n =?	• Lower glycaemic index diet (?) • Caloric reduction diet (?)	Clinico-metabolic parameters (?)
Hood, 1993[3]	RCT	Patients with complete gall stone dissolution (were in gallstone free interval at trial entry); n = 93	• Low does ursodeoxycholic acid • Placebo • High fibre, low refined carbohydrate diet	Gall stone recurrence, timing and frequency of recurrence and its association with biliary symptoms
Frenkiel, 1986[4]	RCT	Patients with radiolucent gallstones (excluded patients who had biliary colic or cholecystitis within one month before randomisation); n = 69	Ursodeoxycholic acid and specific dietary alterations: • Standard cholesterol (500 mg/day) • Low-cholesterol (250 mg/day) • Added-bran (30 g/day) • Substituted medium-chain triglycerides oil (20% of fat)	Bile-acid kinetics; secretion of biliary lipids
Thornton, 1983[5]	RCT (cross-over)	Patients with probable cholesterol gall stone formation; n = 13	• Refined carbohydrate foods • Unrefined carbohydrate foods	Lipid composition of duodenal bile and bile acid kinetics

Conclusions

Currently there is no reviewed evidence on the effectiveness of dietician advice and dietary change for symptomatic gallstone in reducing or abolishing symptoms and in eliminating the need for surgery. Serendipitous identification of some primary studies appears to indicate that the evidence base is very limited and that questions answered with regard to dietary interventions in patients with gallstones are for the most part focused on bile acid secretion and kinetics.

References

1. Is there any evidence that gallstones can be encouraged to dissolve spontaneously providing the patient adheres to a strict diet. Have you any information on the chance of spontaneous remission of symptoms associated with gallstones? Available at: http://www.tripanswers.org/Answer.aspx?qid=2789. [Accessed: 19-05-2010]

2. Kurbanov SK. Optimization of diet therapy in patients with gallstones complicated with obesity and impaired glucose tolerance. [Russian] Voprosy Pitaniia 2003,72(5):22-4

3. Hood KA, Gleeson D, Ruppin DC, Dowling RH. Gall stone recurrence and its prevention: the British/Belgian Gall Stone Study Group's post-dissolution trial. Gut 1993,34(9):1277-88.

4. Frenkiel PG, Lee DW, Cohen H, Gilmore CJ, Resser K, Bonorris GG et al. The effect of diet on bile acid kinetics and biliary lipid secretion in gallstone patients treated with ursodeoxycholic acid. American Journal of Clinical Nutrition 1986,43(2):239-50.

5. Thornton JR, Emmett PM, Heaton KW. Diet and gall stones: effects of refined and unrefined carbohydrate diets on bile cholesterol saturation and bile acid metabolism. Gut 1983,24(1):2-6.

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 (gallstone$ or gall stone$).tw.
2 Gallstones/
3 or/1-2
4 (diet$ or food$ or nutrition).tw.
5 Diet/
6 diet therapy/
7 Nutrition Therapy/
8 or/4-7
9 3 and 8)
10 limit 9 to "reviews (optimized)" (190)
11 limit 9 to "therapy (specificity)" (53)

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Appendix B – Literature search results

Systematic reviews

Source – MEDLINE (Ovid) 1950 – April week 4 2010

Mendez-Sanchez N, Zamora-Valdes D, Chavez-Tapia NC, Uribe M.
Role of diet in cholesterol gallstone formation. [Review]
Clinica Chimica Acta. 376(1-2):1-8, 2007 Feb.

Tseng M, Everhart JE, Sandler RS.
Dietary intake and gallbladder disease: a review. [Review]
Public Health Nutrition. 2(2):161-72, 1999 Jun.

Other reviews

Source – TRIP Database

Is there any evidence that gallstones can be encouraged to dissolve spontaneously providing the patient adheres to a strict diet. Have you any information on the chance of spontaneous remission of symptoms associated with gallstones?
http://www.tripanswers.org/Answer.aspx?qid=2789

Primary studies

Source – MEDLINE (Ovid) 1950 – April week 4 2010

Kurbanov SK.
Optimization of diet therapy in patients with gallstones complicated with obesity and impaired glucose tolerance. [Russian]
Voprosy Pitaniia. 72(5):22-4, 2003.

Moran S, Uribe M, Prado ME, de la Mora G, Munoz RM, Perez MF et al.
Effects of fiber administration in the prevention of gallstones in obese patients on a reducing diet. A clinical trial. [Spanish]
Revista de Gastroenterologia de Mexico. 62(4):266-72, 1997 Oct-Dec.

Hood KA, Gleeson D, Ruppin DC, Dowling RH.
Gall stone recurrence and its prevention: the British/Belgian Gall Stone Study Group's post-dissolution trial.
Gut. 34(9):1277-88, 1993 Sep.

Frenkiel PG, Lee DW, Cohen H, Gilmore CJ, Resser K, Bonorris GG et al.
The effect of diet on bile acid kinetics and biliary lipid secretion in gallstone patients treated with ursodeoxycholic acid.
American Journal of Clinical Nutrition. 43(2):239-50, 1986 Feb.

Arffmann S, Hojgaard L, Giese B, Krag E.
Effect of oat bran on lithogenic index of bile and bile acid metabolism.
Digestion. 28(3):197-200, 1983.

Thornton JR, Emmett PM, Heaton KW.

Diet and gall stones: effects of refined and unrefined carbohydrate diets on bile cholesterol saturation and bile acid metabolism.
Gut. 24(1):2-6, 1983 Jan.

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Archived ARIF Request

Diphosphonates Osteoporosis

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in June 1996.

The Problem Submitted for ARIF to Advise Upon:

A policy for treating osteoporosis is to be developed, therefore: Which patients should be treated with diphosphonates for verified osteoporosis and what role does bone densitometry have in assessment?

Question Reformulated

Important additional elements of the question were identified as follows:

INTERVENTION

1. Type of diphosphonate
2. Dose
3. Duration of treatment

POPULATION

1. Any person (male/female)
2. High risk (however defined - historical risk factors, bone densitometry, symptoms and signs, plain x-rays or biochemical makers)
3. Established clinical osteoporosis

OUTCOME

1. Fragility fractures
2. Bone mass

In relation to outcomes, use of bone mass as an outcome alone was not thought acceptable as its relationship with fragility fracture is highly likely to be confounded by other factors such as physical inactivity/inco-ordination.

Reviews Identified

- Liberman UA et al. Effect of alendronate on bone mineral density and the incidence of fractures in post-menopausal osteoporosis. New England Journal of Medicine 1995;333:1457-1443
- Harris ST et al. Four year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis three years of blinded therapy followed by one year of open therapy. American Journal of Medicine 1993;95:557-567

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Comments

No systematic reviews were identified.

The two references are well conducted randomised trials of the effects of diphosphonates. Bearing in mind that these two trials may not be representative of all research undertaken they suggest:

1. That diphosphonates can reduce the incidence of new vertebral fractures.
2. The amount of any benefit is highly dependent on initial risk.
3. The statistically significant decreases were only identified in patients who had already suffered vertebral fractures prior to starting diphosphonates - i.e. had established osteoporosis.
4. In those patients who were identified as being at risk by bone densitometry alone, the size of benefit in reduced vertebral fractures was very small and could easily have been accounted for by chance.

In conclusion, in ARIF's opinion, the evidence diphosphonates are beneficial in terms of the main objective of reducing fragility fracture is not as yet convincing. There is certainly no clear evidence of benefit to those who are a lower level of risk (relative to those with established osteoporosis) i.e. those who would be identified by bone densitometry.

However, readers should note that more trials are in progress, whose results may further alter the assessment. Further, as the volume of research grows a systematic review of the effects of diphosphonates will become essential in interpreting the available research. We understand that such systematic reviews have been proposed.

This is an area prone to the need for updating as new information is continually becoming available.

Request Carried Out: June 1996

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Archived ARIF Request

Domestic Violence

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in June 2004.

The Problem Submitted for ARIF to Advise Upon:

How effective is routine screening for domestic violence by healthcare professionals?

This request aimed to assess whether introducing a routine screening programme into a primary healthcare setting was justified.

ARIF has undertaken two related requests on Domestic Violence:
What is the effectiveness of brief interventions including alcohol counselling services in reducing the frequency and severity of domestic violence?
What is the effectiveness of counselling for the victims of domestic violence?

Reviews Identified

- Ramsay J, Richardson J, Carter YH, Davidson LL, Feder G. Should health professionals screen women for domestic violence: systematic review. British Medical Journal 2002;325:314-326
- MacMillan HL, Wathen CN, with the Canadian Task Force on Preventive Health Care. Prevention and treatment of violence against women: systematic review and recommendations. Canadian Task Force on Preventive Health Care (CTFPHC) Technical Report 01-4. September 2001. London, ON: Canadian Task Force
- Wathen CN, MacMillan HL. Interventions for violence against women: scientific review. Journal of the American Medical Association 2003;289:589-600
- Davidson LL, Grisso JA, Garcia MC, Garcia J, King VJ, Marchant S. Training programmes for healthcare professionals in domestic violence. Journal of Women's Health and Gender Based Medicine 2001;10:953-969
- Coulthard P, Young S, Adamson L, Warburton A, Worthington HV, Esposito M. Domestic violence screening and intervention programmes for adults with dental or facial injury (Cochrane Review). In: The Cochrane Library, Issue 2, 2004. Oxford: Update Software

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Comments

For screening to be justified, it is necessary to seek and find evidence to support the assumption that screening will increase the identification of abuse cases, which in turn leads to an appropriate response

that reduces subsequent violence and its consequences.

All reviews that were identified concentrated on the abuse of women. The article by Ramsay et al., was commissioned by the United Kingdom National Screening Committee and was the most relevant. The review examined three issues:

- attitudes to routine screening
- identification of abuse cases
- interventions for abuse

The second of these aims directly addressed the problem above. The review was well conducted and the results are likely to be an accurate reflection of the evidence available. Modest increases in identification of abuse cases were seen in some studies but there was no evidence to show that this was sustained beyond the implementation phase of the screening programme.

The review also identified that there was a lack of robust evidence to demonstrate that interventions actually reduce violence and improve the quality of life and mental health of the victims and their families.

The other reviews identified by our searches examined the effectiveness of post-screening interventions and all concluded that there is insufficient evidence to show that any of the interventions identified led to an improvement in outcomes for abused women.

Caution should be taken to not interpret the lack of good quality evidence as a lack of effect, but simply that there is not enough robust evidence on which to base a decision.

In conclusion, although the evidence base does not support or undermine the introduction of a screening programme, it is recommended that routine questioning about domestic violence should still be used for diagnostic assessments of abuse cases. Primary care staff should be alert to signs and symptoms of domestic violence to identify and support those at risk of, or experiencing, abuse.

Request Carried Out: June 2004

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Archived ARIF Request

Doppler Ultrasound Scanning
Low Birth Weight Babies (Poor Foetal Growth)

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The Problem Submitted for ARIF to Advise Upon:

Is there any evidence of the effectiveness and safety of Doppler scanning for the detection of foetal abnormalities?

Question Reformulated

Important outcomes of particular interest were identified and the question reformulated to focus on the early detection of poor foetal growth in high risk women.

Reviews Identified

- Neilson JP, Alfirevic Z. Doppler ultrasound in high risk pregnancies. In: Neilson JP, Crowther CA, Hodnett ED, Hofmeyr GJ (eds.) Pregnancy and Childbirth Module of the Cochrane Database of Systematic Reviews, [updated 02 December 1997]. Available in The Cochrane Library [database on disk and CD-ROM]. The Cochrane Collaboration; Issue 1. Oxford: Update Software; 1998. Updated quarterly.

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Comments

This review is a good systematic review of randomised controlled trials with an appropriate meta-analysis. However, the pooled estimates of effect for some outcomes should be interpreted cautiously.

For example, those:

- Whose confidence intervals are wide and overlap
- Which are based on the results of a single study
- Whose individual results are visually heterogeneous

The results of the review allow the following conclusions to be drawn about the use of Doppler ultrasound in high risk pregnancies:

- It is effective in reducing perinatal mortality
- It is difficult to draw clear conclusions from the available evidence on its effect on perinatal morbidity

- The evidence does not address potential adverse effects or other important outcomes such as low weight birth babies and infant morbidity and mortality

Request Carried Out: March 1998

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Archived ARIF Request

Drama Techniques Health Promotion

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of drama techniques for imparting health promotion messages and bringing about changes in behaviour?

Reviews Identified

No systematic reviews were identified.

Primary Studies Identified

Source - Cochrane Library 2001 Issue 3 (CCTR)

- Harvey B, Stuart J, Swan T Evaluation of a drama-in-education programme to increase AIDS awareness in South African high schools: a randomized community intervention trial. International Journal of STD & AIDS 2000;(11:2):105-11
- Elliott L, Gruer L, Farrow K, Henderson A, Cowan L. Theatre in AIDS education-a controlled study. AIDS Care 1996; 8(3) :321-40
- McEwan RT, Bhopal, R, and Patton W. Drama on HIV and Aids: an evaluation of a theatre-in education programme Health Education Journal 1991;50(4) :155- 160
- Probart CK. A preliminary investigation using drama in community AIDS education
- AIDS Education and Prevention 1989;1(4):268-276

Source - Medline 1996 - 2001

- Jibaja ML, Kingery P, Neff NE, Smith Q, Bowman J, Holcomb JD. Tailored, interactive soap operas for breast cancer education of high-risk Hispanic women. Journal of Cancer Education. 2000; 15(4):237-42
- Oldfield D, Hays BJ, Megel ME. Evaluation of the effectiveness of Project Trust: an elementary school-based victimization prevention strategy. Child Abuse & Neglect. 1996;20(9):821-32
- Kerr MM. MacDonald TH. Project 2000 student nurses' creative approach to peer education. [Review] Nurse Education Today. 1997;17(3):247

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Comments

Although no systematic reviews were identified a number of primary studies were located on the use of drama for the promotion of such health topics as breast cancer awareness, sexual health and smoking cessation.

Given the considerable heterogeneity between the studies in terms of population, intervention and study design it was felt that the most useful approach would be to summarise the characteristics of the studies and highlight those with the most robust design. At the same time it was emphasised that the generalisability of the findings of any of the studies was likely to be limited and that to draw meaningful conclusions about the effectiveness of drama in health promotion would require a systematic review.

Request Carried Out: October 2001

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Archived ARIF Request

Drotrecogin alfa (Activated)
Protein C (Recombinant Human Activated)
Sepsis (Severe)

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of drotrecogin alfa (activated) in the treatment of patients with severe sepsis?

Drotrecogin alfa (activated) is also known as recombinant human protein C (activated).

Reviews Identified

No systematic reviews were identified on this topic.

Trials Identified

- Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely E, Fisher CJ Jr. Efficacy and Safety of recombinant human activated protein C for severe sepsis. New England Journal of Medicine 2001; 344(10):699-709

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Comments

There were no systematic reviews identified on this topic.

The trial by Bernard et al, also known as the PROWESS study, remains the main source of evidence. The trial demonstrates a statistically significant reduction in 28 day all causes mortality in patients treated with drotrecogin alfa (activated) compared to placebo. However, there was an increase in the incidence of severe bleeding associated with administration of the drug.

Although the trial was relatively well conducted and generally robust, it is prone to some criticism. Furthermore, there are concerns regarding the treatment of patients that have conditions that may precipitate bleeding. Currently, data is awaited from further trials regarding the long-term effects and safety of drotrecogin alfa (activated), in addition to its effectiveness in patient groups not enrolled in the PROWESS study.

NICE are due to issue guidance on this topic in August 2004. In advance of NICE guidance, any

patient who receives drotrecogin alfa (activated) should ideally do so as part of a robust evaluation of its clinical effectiveness for the treatment of sepsis within the UK health service.

As new information is likely to become available on this topic, care should be taken if this advice is accessed more than 6 months after this request was last updated

Request Carried Out: March 2002

Updated: October 2003

Updated: November 2004 - NICE has issued full guidance on this topic.

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Archived ARIF Request

Psychological Interventions Combined with Drug Therapy
Drug Therapy Combined with Pyschological Interventions
Severe mental illness (Depression and Schizophrenia)

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The Problem Submitted for ARIF to Advise Upon:

Is there any research evidence on the effects/effectiveness of combined psychological and conventional medical care (pharmacotherapy) to improve outcomes in severe mental illness?

ARIF was asked to help assist in the commission of further research by the West Midlands Department of R&D, by identifying whether there were any systematic reviews relevant to this topic.

Reviews Identified

- Steinbrueck M, Maxwell SE, Howard GS. A meta analysis of psychotherapy and drug therapy in the treatment of unipolar depression with adults. Journal of Consulting and Clinical Psychology 1983;51(6):856-863
- Meterissian GB, Bradwejn J. Comparative studies on the efficacy of psychotherapy, pharmacotherapy, and their combination in depression: was adequate pharmacotherapy provided? Journal of Clinical Psychopharmacology 1989;9(5):334-339

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Comments

These reviews suggest that there is relevant research on the combined effects of psychological and conventional medical care in severe mental illness, particularly depression. This and the fact that these reviews are many years out-of-date, should be taken into account in the commission of future research on this topic.

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DVT
Flying

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The Problem Submitted for ARIF to Advise Upon:

1. Does inactivity when in a cramped seating position (such as during long-haul air travel) increase the risk of the development of DVT in airline passengers?
2. Is there evidence that interventions such as the use of compression stockings, hydration, exercise and aspirin prevent DVT?

Reviews Identified

- Milne R. Venous thromboembolism and travel: is there an association? Journal of the Royal College of Physicians of London 1992;26:47-49.

Other Literature Identified

RCTs

- Scurr JH, Machin SJ, Bailey-King S, Mackie IJ, McDonald S, Coleridge Smith P. Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights: a randomised trial. The Lancet 2001;357:1485-1489

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Comments

The review identified concluded that there was insufficient information to answer the first question posed, despite identifying several epidemiological studies. This could have been due to the fact that the review in question only searched up to 1991. However we could identify no additional relevant published studies since this time.

To help answer the second question, the RCT identified examined the preventive effect of compression stockings versus no stockings. The results suggest that stockings may prevent DVT but may also cause superficial thrombophlebitis in varicose veins. The generalisability of the findings of this trial may be limited by the age of the enrolled population (all over 50 years of age) and the restrictive inclusion criteria.

Further studies are needed to ascertain the link between cramped seated positions and the

development of DVT, before any recommendations can be made regarding implementation of health checks in perceived at-risk groups prior to commencing long haul travel. If a causal association is identified, then rigorous research is required to identify effective preventive measures.

This is an area prone to need regular updating as new information is continually becoming available

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Archived ARIF Request

Guidelines, Policies, Treatment
Dyspepsia - Upper Gastrointestinal Symptoms

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The Problem Submitted for ARIF to Advise Upon:

Is there any information which will assist with the development of local policies and processes for the investigation and referral of patients with upper GI symptoms, outside those for urgent cancer referrals?

Reviews Identified

- Veldhuyzen van Zanten SJ, Bradette M, Chiba N, Armstrong D, Barkun A, Flook N, et al. Evidence-based recommendations for short- and long-term management of uninvestigated dyspepsia in primary care: an update of the Canadian Dyspepsia Working Group (CanDys) clinical management tool. Can J Gastroenterol 2005; 19(5):285-303
- Talley NJ, Vakil N. Guidelines for the management of dyspepsia. Am J Gastroenterol 2005;100(10):2324-2337
- Scottish Intercollegiate Guidelines Network. Dyspepsia. A national clinical guideline. 2003. Report No: 68. www.sign.ac.uk
- Prodigy Guidance. Dyspepsia - symptoms (uninvestigated by endoscopy). 2005. Latest revision July 2005. www.prodigy.nhs.uk
- NICE guideline published in 2004 with amendments in 2005:
  NICE, North of England Dyspepsia Guideline Development Group. Dyspepsia: Managing dyspepsia in adults in primary care. 2004. www.nice.org.uk
  NICE, Indigestion (dyspepsia) in adults. 2004. NICE Clinical Guideline 17. www.nice.org.uk
  NICE, Newcastle Guideline Development and Research Unit. Dyspepsia - management of dyspepsia in adults in primary care. 2005.Clinical Guideline 17. www.nice.org.uk

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Comments

The NICE guideline is the most up to date UK guideline and much of the information within it feeds into the Prodigy documentation. The aim of the NICE guideline was to provide evidence-based recommendations to guide healthcare professionals, patients and carers on the appropriate primary care management of dyspepsia. The guideline discusses the appropriate procedures for investigating, treatment and referral of patients with non-specific upper GI symptoms and seems to offer an

appropriate balance of investigation and treatment against referral in that it considers cost effectiveness and stresses the importance of secondary care providers being aware of the guideline in order to ensure continuity of care. The guidelines consist of a full text document, a Quick Referral Guide and a Patient Information Sheet. The Quick Referral Guide was updated in June 2005 regarding referral for endoscopy in line with the recommendation in the NICE Clinical Guideline on referral for suspected Cancer.

In summary therefore, the recent NICE guideline seems to be an appropriate document on which to base local policy decisions for caring for people with new onset dyspepsia in primary care. It meets most of the questions posed by the AGREE standard for guideline development . It is a national document written from a British NHS perspective and presents the data in 3 formats, which should cater for most users needs.

Request Carried Out: May 2006

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Early Detection and Treatment Mental Illness

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of the early detection and treatment of severe mental illness in children and adolescents?

Reviews Identified

None.

Primary Studies

None.

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Comments

Although the scope of our searches was broad we identified no published evidence addressing this question.

Of peripheral interest is a recent systematic review on early interventions for preventing mental illness in young people.

Nicholas B, Broadstock M. Effectiveness of early interventions for preventing mental illness in young people: a critical appraisal of the literature. NZHTA Report 1999;2(3).

This review can be downloaded from http://nzhta.chmeds.ac.nz/

Although this review looks at the evidence on preventing rather than detecting and treating mental illness it may prove useful to those interested in the topic, rather than the specific question, of this request

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Archived ARIF Request

Prevention
Eating Disorders

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Can eating disorders be prevented?

See related requests: Can mental illness be prevented?, Can postnatal depression be prevented?, Can depression in children and adolescents be prevented?, Can depression in adults be prevented?

Reviews Identified

- Stice E, Shaw H Eating disorder prevention programs: a meta-analytic review (Provisional record)Psychological Bulletin 2004;130(2):206-27
- Pratt BM, Woolfenden SR. Interventions for preventing eating disorders in children and adolescents. Cochrane Database of Systematic Reviews.(2):CD002891, 2002
- Ciliska D, Beyers J, Vohra J, McVey G The effectiveness of primary prevention of eating disorders (Provisional record) Hamilton, ON, Canada: Ontario Ministry of Health, Region of Hamilton-Wentworth, Social and Public Health Services Division; 2001
- Austin SB. Prevention research in eating disorders: theory and new directions. Psychological Medicine. 2000;30(6) :1249-6

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Comments

One review by Stice et al 2004 was critically appraised in detail. Its aim was to examine eating disorder prevention programmes. The review was well conducted. It examined effectiveness using the following risk factors as a proxy for eating pathology - thin-ideal internalisation, body dissatisfaction, dieting, negative affect, and body mass.

A total of 53 trials were identified which assessed one or more of the risk factors. The authors found that 53% of the interventions resulted in significant reductions in one or more of the risk factors. Some intervention effects persisted for up to 2 years. The authors noted that “diversity of content of the interventions implied that there are several approaches to effectively prevent eating pathology, but the more successful interventions decreased attitudinal risk factors and promoted healthy weight control

behaviours".

The results suggest that preventative programmes are effective in particular for reducing the risk factors for eating pathology, and that certain types of programme such as selective, interactive, multi-session programme seem more successful. Interventions in female groups and in participants over 15 years also appear effective.

The authors acknowledge that more research is needed before these interventions can be recommended as a therapeutic tool to determine the strength of effect of specific programme elements and to investigate if such interventions can be as effective in natural conditions and whether they offer a lasting benefit. The use of risk factors as a proxy for eating disorder pathology may also be difficult when interpreting clinical benefit.

Request Carried Out: August 2005

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Archived ARIF Request

Echocardiography/Heart Failure (LVF) ACE Inhibitors

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The Problem Submitted for ARIF to Advise Upon:

Is GP open access to echocardiography for the diagnosis of heart failure (LVF - Left Ventricular Failure) likely to be effective in maximising the proven benefits of ACE inhibition?

Reviews Identified

- Centre for Health Services Research, University of Newcastle and Centre for Health Economics, University of York. Evidence based clinical practice guidelines: ACE inhibitors in the primary care management of adults with symptomatic heart failure, 1997. pp45.
- Latini R et al. ACE inhibition post MI. Circulation 1995;92:3132-3137
- Garg R et al. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Journal of the American Medical Association 1995;273;1450-1456

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Comments

The first reference is particularly recommended on the basis that the clinical guidelines are truly based on systematic reviews of the available evidence.

For those who have a history/symptoms/signs/initial investigations suggestive of the diagnosis of left ventricular failure it seems likely that greater availability of echocardiography through open access will lead to maximisation of the proven benefit of ACE inhibition, provided that:

1. All those with clinical heart failure do not already receive echocardiography.
2. Open access actually results in more persons with clinical heart failure receiving an echocardiograph.
3. Practitioners actually change their prescribing on the basis of the echocardiography results.

The effect of open access echocardiography where individuals are asymptomatic is much more difficult.

Since this request was carried out ARIF has received correspondence from a health care worker who has undertaken a review of the effects of open access to echocardiography for heart failure in primary care. Readers interest in this topic may benefit from direct contact with the individual, which in the first instance should be via the ARIF office.

This is an area prone to the need for regular updating.

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Archived ARIF Request

Elderly Health Promotion, Disease Prevention and Rehabilitation

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What are the effects/effectiveness of interventions to promote health, prevent disease and rehabilitate older patients?

Question Reformulated

ARIF addressed this wide-ranging question by identifying any reviews of research on interventions which had been applied to the elderly, relevant to health promotion, disease promotion and rehabilitation. The results were presented as a list of the interventions where there appeared to be good reviews of research, together with the best review(s) identified in that area, as a starting point for further investigation. The reviews given were not appraised in detail although all were confirmed to be reasonably systematic in their approach.

The list did not include interventions where reviews of research are available on the effects in the general adult population, which might be reasonably generalised to the older person.

Reviews Identified

GENERAL:

- Victor CR, Higginson I. Effectiveness of care of older people: a review. Quality in Health Care 1994;3:210-216

This is a useful background review setting out a broad framework for the consideration of the range of interventions which might be effective.

HEALTH PROMOTION/DISEASE PREVENTION:

Hypertension

- Mulrow CD et al. Hypertension in the elderly: implications and generalizability of randomized trials. Journal of the American Medical Association 1994;272:1932-1938

Assessment

- Stuck AE, Siu AL, Wieland D et al. Comprehensive geriatric assessment: a meta-analysis of controlled trials. Lancet 1993;342:1032-36

Preventing Fall and Injury

- NHS Centre for Reviews and Dissemination. Preventing falls and subsequent injuries in the older people. York: NHS Centre for Reviews and Dissemination, 1996. Pp16 (Effective Health Care Vol 2. Issue 1.)

This area interrelates closely with prevention of osteoporosis and its sequelae, particularly hip fracture in the elderly (see below).

Osteoporosis and Hip Fracture (Bone Densitometry Measurement, Bisphosphonates, Hormone Replacement Therapy)

- Sheldon TA. Screening for osteoporosis to prevent fractures. York: NHS Centre for Reviews and Dissemination, 1992. Pp. 12.
- US Congress, Office of Health Technology Assessment. Effectiveness and costs of osteoporosis screening and hormone replacement therapy. Volume I: Cost effectiveness analysis. Volume II: Evidence on benefits , risks and costs. Washington DC: US Government Printing Office, August 1995. (OTA-BH-H-160 & OTA-BP-H-144).

These reviews strongly suggest that bone densitometry should not be part of a health promotion / disease prevention strategy for the elderly.

Vaccination (Influenza)

- NHS Centre for Reviews and Dissemination. Influenza vaccination and older people. York: NHS Centre for Reviews and Dissemination, 1996. Pp4 (Effectiveness Matters Vol 2. No 4.)

Secondary Prevention of Stroke (Aspirin and Anticoagulation in Non-Rheumatic Atrial Fibrillation)

Good evidence on these interventions is provided by three Cochrane Reviews on the subject. However the implications for provision of services to monitor anticoagulation control need to be carefully considered.

Hyperlipidaemia

The following has been suggested as a useful briefing paper by NHS CRD in the DARE database:

- Wise GR, Doram K, Stoletniy L, Marais HJ. Controversies in the management of hyperlipidemia in the elderly. Cardiology in the Elderly 1994;2(3):253-264

Cancer Screening (Prostate)

- Office of Technology Assessment. Costs and Effectiveness of Prostate Cancer Screening in Elderly Men. Washington DC: U.S. Congress. Office of Technology Assessment, 1995. Pp 130

There are clearly many potentially important issues in this area eg breast screening and screening for colo-rectal cancer. Of these, only the role of screening for prostate screening in men appears to have been adequately reviewed and, as a recent Effectiveness Matters publication reports, the evidence that this should be an important component of prevention strategies in older persons at the current time is questionable.

Screening for Hearing Loss

- Mulrow CD, Lichtenstein MJ. Screening for hearing impairment in the elderly. Rationale and strategy. Journal of General Internal Medicine 1991;6:249-258

This review provides evidence on the availability of reliable tools to screen for hearing loss, although uncertainty is acknowledged on the community effectiveness of a screening programme.

REHABILITATION:

Stroke

-

Stroke Unit Trialists' Collaboration. A systematic review of specialist multidisciplinary team (stroke unit) care for stroke inpatients. In: Warlow C, Van Gijn J, Sandercock P (eds.) Stroke Module of The Cochrane Database of Systematic Reviews , [updated 02 December 1996]. Available in The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration; Issue 1. Oxford: Update Software; 1997. Updated quarterly.

Incontinence

- Fantl JA et al. Urinary incontinence in adults: acute and chronic management. Rockville MD: US Department of Health and Human Services. Public Health Service, Agency for Health Care Policy and Research, March 1996. (Clinical Practice Guideline No 2; AHCPR publication No 96-0682).

Pressure Sores

- University of York, NHS Centre for Reviews and Dissemination; University of Leeds, Nuffield Institute for Health. The prevention and treatment of pressure sores: how effective are pressure-relieving interventions and risk assessment for the prevention and treatment of pressure sores? York: NHS Centre for Reviews and Dissemination, 1995. Pp16. (Effective Health Care Vol 2. Issue 1.)

OTHER:

The following review articles may provide some further useful information to inform your strategy:

Menal Health

- Burckhardt C. The effect of therapy on the mental health of the elderly. Research in Nursing & Health 1987;10:277-285
- Okun MA, Olding RW, Cohn CM. A meta-analysis of subjective well-being interventions among elders. Psychological Bulletin 1990;108(2):257-266
- Cole MG. Effectiveness of three types of geriatric medical services: lessons for geriatric psychiatric services. Canadian Medical Association Journal 1991;144(10):1229-1240

Home Visiting

- Ciliska D, Hayward S, Thomas H, Mitchell A, Dobbins M, Underwood J, Rafael A, Martin E. The effectiveness of home visiting as a delivery strategy for public health nursing interventions: a systematic overview. Hamilton, Ontario: McMaster University; Toronto: University of Toronto, Quality of Nursing Worklife Research Unit,1994. Pp 48

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Comments

Of the public health nursing interventions investigated, those targeting the elderly were only one of many activities for which evaluations of home visiting were obtained. The validity of any conclusions with regard to home visiting for the elderly may therefore be limited, although the references identified would provide a useful starting point for further investigation of this area.

Please note, this is an area prone to need for regular updating as new information is continually becoming available, particularly new systematic reviews of existing research.

Request Carried Out: January 1997

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Eye Movement Desensitisation and Reprocessing (EMDR) Post Traumatic Stress Disorder

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of EMDR in the management of post traumatic stress disorder (PTSD) arising from sexual abuse?

Question Reformulated

A number of issues around the question required clarification:

- The diagnosis of PTSD revolves around a collection of symptoms, some or all of which may be present in people thought to be suffering from the condition, which has implications for the interpretation and applicability of research on the effectiveness of any potential treatments.
- Individuals with a diagnosis of PTSD have different combinations of symptoms that are troublesome, therefore specific treatments cannot be viewed in isolation and care packages need to be tailored to the individual.
- EMDR is one treatment option for PTSD which falls within the category of cognitive behavioural treatments. It involves a combination of exposure based therapy, in which the individual confronts the feared memory, with anxiety management techniques, which teaches the individual to control feelings of arousal provoked by the memory.
- Specifically, it involves the patient invoking the traumatic memory and rating the level of anxiety it causes. They are then asked to think about the traumatic event while focusing on an object which is moved back and forth in front of the face. Following this, the level of anxiety caused by the memory is rated again. The process is repeated until the anxiety rating is reduced.

Reviews Identified

- Solomon S, Gerrity E, Muff A. Efficacy of treatments for post-traumatic stress disorder. An empirical review. JAMA 1992;268(5):633-638

Trials Identified

- Wilson S, Becker L, Tinker R. Eye movement desensitisation and reprocessing (EMDR) treatment for psychologically traumatised individuals. Journal of Consulting and Clinical Psychology 1995; 63(6):928-937
- Vaughn K, Armstrong M, Gold R, O'Connor N, Jenneke W, Tarrier N. A trial of eye movement

desensitisation compared to image habituation training and applied muscle relaxation in post-traumatic stress disorder. J Behav Ther & Exp Psychiat. 1994;25(4):283-291

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Comments

The review identified is a good systematic review on the wider range of treatments available for PTSD. It does not specifically address the effectiveness of EMDR but helps set the context within which it might be applied.

The trials identified were both reasonably good randomised controlled trials which compared EMDR with an alternative in the treatment of PTSD, the participants of which both included victims of sexual abuse. Both were small studies with a maximum duration of follow-up of only 3 months. Both experienced problems associated with the selection of an appropriate control group due to the complex nature of the intervention and the ethics of psychological research. The main limitation of both studies related to the outcomes measured. Both used a variety of psychotherapy scales, none of which considered functional or quality of life issues. Without information on health benefits it is difficult to make an overall assessment of effectiveness.

Bearing this in mind, their results tentatively suggest that EMDR may be a promising treatment in PTSD, particularly for intrusive symptoms. It is clearly more effective than no treatment but its role relative to other similar therapies is less clear. More information is required as to its cost-effectiveness and its acceptability to patients.

Request Carried Out: July 1998

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Emergency Admissions

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The Problem Submitted for ARIF to Advise Upon:

What research evidence is there on the reasons for and interventions to reduce rising numbers of emergency admissions?

ARIF was asked to help assist in the commission of further research by the West Midlands Department of R&D, by identifying whether there were any systematic reviews on this topic.

Reviews Identified

- Pencheon D, Nicholson D, Hadridge P. Emergency Care Handbook. Milton Keynes: NHS (Anglia & Oxford Region), 1995. pp85. [Obtainable from: Philip Hadridge, Service Development Manager, Anglia & Oxford Region, 6-12 Capital Drive, Linford Road, Milton Keynes, MK14 6QP. Phone 01908 844489.]

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Comments

No truly systematic reviews were identified.

The review above, was in the opinion of ARIF, the most useful background review setting a clear framework and context for considering rises in emergency admissions.

Subsequently, building on the review above, the West Midlands Department of R&D commissioned a systematic review and modelling exercise from a joint project team between the University of York and the Coventry Business School. The result of the REAP (Rises in Emergency Admissions Project) will be available in early 1998. Further details may be obtained via the Research & Development Department, NHS Executive West Midlands, Bartholomew House, 142 Hagley Rd, Birmingham. B16 9PA. Phone: 0121 224 4600.

This is an area prone to need for regular updating as new information is continually becoming available.

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Lung Reduction Surgery
Emphysema

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The Problem Submitted for ARIF to Advise Upon:

What are the effects/effectiveness of lung reduction surgery in severe emphysema?

Reviews Identified

- Jansenn W. Treatment for emphysema: an overview of lung volume reduction surgery. Perspectives in Respiratory Nursing 1996;7(1):3-5

Trials Identified

- McKenna RJ Jr et al. A randomized, prospective trial of stapled lung reduction versus laser bullectomy for diffuse emphysema. Journal of Thoracic Cardiovascular Surgery 1996;111:317-22
- Eugene J. Video-thoracic surgery for the treatment of end stage bullous emphysema and chronic obstructive pulmonary disease. American Surgeon 1995;61(10):934-6

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Comments

The references identified provide a useful starting point in considering the question.

However, the review is not systematic and the primary research requires careful interpretation.

With the proviso that the research identified may not be representative, surgery (stapling and laser bullectomy) does seem to have beneficial effects on physiological measurements and oxygen requirements. Whether these benefits are also manifest in improved quality of life and what the cost of these benefits is, is not clear.

ARIF is undertaking a more detailed review of the available literature, which it is hoped will be complete by January 1998.

Request Carried Out: July 1997

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Endoscopic Laser Foraminoplasty Lumbar Disc Prolapse

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence base for Endoscopic Laser Foraminoplasty?

Question Reformulated

Clarification that the intervention is one of a number of specific options available in percutaneous surgery for lumbar disc prolapse.

Reviews Identified

- Gibson JNA, Waddell G. The surgical management of lumbar disc prolapse [Protocol]. In: Bombardier C, Nachemson A, Deyo R, de Bie R, Bouter L, Shekelle P, Waddell G, Roland M, Guillemin F (eds) Back Review Module of The Cochrane Database of Systematic Reviews, [updated 01 September 1997]. Available in The Cochrane Library [database on disk and CD-ROM]. The Cochrane Collaboration; Issue 4. Oxford: Update Software; 1997. Updated quarterly.

Other Literature Identified

Case Series:

- Knight MTN. Endoscopic laser foraminoplasty on the lumbar spine - early experience. Submitted to Minimally-Invasive-Neurosurgery. (German)
- Knight M, Vajda A, Jakab G, Awan S. Endoscopic laser foraminoplasty: an alternative to open spinal decompression or fusion. International Laser Congress; Athens, Greece; 25-28 September 1996

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Comments

No reviews were identified on endoscopic laser foraminoplasty. The review protocol identified relates to the broader category of laser assisted percutaneous and endoscopic surgery for lumbar disc prolapse, for which laser foraminoplasty is one of several treatment options. It is currently with the Cochrane

Editorial Board and is due for publication in the summer.

Together the two papers on endoscopic laser foraminoplasty report the results of one case series. The methodological quality of the study is poor and it is highly prone to bias. With this in mind, the study appears to show that patients undergoing a primary procedure, and those who have undergone previous conventional surgery, experience some reduction in pain post-operatively.

Interrogation of the evidence base indicates that endoscopic laser foraminoplasty is still an experimental procedure which has not been properly evaluated, although the evaluation of the general category of laser assisted endoscopic and percutaneous interventions in the management of lumbar disc prolapse appears to be slightly more developed.

This is an area prone to need for regular updating as new information is continually becoming available.

Request Carried Out: January 1998

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Endoscopy
Gastrointestinal Disease

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The Problem Submitted for ARIF to Advise Upon:

What would be the evidence base to inform the development of guidelines for a local open access endoscopy service to diagnose upper gastrointestinal problems.

Reviews Identified

- Axon ATR, Bell GD, Jones RH et al. Guidelines on appropriate indications for upper gastrointestinal endoscopy. British Medical Journal 1995; 310: 853-856
- Helicobacter pylori and peptic ulcer. York: NHS Centre for Reviews and Dissemination, 1995. pp4 (Effectiveness matters Vol 1 Issue 2)

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Comments

The first reference suggested would be a useful starting point from which to develop local guidelines. However, it was confirmed by correspondence with the original authors, that although the guidelines were informed by a review of the research evidence, this review was not systematic and hence the guidelines were not completely evidence based.

The second reference points to a related area where there are systematic reviews of evidence indicating the effectiveness of helicobacter pylori eradication. In developing local guidelines on open access endoscopy the opportunity should be taken to reinforce the implementation of this evidence.

Request Carried Out: March 1996

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Enzyme Potentiated Desensitisation (EPD)
Multiple Allergies
Gulf War Syndrome

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of enzyme potentiated desensitisation (EPD) for treating patients with severe allergies?

Question Reformulated

Due to ambiguity around what could or could not be considered as a severe allergic condition, we sought clarification from the requestor regarding the specific population and conditions for which evidence on the effectiveness of EPD was required. As a result of this enquiry, we focused our attention on adult patients with either multiple allergy or Gulf War syndrome.

Reviews Identified

No systematic reviews were identified.

Primary Studies

- Fell P, Brostoff J. A single-dose desensitisation for summer hay fever. Results of a double-blind study - 1988. Eur.J.Clin.Pharmacol 1990;38:77-79
- Astarita C, Scala G, Sproviero S, Franzese A. A double-blind placebo-controlled trial of enzyme potentiated desensitisation in the treatment of pollenosis. J.Invest.Allergol.Clin.Immunol. 1996;6(4):248-255
- Di Stanislao C , Di Berardino L, Bianchi I, Bologna G. A double-blind, placebo-controlled study of preventive immunotherapy with EPD in the treatment of seasonal allergic disease. Allergie et Immunologie 1997;30(2):39-42
- Troise C, Bignardi D, Modena P, Pissacroia C, Di Berardino F. Preventive symptomatic immunotherapy versus placebo in seasonal rhinitis due to grasses in children and to Parietaria in adult patients. Allergie et Immunologie 2000;32(6):246-9

Other Literature

- Bagnall AM, Whiting P, Wright K, Sowden AJ. The effectiveness of interventions used in the treatment and management of chronic fatigue syndrome and/or myalgic encephalomyelitis in adults

and children. The NHS Centre for Reviews and Dissemination, University of York, York.
http://www.york.ac.uk/inst/crd/CRD_Reports/crdreport22.pdf

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Comments

Our searches on the topic identified no systematic reviews on the effectiveness of EPD.

There is ambiguity surrounding the definitions of both Gulf War Syndrome and multiple allergies. As both conditions could be loosely grouped with other conditions such as multiple chemical sensitivities, myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS) we looked at a recent systematic review (Bagnall et al 2001) on the effectiveness of treatments for CFS to ascertain whether the review identified any evidence on the effectiveness of EPD for CFS. Although the review methodology would have permitted the inclusion of randomised and non-randomised controlled trials on EPD for CFS, none were identified.

We identified a number of primary studies examining EPD in the treatment of allergies, but none of these enrolled patients with Gulf War syndrome or multiple allergies. In the absence of directly relevant evidence on these conditions, we identified those studies we considered would be the most useful and accessible reading on EPD for allergic conditions. The following are the criteria on which this decision was based: the study had to enroll adult participants with an allergic condition to one specific allergen, the trial had to be performed under randomised double blind controlled conditions and the report of the trial had to be in English. The resulting trials are listed above. No attempt to summarise these was undertaken in the context of this request as they were not felt sufficiently close to the conditions of interest.

Request Carried Out: October 2001

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Specialist Epilepsy Clinics
Epilepsy

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The Problem Submitted for ARIF to Advise Upon:

Do specialist epilepsy clinics offer advantages over general neurology clinics?

Reviews Identified

None identified.

Trials Identified

- Morrow J. An assessment of epilepsy clinics. In: Quality of Life and Quality of Care in Epilepsy (Ed. D. W. Chadwick). London: Royal Society of Medicine, 1990

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Comments

As no reviews were identified for this request we proceeded to search for any relevant primary research. One randomised trial was identified which compared an epilepsy clinic with a general neurology clinic for a variety of outcomes including seizure control, drug toxicity, additional use of health service resources, patient satisfaction and social and occupational functioning.

For all outcomes, except social and occupational functioning, the results favoured the epilepsy clinic. However, the study was not blinded and it is possible that some bias may have occurred, particularly for the more subjective outcomes. For seizure control, the benefits of the epilepsy clinic are evened out in the long-term, and the data presented on drug toxicity do not clearly demonstrate an advantage for the epilepsy clinic.

This trial tentatively suggests that there are benefits for epilepsy patients managed in epilepsy clinics over those managed in general neurology clinics, but the results should be viewed with caution. Clearly, the paucity of relevant, robust research, indicates that this is an area where more work should be undertaken.

Request Carried Out: September 1997

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Vagal Nerve Stimulation Epilepsy

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The Problem Submitted for ARIF to Advise Upon

How effective is vagal nerve stimulation (VNS) for intractable epilepsy?

Reviews Identified

- Fisher RS et al. Assessment of vagal nerve stimulation for epilepsy: report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. Neurology 1997;49:293-297

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Comments

The review identified is not systematic but does represent a timely, and apparently comprehensive, summary of the available literature on what is a novel and potentially important intervention. It is a well-structured and balanced narrative review, which addresses all the important issues. It concludes that VNS is a promising, but still investigational intervention. The review systematically assesses the validity of the included studies, and concludes by listing a number of reasons why the clinical significance of the results of even the most robust primary research needs further clarification.

This is an area prone to need for regular updating as new information is continually becoming available.

Request Carried Out: November 1997

Update: January 2002 - This request was updated in the context of a further request on VNS for refractory epilepsy.

Reviews Identified

- Bryant J. Vagus nerve stimulation in epilepsy Wessex Institute for Health Research and Development DEC report No 82 March 1998
- Fisher RS and Handforth A Reassessment of vagus nerve stimulation for epilepsy A report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

Neurology 1999;53:666-669

Trials Identified

- Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, Henry TR, Collins SD, Vaughn BV, Gilmartin RC, Labar DR, Morris GL 3rd, Salinsky MC, Osorio I, Ristanovic RK, Labiner DM, Jones JC, Murphy JV, Ney GC, Wheless JW. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 1998;51(1):48-55

Comments

The Wessex DEC review (Bryant 1998) was systematic, comprehensive and well conducted. Although the evidence on the effectiveness of VNS for epilepsy came from a RCT of acceptable quality, patient numbers remained small and outcome measures were impossible to delineate in terms of quality of life measurements. The review concluded that the treatment was not yet proven and that further evidence was required pertaining to the effectiveness of VNS.

Since the publication of the Wessex review further studies in this area have been published. It appears from the RCTs of this treatment that a seizure reduction rate of approximately 30% can be achieved by VNS in patients with refractory partial seizures. However, as previously, questions relating to the clinical significance of the results of even the most robust primary research need further clarification or remain unanswered.

This is an area prone to need for regular updating as new information is continually becoming available.

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Esomeprazole for peptic ulcer

Synopsis

Question:	What is the evidence that esomeprazole is more effective and cost-effective than omeprazole or lansoprazole for peptic ulcer disease in adults?
Evidence Identified:	Edwards SJ, Lind T, Lundell L, DAS R. Systematic review: standard- and double-dose proton pump inhibitors for the healing of severe erosive oesophagitis - a mixed treatment comparison of randomized controlled trials. Alimentary Pharmacology & Therapeutics 2009,30(6):547-56
Comments:	One systematic review was identified. The review evidence suggests that esomeprazole 40mg has better endoscopic healing rates than omeprazole 20mg for severe erosive oesophagitis at both four weeks and eight weeks of treatment. Compared with lansoprazole 30mg, esomeprazole 40mg also seems more effective at four weeks, and tends to be but is not significantly better at eight weeks. Esomeprazole appeared to be the most effective treatment among licensed PPIs for the healing of severe erosive oesophagitis. However, the reliability of the finding is uncertain due to limited data being presented about the quality of the trials and/or patient/study characteristics. No relevant evidence was found regarding symptom control of peptic ulcer disease and cost of treatment.
Date Completed:	October 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Esomeprazole for peptic ulcer

Request completed: October 2010

Question

What is the evidence that esomeprazole is more effective and cost-effective than omeprazole or lansoprazole for peptic ulcer disease in adults?

Question clarification

Esomeprazole, omeprazole and lansoprazole are proton pump inhibitors (PPIs), which are acid suppressants and licensed as treatments for peptic ulcer disease. For licensed dose see Appendix A.

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol (www.arif.bham.ac.uk/strategy.shtml). Text and index terms were used to represent the population and the intervention. Sources were searched from their inception to August 2010. No language restriction was applied to the searches. As an example the MEDLINE search can be found in Appendix B. The following inclusion criteria were used for study selection:

Population	Adult patients with established peptic ulcer disease
Intervention	Esomeprazole
Comparator	Omeprazole; lansoprazole
Outcome	Peptic ulcer disease symptom control and ulcer healing
Study design	Systematic reviews and health technology assessments

Results

Full search results can be found in Appendix C. One systematic review, by Edwards et al,[1] was identified as being the most recent and relevant to the question posed above. No relevant reviews on the cost-effectiveness were found.

The review was published in 2009. It aimed to compare the effectiveness of five European-licensed doses of proton pump inhibitors (PPIs), i.e. esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg and 40 mg, pantoprazole 40 mg and rabeprazole 20 mg, for healing severe erosive

oesophagitis. Severe erosive oesophagitis was defined as grades C and D in the Los Angeles (LA) classification system or comparable grades in other erosive oesophagitis classification systems.[i] The outcomes assessed were endoscopic healing rates after the initiation of PPI treatment at four and eight weeks. Only randomised controlled trials (RCTs) which contained a direct comparison of a European-licensed healing dose of a PPI compared with at least one alternative European-licensed healing dose of a PPI, and included endoscopic healing data for severe grades at four and/or eight weeks, were sought. A mixed treatment comparison (MTC) analysis was used to combine direct treatment comparisons with indirect trial evidence. The review's searches were conducted up to 2008.

A total of 12 RCTs were identified as being relevant for the network for the MTC analysis, all were clearly adequate or possibly adequate in terms of methodological quality for inclusion (based on randomisation, allocation concealment, method of blinding and patients lost to follow-up).

The 12 RCTs were published between 1988 and 2006 and encompassed the following six direct comparisons:

1. **Esomeprazole 40mg vs. omeprazole 20mg: 3 trials**
2. **Esomeprazole 40mg vs. lansoprazole 30mg: 3 trials**
3. Esomeprazole 40mg vs. pantoprazole 40mg: 1 trial
4. Omeprazole 20mg vs. lansoprazole 30mg: 2 trials
5. Omeprazole 40mg vs. lansoprazole 30mg: 1 trial
6. Omeprazole 20mg vs. omeprazole 40mg: 2 trial

As can be seen, only three trials that compared esomeprazole 40mg with omeprazole 20mg, and three trials that compared esomeprazole 40mg with lansoprazole 30mg, were directly relevant to this report.

No detailed information regarding characteristics of the trials, e.g. demographic characteristics of the patients, duration of the condition, previous and concurrent treatment, compliance with the treatment, etc, was reported. Thus the degree of clinical heterogeneity between the trials is unclear. The review authors stated that no papers were excluded from the primary analysis as a result of the quality assessment. However, specific details regarding the quality of the trials were not reported.

[i] In the Savary-Miller classification system, grades 3 and 4 were deemed to correspond to severe erosive oesophagitis (see 'MATERALS AND METHODS' section on page 548 of the publication[1]). For more information about LA classification system and Savary-Miller classification system see Appendix D.

The review authors extracted the endoscopic healing rates at four and eight weeks, and re-calculated the rates if they were not based on intention-to-treat (ITT) analysis. Bayesian statistical inference was used to provide 95% credible intervals (95% CrI) and calculate direct probability statements for which treatment was the most effective. The MTC was conducted comparing omeprazole 20mg with other PPIs at four weeks using a fixed effect model and at eight weeks using a random effect model. Sensitivity analysis was conducted by using the alternative models. However, of the MTC analysis, only the results from the comparison of esomeprazole 40mg versus omeprazole 20mg were relevant to the current report. Summary results of the MTC at four weeks and eight weeks were displayed in two forest plots respectively. However, the forest plots only presented pooled estimates for each comparison but did not indicate the number of direct and indirect comparisons contributing to this.

The MTC showed that esomeprazole 40mg demonstrated a significantly higher endoscopic healing rate compared with omeprazole 20mg both at four weeks (odds ratio = 1.84; 95%CrI 1.50 to 2.22) and eight weeks (odds ratio = 1.91; 95%CrI 1.13 to 2.88). Among the PPIs in the MTC network, esomeprazole 40mg showed the highest probability of being the most effective treatment at four weeks (68%), followed by omeprazole 40mg (32%), while the probability for either lansoprazole 30mg, omeprazole 20mg or pantoprazole 40mg being most effective was zero. At eight weeks esomeprazole 40mg remained the highest probability of being most effective, followed by omeprazole 40 mg (18%), pantoprazole 40mg (12%), lansoprazole 30mg (2%) and omeprazole 20mg (0). See Table 1 below for details. A sensitivity analysis using the alternative models presented broadly similar results.

Table 1 Summary results of each PPI compared with omeprazole 20 mg from MTC analysis at 4 weeks (fixed effects) and 8 weeks (random effects) (data from table 2 on page 552 of the publication)

	OR (95% CrI)		Probability of most effective (%)	
	4 weeks	**8 weeks**	**4 weeks**	**8 weeks**
Esomeprazole 40mg	1.84 (1.50 to 2.22)	1.91 (1.13 to 2.88)	68	68
Omeprazole 40mg	1.65 (0.80 to 3.03)	1.44 (0.63 to 2.84)	32	18
Pantoprazole 40mg	1.02 (0.71 to 1.43)	1.39 (0.43 to 3.26)	0	12
Lansoprazole 30mg	1.21 (0.96 to 1.51)	1.23 (0.72 to 1.99)	0	2
Omeprazole 20mg	**1.00 (n/a)**	**1.00 (n/a)**	0	0

Of the MTC, only one comparison, i.e. Esomeprazole 40mg versus omeprazole 20mg, is relevant to the question posed in this report, this report thus conducted pair-wise meta-analyses using the available primary data reported in table 1 on page 551 of the review publication,[1] to pool the three trials that compared esomeprazole 40mg with omeprazole 20mg, and the three trials that compared esomeprazole 40mg with lansoprazole 30mg, respectively (see Figure 1- Figure 4 below).

The pooled estimates of direct comparison showed that, compared with omeprazole 20mg, esomeprazole 40mg had a significantly better endoscopic healing rate both at four weeks (odds ratio = 1.95; 95%CI 1.57 to 2.42) (see Figure 1) and eight weeks (odds ratio = 2.24; 95%CI 1. 65 to 3.04) (see Figure 2). These results are consistent with the above results from the MTC.

Compared with lansoprazole 30mg, esomeprazole 40mg demonstrated a significantly higher endoscopic healing rate at four weeks (odds ratio = 1.46; 95%CI 1.23 to 1.72) (see Figure 3). At eight weeks the healing rate tended to be higher with esomeprazole 40 mg than lansoprazole 30mg, however, the difference was not statistically significant (odds ratio = 1.31; 95%CI 0.76 to 2.26). In the analysis at eight weeks, significant heterogeneity between the studies was observed (see Figure 4).

Disease symptom control, adverse events and long term effects were not investigated in the review.

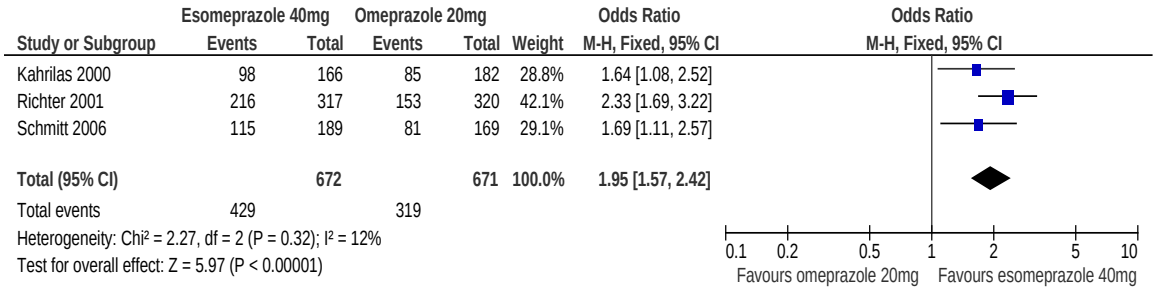

Figure 1 Endoscopic healing rate at week 4: esomeprazole 40mg vs. omeprazole 20mg

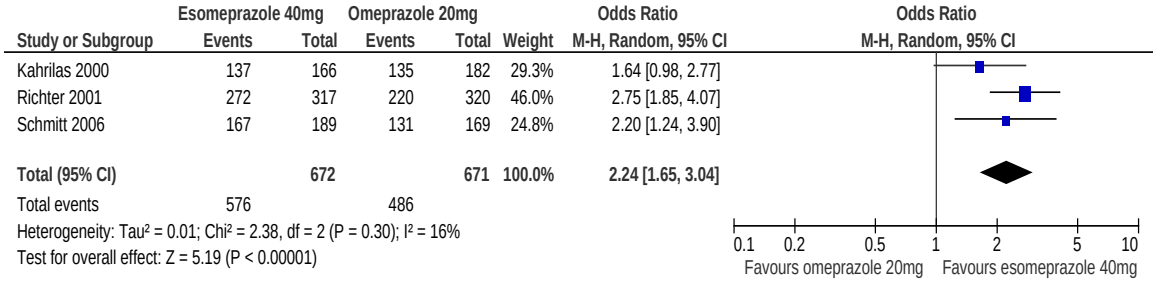

Figure 2 Endoscopic healing rate at week 8: esomeprazole 40mg vs. omeprazole 20mg

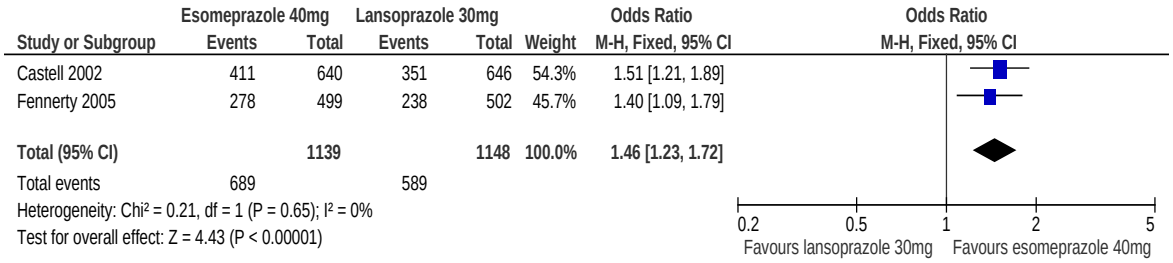

Figure 3 Endoscopic healing rate at week 4: esomeprazole 40mg vs. lansoprazole 30mg[ii]

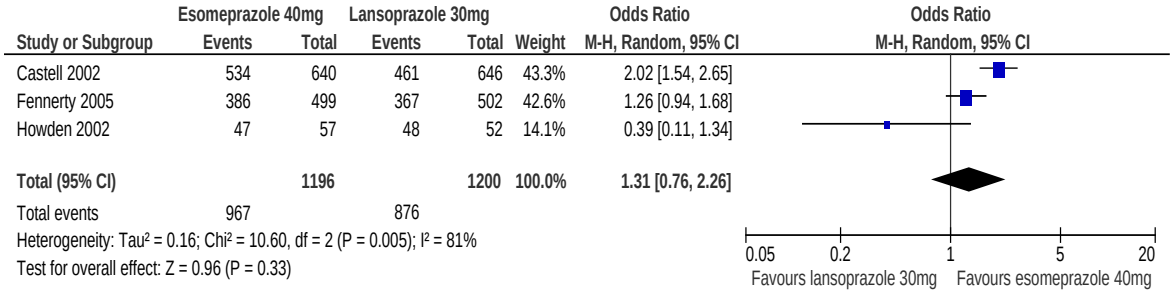

Figure 4 Endoscopic healing rate at week 8: esomeprazole 40mg vs. lansoprazole 30mg

Discussion

From the evidence presented in the review, mixed treatment comparison and direct pair-wise comparison of esomeprazole 40mg versus omeprazole 20mg both suggested that esomeprazole 40mg is more effective than omeprazole 20mg for severe erosive oesophagitis in terms of endoscopically verified healing rates at four weeks and eight weeks following the treatments. Compared with lansoprazole 30mg, esomeprazole 40mg also seems more effective at four weeks, and tends to be but is not significantly better than lansoprazole 30mg at eight weeks. Esomeprazole appeared to be the most effective treatment among licensed PPIs for the healing of severe erosive oesophagitis.

However, there are areas of uncertainty around the evidence, which limited the reliability and generalisability of the findings. Firstly, there was no detailed information regarding the characteristics of the trials, nor was there sufficient information regarding the patient baseline characteristics. Thus, the degree of heterogeneity between the studies is unclear. As such, it is not known how appropriate it was to combine the trials results. Secondly, no detailed information regarding the quality of the trials was reported, thus it is unclear how reliable the trials results are.

[ii] In one study that had this comparison there was no healing data available at four weeks. Thus this study was not included in the four weeks meta-analysis.

Thirdly, it is uncertain whether the statistical non-significance was due to insufficient pooled sample size to identify statistically significant differences, as no power calculation was reported. Furthermore, the fact that healing rates were not presented by initial grade of oesophagitis in the trials, which was stated as being a limitation of the research by the review authors, also limited the generalisability of the findings.

Conclusions

The review evidence suggests that esomeprazole 40mg has better endoscopic healing rates than omeprazole 20mg for severe erosive oesophagitis at both four weeks and eight weeks following the treatments. Compared with lansoprazole 30mg, esomeprazole 40mg also seems more effective at four weeks, and tends to be but is not significantly better than lansoprazole 30mg at eight weeks. Esomeprazole appeared to be the most effective treatment among licensed PPIs for the healing of severe erosive oesophagitis. However, the reliability of the finding is uncertain due to limited data being presented about the quality of the trials and/or patient/study characteristics.

No relevant evidence was found regarding symptom control of peptic ulcer disease and cost of treatment.

References

1. Edwards SJ, Lind T, Lundell L, DAS R. Systematic review: standard- and double-dose proton pump inhibitors for the healing of severe erosive oesophagitis -- a mixed treatment comparison of randomized controlled trials. Alimentary Pharmacology & Therapeutics 2009,30(6):547-56

Appendix A – Licensed PPI dose for adults aged 18 years and over

(From British Formulary, online 1010 ed. London: British Medical Association and Royal Pharmaceutical Society. http://bnf.org/ [accessed on 04-10-2010])

PPI	Indication and dose (oral)
Esomeprazole (tablet)	• Helicobacter pylori Eradication in adults: 20 mg twice daily • NSAID-associated* gastric ulcer, adult over 18 years, 20 mg once daily for 4–8 weeks; prophylaxis in patients with an increased risk of gastroduodenal complications who require continued NSAID treatment, 20 mg daily • Gastro-oesophageal reflux disease (in the presence of erosive reflux oesophagitis), adult and child over 12 years, 40 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed or symptoms persist; maintenance 20 mg daily; child 1–12 years, body-weight 10–20 kg, 10 mg once daily for 8 weeks; body-weight over 20 kg, 10–20 mg once daily for 8 weeks • Symptomatic treatment of gastro-oesophageal reflux disease (in the absence of oesophagitis), adult and child over 12 years, 20 mg once daily for up to 4 weeks, then 20 mg daily when required; child 1–12 years, body-weight over 10 kg, 10 mg once daily for up to 8 weeks • Zollinger–Ellison syndrome, adult over 18 years, initially 40 mg twice daily, adjusted according to response; usual range 80–160 mg daily (above 80 mg in 2 divided doses)
Omeprazole (tablet)	• Helicobacter pylori eradication in adults: 20 mg twice daily • Benign gastric and duodenal ulcers, 20 mg once daily for 4 weeks in duodenal ulceration or 8 weeks in gastric ulceration; in severe or recurrent cases increase to 40 mg daily; maintenance for recurrent duodenal ulcer, 20 mg once daily; prevention of relapse in duodenal ulcer, 10 mg daily increasing to 20 mg once daily if symptoms return • NSAID-associated duodenal or gastric ulcer and gastroduodenal erosions, 20 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed; prophylaxis in patients with a history of NSAID-associated duodenal or gastric ulcers, gastroduodenal lesions, or dyspeptic symptoms who require continued NSAID treatment, 20 mg once daily • Zollinger–Ellison syndrome, initially 60 mg once daily; usual range 20–120 mg daily (above 80 mg in 2 divided doses) • Gastric acid reduction during general anaesthesia (prophylaxis of acid aspiration), 40 mg on the preceding evening then 40 mg 2–6 hours before surgery • Gastro-oesophageal reflux disease, 20 mg once daily for 4 weeks, continued for further 4–8 weeks if not fully healed; 40 mg once daily has been given for 8 weeks in gastro-oesophageal reflux disease refractory to other treatment; maintenance 20 mg once daily • Acid reflux disease (long-term management), 10 mg daily increasing to 20 mg once daily if symptoms return • Acid-related dyspepsia, 10–20 mg once daily for 2–4 weeks according to response
Lansoprazole (tablet)	• Benign gastric ulcer, 30 mg daily in the morning for 8 weeks • Duodenal ulcer, 30 mg daily in the morning for 4 weeks; maintenance 15 mg daily • NSAID-associated duodenal or gastric ulcer, 30 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed; prophylaxis, 15–30 mg once daily • Helicobacter pylori eradication in adults: 30 mg twice daily • Zollinger-Ellison syndrome (and other hypersecretory conditions), initially 60 mg once daily adjusted according to response; daily doses of 120 mg or more given in two divided doses • Gastro-oesophageal reflux disease, 30 mg daily in the morning for 4 weeks, continued for further 4 weeks if not fully healed; maintenance 15–30 mg daily • Acid-related dyspepsia, 15–30 mg daily in the morning for 2–4 weeks

*NSAID: non-steroid anti-inflammatory drug

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Appendix B – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 (esomeprazole or nexium).mp.
2 limit 1 to (humans and "reviews (specificity)")

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Appendix C – Literature search results

Systematic reviews

Source - Cochrane Library (CDR) 2010 Issue 8

Wang Yiping, Pan Tao, Wang Qiong, Guo Zhen. Additional bedtime H2-receptor antagonist for the control of nocturnal gastric acid breakthrough. Cochrane Database of Systematic Reviews: Reviews 2009 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD004275.pub3

Neumann Ignacio, Martin Janet, Letelier Luz M, Howden Colin W, Claro Juan Carlos, Leontiadis Grigorios I. Comparison of different regimens of proton pump inhibitors for acute peptic ulcer bleeding. Cochrane Database of Systematic Reviews: Protocols 2009 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD007999

Ford Alex C, Delaney Brendan, Forman David, Moayyedi Paul. Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients. Cochrane Database of Systematic Reviews: Reviews 2006 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD003840.pub4

Rostom Alaa, Dube Catherine, Wells George A, Tugwell Peter, Welch Vivian, Jolicoeur Emilie, McGowan Jessie, Lanas Angel. Prevention of NSAID-induced gastroduodenal ulcers. Cochrane Database of Systematic Reviews: Reviews 2002 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD002296

Sreedharan Aravamuthan, Martin Janet, Leontiadis Grigorios I, Dorward Stephanie, Howden Colin W, Forman David, Moayyedi Paul. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. Cochrane Database of Systematic Reviews: Reviews 2010 Issue 7 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD005415.pub3

Source – Cochrane Library (DARE) 2010 Issue 3

Salas M, Ward A, Caro J
Are proton pump inhibitors the first choice for acute treatment of gastric ulcers: a meta analysis of randomized clinical trials
BMC Gastroenterology 2002; 2: 17
US: http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12002008402/frame.html

Klok R M, Postma M J, Van Hout B A, Brouwers J R
Meta-analysis: comparing the efficacy of proton pump inhibitors in short-term use
Alimentary Pharmacology and Therapeutics 2003; 17 (10): 1237 - 45
US: http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12003001172/frame.html

Source – Cochrane Library (HTA Database) 2010 Issue 3

Canadian Coordinating Office for Health Technology Assessment
Esomeprazole magnesium. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2001
http://www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-32002000443/frame.html

Source – MEDLINE (Ovid) 1950 – August week 2

Edwards SJ. Lind T. Lundell L. DAS R.
Systematic review: standard- and double-dose proton pump inhibitors for the healing of severe erosive oesophagitis -- a mixed treatment comparison of randomized controlled trials. [Review] [154 refs]
Alimentary Pharmacology & Therapeutics. 30(6):547-56, 2009 Sep 15.

Kirchheiner J. Glatt S. Fuhr U. Klotz U. Meineke I. Seufferlein T. Brockmoller J.
Relative potency of proton-pump inhibitors-comparison of effects on intragastric pH. European Journal of Clinical Pharmacology. 65(1):19-31, 2009 Jan.

Zhao F. Wang J. Yang Y. Wang X. Shi R. Xu Z. Huang Z. Zhang G.
Effect of CYP2C19 genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for Helicobacter pylori eradication: a meta-analysis.
Helicobacter. 13(6):532-41, 2008 Dec.

Gralnek IM. Dulai GS. Fennerty MB. Spiegel BM.
Esomeprazole versus other proton pump inhibitors in erosive esophagitis: a meta-analysis of randomized clinical trials.
Comment in: Gastroenterology. 2007 Apr;132(4):1622-4; PMID: 17418175]
Clinical Gastroenterology & Hepatology. 4(12):1452-8, 2006 Dec.

Wang X. Fang JY. Lu R. Sun DF.
A meta-analysis: comparison of esomeprazole and other proton pump inhibitors in eradicating Helicobacter pylori.[Erratum appears in Digestion. 2006;74(3-4):235]
Digestion. 73(2-3):178-86, 2006.

Gisbert JP. Pajares JM.
Esomeprazole-based therapy in Helicobacter pylori eradication: a meta-analysis. [Review] [18 refs]
Comment in: Dig Liver Dis. 2004 Apr;36(4):243-7; PMID: 15115334]
Digestive & Liver Disease. 36(4):253-9, 2004 Apr.

Vergara M. Vallve M. Gisbert JP. Calvet X.
Meta-analysis: comparative efficacy of different proton-pump inhibitors in triple therapy for Helicobacter pylori eradication.
Alimentary Pharmacology & Therapeutics. 18(6):647-54, 2003 Sep 15.

Raghunath AS. Green JR. Edwards SJ.
A review of the clinical and economic impact of using esomeprazole or lansoprazole for the treatment of erosive esophagitis. [Review] [32 refs]
Clinical Therapeutics. 25(7):2088-101, 2003 Jul.

Kale-Pradhan PB. Landry HK. Sypula WT.
Esomeprazole for acid peptic disorders. [Review] [36 refs]
Annals of Pharmacotherapy. 36(4):655-63, 2002 Apr.
Abstract

Source – NICE web site

Newcastle Guideline Development and Research Unit. Dyspepsia: managing dyspepsia in adults in primary care. CG17. NICE; 2004
http://guidance.nice.org.uk/CG17/Guidance/pdf/English

Economic evaluation

Source – Cochrane Library (EED) 2010 Issue 3

Barry M, Nagle V, O'Morain C, Bennett K, Keeling P W
'Best practice' for Helicobacter pylori eradication in the primary care setting
Irish Medical Journal 2006; 99 (1): 11-12
US: http://www.mrw.interscience.wiley.com/cochrane/cleed/articles/NHSEED-22006006335/frame.html

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Appendix D – Los Angeles classification system and Savary-Miller classification system:

Available at: http://www.patient.co.uk/doctor/Gastro-Oesophageal-Reflux-Disease.htm. [Accessed: 26-10-2010]

1. **Los Angeles Classification of Esophagitis**

    - Grade A: mucosal break < 5 mm in length
    - Grade B: mucosal break > 5mm
    - Grade C: mucosal break continuous between > 2 mucosal folds
    - Grade D: mucosal break >75% of esophageal circumference

2. **Savary-Miller classification system**

    - Grade I: single or multiple erosions on a single fold. Erosions may be exudative or erythematous.
    - Grade II: multiple erosions affecting multiple folds. Erosions may be confluent.
    - Grade III: multiple circumferential erosions.
    - Grade IV: ulcer, stenosis or oesophageal shortening.
    - Grade V: Barrett's epithelium. Columnar metaplasia in the form of circular or non-circular (islands or tongues) extensions.

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Archived ARIF Request

Exercise Referral Schemes
Exercise

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in September 1997 and update in April 2003.

The Problem Submitted for ARIF to Advise Upon:

Is there any evidence that participants in exercise referral schemes sustain increased levels of physical activity?

Reviews Identified

- Hillsden M et al. Randomised controlled trials of physical activity promotion in free living populations: a review. Journal of Epidemiology and Community Health 1995; 49: 448-453

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Comments

The review identified is a well-conducted, systematic review of randomised controlled trials which, given the extreme heterogeneity of the included studies, does not attempt a meta-analysis but summarises the results using a qualitative synthesis. While the applicability of the review is limited by the fact that most subjects were white, middle-class American volunteers, it does represent the best available evidence on the topic.

The review does not directly consider exercise referral schemes, but it does suggest that it is possible to increase the exercise levels of previously sedentary subjects.

Interventions which achieved sustained levels of high participation displayed certain common features:

1. home based programmes
2. unsupervised informal exercise
3. frequent professional contact
4. walking as the promoted exercise
5. moderate intensity exercise

Exercise referral schemes usually consist of GP referrals to a leisure centre or sports facility and as most of the features which contributed to success in the included trials are not typical of such schemes, the review does not provide evidence of their effectiveness.

Request Carried Out: September 1997

Updated: 2003

Reviews Identified

- Eakin EG, Glasgow RE, Riley KM. Review of primary care-based physical activity intervention studies: effectiveness and implications for practice and future research. Journal of Family Practice 2000;49(2):158-168
- Eaton CB, Menard LM. A systematic review of physical activity promotion in primary care office settings British Journal of Sports Medicine 1998;32(1):11-6
- Riddoch C et al Effectiveness of physical activity promotion schemes in primary care: a review London: HEA; 1998 (Health Promotion Effectiveness Review No 14)

Comments

In all three reviews, interventions given in the primary care setting were moderately effective in increasing exercise participation (including household work and leisure activities) in the short term. However in all the included trials in all three reviews, there was substantial heterogeneity in the interventions, the definition of "sedentary patients", study design and assessment tools. There was also substantial variation in the follow up times, with time to follow up ranging from four weeks to 12 months after completion of the intervention. While there were increases in exercise participation, most subjects did not increase their exercise levels to those recommended for the maintenance of good health. As in the previous request, features of successful interventions included:

1. Moderate intensity exercise
2. Frequent professional contact
3. Unsupervised informal exercise

In addition, other factors such as the use of tailored exercise prescription, and the use of written materials such as manuals, exercise diaries, and pamphlets were also shown to be useful for increasing exercise participation. Again, as above, exercise referral schemes usually consist of GP referrals to a leisure centre or sports facility and as most of the features which contributed to success in the included trials are not typical of such schemes, the review does not provide evidence of their effectiveness.

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Archived ARIF Request

a - Galactosidase A
Fabry's Disease

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in May 2002.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of a-galactosidase A in the treatment of Fabry's Disease.

Fabry's disease is a rare genetic disorder of lipid metabolism characterised by deficiency of the enzyme alpha-galactosidase A which leads to the accumulation of fatty deposits within various organs in the body. Symptoms of the disease include abdominal pain and visual impairment. Later in the course of the disease there maybe serious complications due to kidney failure, heart irregularities and progressive neurological abnormalities.

More information on Fabry's Disease can be found on the website of the Fabry Support & Information Group

Reviews Identified

No systematic reviews were identified.

Trials Identified

- Schiffmann R, Kopp JB, Austin HA 3rd, Sabnis S, Moore DF, Weibel T, Balow JE, Brady RO. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA 2001;285: 2743-49
- Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S, Caplan L, Linthorst GE, Desnick RJ, International Collaborative Fabry Disease Study Group Safety and efficacy of recombinant human alpha-galactosidase A--replacement therapy in Fabry's disease. New England Journal of Medicine 2001;345:9-16

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Comments

We identified no systematic reviews on this topic. However, our search did reveal the existence of two published reports of randomised controlled trials that assess the efficacy and safety of recombinant human a-galactosidase A in patients with Fabry's disease. The trials are generally well conducted and as such, their results can probably be relied upon. Both trials use different manufacturers preparations of a-galactosidase A. The results suggest that a-galactosidase A appears to be a promising treatment

for Fabry's Disease. However, the trials report follow up of only 1 year of treatment (including open phases) and therefore the benefit of long-term treatment, the occurrence of adverse events from continuation of treatment beyond this period, and cost effectiveness of treatment are unclear.

Request Carried Out: May 2002

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Sympathectomy
Facial Blushing

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in June 2003.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of sympathectomy for facial blushing?

Sympathectomy involves cutting the sympathetic ganglia and nerves in the upper thorax that supply the face and upper body. Endoscopic thoracic sympathectomy has replaced the open thoracic procedure and can be done on an outpatient basis.

Reviews Identified

- Ahmed O. Endoscopic thoracic sympathectomy for treating facial blushing. Clayton: Centre for Clinical Effectiveness, Monash University; 2001. [Evidence Centre Report] http://www.mihsr.monash.org/cce/res/pdf/c/541.pdf

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Comments

The review by Ahmed identified three case series. As these studies are retrospective and do not employ a control group they are subject to bias and confounding and the findings should be treated with caution. There were other methodological weaknesses that were common to all of the studies as follows:

- The characteristics of the included patients was not clear, particularly in relation to the severity of the symptoms and the extent of previous treatment
- The methods of outcome assessment were poorly described and not validated

In conclusion, the evidence base on the effect of sympathectomy for facial blushing is limited and firm conclusions cannot be drawn from the findings of the three case series reports included in the review. At this time, the benefits and side effects associated with sympathectomy have not been properly evaluated and reported which leads us to suggest that any patient who receives this intervention does so as part of a well controlled trial and that they are followed up well after the procedure.

Request Carried Out: June 2003

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Archived ARIF Request

Facilitating Introduction Gay Men

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in December 2001.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of facilitating the introduction of gay men into the gay community on reducing risk-taking behaviour and HIV/AIDS infection or transmission?

For the purposes of this request, we took "facilitation" to be any method by which assistance would be given to gay men in making contact with their gay peers. We took a "community" to be broadly defined as any group of any men who meet on a regular basis or who have contact with one another, in contrast to a gay man being isolated without contact with other gay men.

Reviews Identified

No systematic reviews were identified. However a protocol for a systematic review was found:

- Johnson W, Peersman G. Interventions to modify sexual risk behaviours for preventing HIV infection in men who have sex with men (Protocol for a Cochrane Review). In: The Cochrane Library, Issue 3, 2001. Oxford: Update Software. Review expected to be published in: Issue 1, 2002

Primary Studies

- Seibt AC, Ross MW, Freeman A Krepcho M, Hedrich A, McAlister A, Fernandez-Esquer ME. Relationship between safe sex and acculturation into the gay subculture. AIDS Care 1995:7(Supp 1);S85-88

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Comments

At this time there are no completed systematic reviews in this area. A protocol by Johnson and Peersman on interventions to modify sexual risk behaviours to reduce HIV in men who have sex with men has been lodged with the Cochrane Library.

Given the absence of completed systematic reviews at this time, we focused on the primary study by Seibt et al. This study examined the relationship between acculturation into the gay subculture and practicing of safe sex. Acculturation was defined as the acquisition or incorporation of the customs of

an alternate society. The results suggested that acculturation into the gay community is associated with safer sexual behaviour. The results of this study need to be interpreted with substantial caution, as it is a case-series and vulnerable to bias and confounding. The other caveat is that this case-series did not address facilitation of introduction of gay men into the gay community, but examined the relationships between membership of an organisation and reading of gay literature for gay men and the reported practicing of safe sex.

In conclusion, there is extreme paucity of evidence on the effectiveness of facilitating introduction of gay men into the gay community. A forthcoming systematic review from the Cochrane library may shed further light on interventions relating to facilitation and the provision of peer support networks for gay men, with regard to reducing risk-taking sexual behaviour.

Request Carried Out: December 2001

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Archived ARIF Request

Tension Free Vaginal Tape (TVT) Female Urinary Incontinence

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in November 1999.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness and cost effectiveness of tension free vaginal tape compared to standard vaginal hysterectomy or colposuspension for female urinary incontinence?

Question Reformulated

This new surgical procedure involves the insertion of a length of tape through the top of the vagina to provide internal support for displaced pelvic structures, and is considerably less invasive than traditional surgical techniques for the treatment of urinary incontinence in women.

Reviews Identified

None.

Other Literature Identified

- Ulmsten U, Falconer C, Johnson P et al. A multicenter study of tension-free vaginal tape (TVT) for surgical treatment of stress urinary incontinence. International Urogynecology Journal & Pelvic Floor Dysfunction 1998;9(4):210-213
- Wang AC, Lo TS. Tension-free vaginal tape. A minimally invasive solution to stress urinary incontinence in women. Journal of Reproductive Medicine 1998;43(5):429-434
- Ulmsten U, Johnson P, Rezapour M. A three year follow-up of tension free vaginal tape for surgical treatment of female stress urinary incontinence. British Journal of Obstetrics & Gynaecology 1999;106(4):345-35

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Comments

No systematic reviews were identified so we went on to search for the primary literature. No comparative studies appear to have been undertaken, but several relevant case series were identified.

The three cited were all of good size with adequate follow-up, and were largely well conducted. However, all three are prone to the high potential for bias that is inherent in study designs without

parallel control groups. The results of all three studies are remarkably consistent, demonstrating high success and low failure rates. Major adverse effects were rare and rates for moderate complications were low. No information is provided about the levels of pain or distress experienced by women during surgery. This is potentially important as resource use and complication rates appear to be minimised when the procedure is performed under a local anaesthetic, and are closer to those of traditional surgical techniques when an epidural anaesthetic is required.

In summary, this appears to be a promising alternative to major surgery for some women with urinary incontinence, although the nature of the existing evidence base is such that it can only be described as experimental at this point in time.

This is an area prone to need for regular updating as new information is continually becoming available. This topic is one of several being considered by the West Midlands Development and Evaluation Service.

Request Carried Out: November 1999

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Archived ARIF Request

Uterine Arterial Embolisation
Uterine Fibroids
Fibroids

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in December 2002.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of uterine arterial embolisation (UAE) in the treatment uterine fibroids?

Reviews Identified

No systematic reviews were identified.

Primary Studies

No controlled trials were identified.

Several large case series were identified:

- McLucas B, Adler L, Perrella R. Uterine fibroid embolization: nonsurgical treatment for symptomatic fibroids. Journal of the American College Surgeons 2001;192:95-105
- Spies JB, Ascher SA, Roth AR, Kim J, Levy EB, Gomez-Jorge J. Uterine artery embolization for leiomyomata. Obstetrics & Gynecology 2001; 98: 29-34
- Brunereau L, Herbreteau D, Gallas S, Cottier JP, Lebrun JL, Tranquart F. Uterine artery embolization in the primary treatment of uterine leiomyomas: technical features and prospective follow-up with clinical and sonographic examinations in 58 patients. American Journal of Roentgenology. 2000; 175:1267-72
- Hutchins FL, Worthington-Kirsch R, Berkowitz RP. Selective uterine artery embolization as primary treatment for symptomatic leiomyomata uteri. J Am Assoc Gyncecol Laparosc 1999; 6(3): 279-84

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Comments

No systematic reviews and no published trial were identified. The case series published so far on UAE (see above for list of those enroling the largest sample of patients) show similar and promising results. As such, UAE may be an alternative to hysterectomy and myomectomy in women with symptomatic

fibroids. However, an important caution to be noted is that uncontrolled studies such as these case series are vulnerable to bias and confounding and can overestimate the efficacy of new treatments. In addition, there has been no comparison of UAE with other emerging treatments for symptomatic fibroids including myolysis and laparoscopic bipolar coagulation. More robust information is required on the long-term effectiveness of UAE and in particular the effect of UAE on fertility as it may be a preferable treatment for women who have not completed childbearing.

Trials are currently ongoing including at least one comparing UAE with hysterectomy.

This topic is prone to require updating as more information becomes available.

NICE are due to issue guidance on this topic in mid-2003.

Request Carried Out: December 2002 (this page replaces that on a similar request undertaken in April 1998).

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These pages are maintained by Ann Massey

Financial incentives for increasing levels of physical activity

Synopsis

Question:	What is the effectiveness and cost-effectiveness of providing financial incentive schemes to motivate increasing levels of physical activity?
Evidence Identified:	Paul-Ebhohimhen V, Avenell A. Systematic review of the use of financial incentives in treatments for obesity and overweight. Obesity Reviews 2008;9(4):355-367 Kavanagh J, Trouton A, Oakley A, Powell C. A systematic review of the evidence for incentive schemes to encourage positive health and other social behaviours in young people. London: EPPI-Centre, Social Science Research Unit, Institute of Education, University of London. 2006 Kavanagh J, Stansfield C, Thomas J. Incentives to improve smoking, physical activity, dietary and weight management behaviours: a scoping review of the research evidence Social Science Research Unit, Institute of Education, University of London. London: EPPI Centre; 2009 NICE. Should incentives be used to encourage healthy living? Newsletter of meeting of NICE Citizens Council May 2010
Comments:	Reviewed evidence on the effectiveness of financial incentives schemes to motivate increasing levels of physical activity is sparse. There is no reviewed evidence on the cost effectiveness regarding this issue. Very limited data suggested that behavioural treatments involving the use of financial incentives for obesity and over weight have no significant effect on weight loss; however, the behavioural treatments were multi-faceted and physical activity was neither the only component of the interventions nor necessarily the component the financial incentives focused on.
Date Completed:	June 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Financial incentive schemes for increasing levels of physical activities

Request completed: June 2010

Question

What is the effectiveness and cost-effectiveness of providing financial incentive schemes to motivate increasing levels of physical activity?

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol (www.arif.bham.ac.uk/strategy.shtml). Text and index terms were used to represent the population and the intervention. Sources were searched from their inception to June 2010. No language restriction was applied to the searches. The MEDLINE search can be found in Appendix A. The following inclusion criteria were used for study search and selection:

Population	Any (universal as well as particular groups)
Intervention	Financial incentives of any form that are used as motivation to improve levels of physical activity
Comparator	Any approaches without financial incentives (e.g. ask, advise, or assist type approach)
Outcome	Levels of physical activity; any consequence of physical activities (e.g. weight loss; increased fitness); cost-effectiveness
Study design	Systematic reviews and health technology assessments

Results

Two systematic reviews,[1;2] one scoping review[3] and one newsletter of the NICE Citizens Council meeting[4] were identified that provided relevant information. No studies were identified that evaluated cost-effectiveness of financial incentive schemes for increasing levels of physical activities. Full search results can be found in Appendix B.

The systematic review by Paul-Ebhohimhen & Avenell[1] focused on randomised controlled trials (RCTs) of behavioural obesity treatments involving the use of financial incentives to bring about weight loss.

Initial searches were up to 2001 and were then updated. However, the date of the update was not reported (the review was published in 2008). The review was of good methodological quality, with systematic search and study selection strategies, and appropriate quality assessment of the included studies. Meta-analyses were used for the data analysis.

Nine RCTs were included. All were published between 1974 and 1998 and none were UK based. Thus the studies might not be considered as totally relevant to current practice. Sample sizes were fairly small ranging from 38 to 202 people. Population were adults aged 18 years or older with a body mass index of ≥ 28kg/m^2. Comparisons were various obesity treatment strategies (e.g. diet, exercise, monitoring of caloric intake, group discussion, providing information, etc.) with or without the use of financial incentives compared with each other. The treatment strategies were multi-faceted and in none of the studies physical activity was used as a single intervention. Financial incentive was offered for weight loss, compliance with behaviour change or attendance at sessions. In two studies the participants were given money as incentives whereas in the other studies the participants paid deposit money first and then received refunds from their deposit if they achieved certain goals. Outcome measures were weight loss and other behaviour change at a minimum of one year follow-up. Only two studies measured physical activity level as an outcome, in one of these financial incentives were used as the motivation for attendance at exercise session and in the other for weight loss.

Table 1 below outlines the feature of the intervention, financial incentive and outcome measure of the studies.

Meta-analysis of weight change at a follow-up of 12 months, 18 months and 30 months all showed no statistically significant difference between the groups with and without the use of financial incentives. Meta-analysis by amount of incentives and by mode of incentive delivery also showed no significant difference on weight change. A very weak favourable trend was observed: where the financial incentive was to the value of at least 1.2% personal disposable income rather than less or no incentives; reward for group performance rather than for individual performance; reward for behaviour change rather than for weight loss; and reward by non-psychologist rather than psychologist. However, all the meta-analyses were based on small sample sizes ranging from only 13 to 172 people. No analyses specifically for physical activity level change were conducted.

The systematic review by Kavanagh and colleagues[2] aimed to assess the evidence of the effectiveness of incentive schemes to improve health and other social behaviours in young people aged 11-19.

Searches were up to 2005. The review was of good methodological quality. A total of 129 studies met the review's inclusion criteria, of which 28 were conducted in the UK. Incentives were a wide range of financial or other tangible incentives, such as cash payments, entry into raffles or lotteries, reduced-cost access to a range of resources, or achievement recognition, etc. The focus of the incentives included changes in health behaviour, educational behaviour and social behaviour. Of the 129 studies only four focused on the impact of incentives on physical activity, with three of the

four being specifically on process evaluation assessing in what conditions (e.g. focused areas, groups of young people, etc) incentive schemes are more or less effective. No further detailed information about the four studies was reported in the review, and it is unclear whether the incentives in the studies were of financial or other tangible incentives.

The systematic review also searched for ongoing incentive-based schemes and identified two which were UK based: “Fitbods” and “Fit to Succeed”, targeting physical activity and one which was US based, “Fun, Food and Fitness Project”, targeting in internet-based physical fitness programme. Incentives in the “Fitbods” scheme were a certificate and small gifts, in the “Fit to Succeed” scheme they were free taster sessions, discounts and money off vouchers at leisure centres for children, families and teachers, and in the US based scheme were gift vouchers. However, the evaluations of the schemes were not included in the review.

The aim of the scoping review by Kavanagh and colleagues[3] was to identify the nature and extent of the literature on the effectiveness of incentives used to motivate healthy behaviours on smoking, diet, physical activity and healthy weight maintenance. As a scoping review it aimed to provide an overview picture (e.g. nature and size) of the current research literature; it did not contain synthesised findings or an assessment of the quality of the literature it identified. Incentives were defined as any tangible benefit externally provided to promote pre-specified health behaviour changes in the direct or indirect recipient of the intervention, e.g. access to a range of free or reduced cost health and leisure facilities, prizes, payments and pledging.

Searches were undertaken in bibliographic databases, websites and research registers for research published between1999-2009. A total of 128 studies were identified, of which seven were known to be UK based. Twenty-six studies had a focus of physical activity, however, details of the type of study design, population, country where the study was conducted, and the nature of the incentives (e.g. financial or other tangible) were not reported.

The newsletter of the NICE Citizens Council meeting in May 2010[4] described a “Pounds for Pounds programme”, which was the first public evaluation by the NHS of a weight loss incentive scheme. Details about the programme were not reported. It stated that overall 67% of 401 participants obtained an average weight loss of 18Ibs after three months in the programme, but the achievement declined at a longer time follow-up with only a quarter of the participants staying in the programme for a year, despite the financial incentives on offer. It concluded that there were high dropout rates thus it is very difficult to interpret the results to show how successful this would be on a population approach.

From the limited information provided in the newsletter, regarding financial incentive and level of physical activity it is impossible to tell how relevant the “Pounds for Pounds programme” is to increasing levels of physical activity.

Conclusions

In conclusion, reviewed evidence on the effectiveness of financial incentives schemes to motivate increasing levels of physical activity is sparse. There is no reviewed evidence on the cost effectiveness regarding this issue. Very limited data suggested that behavioural treatments involving the use of financial incentives for obesity and over weight have no significant effect on weight loss; however, the behavioural treatments were multi-faceted and physical activity was neither the only component of the interventions nor necessarily the component the financial incentives focused on.

Table 1. Outline of the studies in the review Paul-Ebhohimhen & Avenell 2008

Study	N	Intervention and financial incentive	Outcome
Jeffery 1990	175	Intervention for all groups involved lessons on diet, exercise and behaviour. Comparison groups = 8 Deposit refund was used for attendance at one year follow-up and for doing home work (one page record of weight and changes made) and accessing telephone consultation as needed	Weight and BMI
Jeffery 1983; Jeffery 1984	89	Intervention for all groups involved educational programme on behaviour, diet and exercise; weekly group meetings; calorie and exercise records. Comparison groups = 6 Deposit refund for weight loss	Weight ; % at least achieving contracted goal
Jeffery 1984	59	Intervention for all groups involved instructional programme on diet, exercise and behaviour; weekly group meetings; individual weight loss objectives. Comparison groups = 6 Deposit refund for weight loss and/or attendance	Weight
Jeffery 1993	202	Intervention involved SBT with 20 weekly meetings and weigh ins, then monthly meetings and weekly weigh ins till 18 months, for all groups, except no treatment control group. Comparison groups = 5 Financial incentives (free supply) for weight loss	Weight (BMI); Perceived barriers to abstinence; Caloric intake from fat; Total caloric intake; **Physical activity levels**
Jeffery 1998	160	Intervention for all groups involved SBT. Comparison groups = 5 Financial incentive (free supply) for attendance at exercise sessions	Weight change; Psychological status; Caloric intake from fat; Total caloric intake; **Physical activity levels**
Kramer 1986	85	Intervention involved prior 16 weeks behavioural treatment with use of financial contingencies across all groups based on average group weigh loss. Comparison groups = 3 Immediate and at one year refund was made for the control group; financial contingencies were used either for attendance only, or for both attendance and weight maintained	Weight; % initial weight loss maintained; % subjects maintaining weight in groups
Mahoney 1974	49	Intervention for all groups involved self-control program (*no further details about self-control program*) with weekly weigh ins and group meetings, and given pamphlets on dietary behaviour control. Comparison groups = 4 Financial incentives were self-reward either for weight loss or for habit improvement	% subjects maintaining or improving weight loss
Saccone & Israel 1978	49	Interventions for all groups involved basic program on behaviour, diet and exercise. Comparison groups = 7 Financial incentives were reward either for weight loss or eating behaviour change	Weight
Wing 1981	38	Intervention for all groups involved educational programme on behaviour, diet and exercise; weekly (monthly during maintenance) group meetings; self-monitoring diaries and weight charts. Comparison groups = 2 Financial incentives were first 8 week checks returned for attendance then 7 returned monthly for weight loss, or first 8 week checks returned for weight loss and then other 7 returned monthly for attendance	Weight

BMI: body mass index. **SBT**: standard behavioural treatment. *No further details on definition of SBT were reported*.

References

1. Paul-Ebhohimhen V, Avenell A. Systematic review of the use of financial incentives in treatments for obesity and overweight. Obesity Reviews 2008;9(4):355-367.

2. Kavanagh J, Trouton A, Oakley A, Powell C. A systematic review of the evidence for incentive schemes to encourage positive health and other social behaviours in young people. London: EPPI-Centre, Social Science Research Unit, Institute of Education, University of London. 2006.

3. Kavanagh J, Stansfield C, Thomas J. Incentives to improve smoking, physical activity, dietary and weight management behaviours: a scoping review of the research evidence Social Science Research Unit, Institute of Education, University of London. London: EPPI Centre; 2009. Available at: http://eppi.ioe.ac.uk/cms/Default.aspx?tabid=2468&language=en-US [Accessed: 21-06-2010]

4. NICE. Should incentives be used to encourage healthy living? Newsletter of meeting of NICE's citizens council May 2010. Available at: http://www.nice.org.uk/newsroom/features/HealthyLivingIncentives.jsp [Accessed: 22-06-2010]

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 (incentive$ or reward$ or contest$ or competition$ or prize$ or payment$ or money or voucher$).mp.
2 "awards and prizes"/
3 or/1-2
4 exercise/ or physical fitness/ or aerobic exercise/ or yoga/ or walking/ or running/ or swimming/
5 exp Sports/
6 physical activit$.mp.
7 4 or 5 or 6
8 3 and 7
9 limit 8 to "reviews (specificity)"
10 limit 8 to "therapy (specificity)"

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Appendix B – Literature search results

Systematic reviews

Source – EMBASE (Ovid) 1980 to 2010 Week 21

Martin S.N, Crownover B.K, Kovach F.E.
Q/What's the best way to motivate patients to exercise?
Journal of Family Practice. 2010;59(1):43-44.

Source - TRIP Database

Kavanagh J, Trouton A, Oakley A, Powell C.
A systematic review of the evidence for incentive schemes to encourage positive health and other social behaviours in young people. London: EPPI Centre,
Social Science Research Unit, Institute of Education, University of
London; 2006
http://eppi.ioe.ac.uk/EPPIWebContent/hp/reports/incentives/Incentives_systematic_review.pdf

Source – ARIF Database

Paul-Ebhohimhen V, Avenell A. Systematic review of the use of financial incentives in treatments for obesity and overweight. Obesity Reviews 2008; 9(4):355-367.

Source – HTA Vortal

Kane RL, Johnson PE, Town RJ, Butler M. Economic Incentives for Preventive Care. Evidence Report/Technology Assessment No. 101.
Rockville, MD. Agency for Healthcare Research and Quality. August 2004.
http://www.ahrq.gov/downloads/pub/evidence/pdf/ecinc/ecinc.pdf

Other reviews

Source – EPPI Centre

Kavanagh J, Stansfield C, Thomas J. Incentives to improve smoking, physical activity, dietary and weight management behaviours: a scoping review of the research evidence Social Science Research Unit, Institute of Education, University of London. London: EPPI Centre; 2009
http://eppi.ioe.ac.uk/cms/Default.aspx?tabid=2468&language=en-US

Primary studies

Source - MEDLINE(Ovid) 1950 to May Week 4 2010

Finkelstein EA, Brown DS, Brown DR, Buchner DM.
A randomized study of financial incentives to increase physical activity among sedentary older adults.
Preventive Medicine 2008;47(2):182-7.

Gomel M, Oldenburg B, Simpson JM, Owen N.
Work-site cardiovascular risk reduction: a randomized trial of health risk assessment, education, counseling, and incentives.
American Journal of Public Health 1993;83(9):1231-8.

DeVahl J, King R, Williamson JW.
Academic incentives for students can increase participation in and effectiveness of a physical activity program.
Journal of American College Health 2005;53(6):295-8.

Harland J. White M. Drinkwater C. Chinn D. Farr L. Howel D.
The Newcastle exercise project: a randomised controlled trial of methods to promote physical activity in primary care.
Comments
Comment in: BMJ. 2000 May 27;320(7247):1471; author reply 1473-4; PMID: 10877561],
Comment in: BMJ. 2000 May 27;320(7247):1471; author reply 1473-4; PMID: 10877562],
Comment in: BMJ. 2000 May 27;320(7247):1471-2; author reply 1473-4; PMID: 10877563],
Comment in: BMJ. 2000 May 27;320(7247):1472; author reply 1473-4; PMID: 10877564],
Comment in: BMJ. 2000 May 27;320(7247):1470-1; author reply 1473-4; PMID: 10877560],
Comment in: BMJ. 2000 May 27;320(7247):1473; PMID: 10877567], Comment in: BMJ. 2000 May 27;320(7247):1474; PMID: 10877568], Comment in: BMJ. 2000 May 27;320(7247):1473; PMID: 10877566], Comment in: BMJ. 2000 May 27;320(7247):1472; author reply 1473-4; PMID: 10877565]
BMJ 1999;319(7213):828-32.

Wing RR, Jeffery RW, Pronk N, Hellerstedt WL.
Effects of a personal trainer and financial incentives on exercise adherence in overweight women in a behavioral weight loss program.
Obesity Research 1996;4(5):457-62.

Gomel M. Oldenburg B. Simpson JM. Owen N.
Work-site cardiovascular risk reduction: a randomized trial of health risk assessment, education, counseling, and incentives.
American Journal of Public Health 1993;83(9):1231-8.

Economic evaluations

Source – Cochrane Library (Wiley) 2010 Issue 3 (NHS EED)

Cobiac LJ, Vos T, Barendregt JJ. Cost-effectiveness of interventions to promote physical activity: a modelling study PLoS Medicine 2009; 6(7)
http://www.mrw.interscience.wiley.com/cochrane/cleed/articles/NHSEED-22009102454/frame.html

Lu C, Schultz A B, Sill S, Petersen R, Young J M, Edington D W. Effects of an incentive-based online physical activity intervention on health care costs Journal of Occupational and Environmental Medicine 2008; 50(11): 1209-1215
http://www.mrw.interscience.wiley.com/cochrane/cleed/articles/NHSEED-22009100937/frame.html

Background information

Source – NICE website

Should incentives be used to encourage healthy living? Newsletter of meeting of NICE's citizens council May 2010
http://www.nice.org.uk/newsroom/features/HealthyLivingIncentives.jsp

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Archived ARIF Request

Follicle Stimulating Hormone Infertile Women

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in September 2002.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of recombinant follicle stimulating hormone (rFSH) compared to human-derived urinary follicle stimulating hormone (uFSH) in assisted conception in infertile women?

Reviews Identified

- Daya S, Gunby J. Recombinant versus urinary follicle stimulating hormone for ovarian stimulation in assisted reproduction cycles (Cochrane Review). In: The Cochrane Library, Issue 2, 2002. Oxford: Update Software.

Trials Identified

Contact ARIF for details.

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Comments

We identified a number of systematic reviews, the most relevant is that by Daya and Gunby. In general, this is a good review and its broad scope has been well managed. The findings suggest that rFSH is more effective than uFSH for ovarian stimulation in infertile couples undergoing in-vitro fertilisation (IVF) and that there is little or no difference in effectiveness between the two rFSH products available (follitropin alpha and beta). Insufficient information at the time of the review means we are unable to say whether this benefit extends to fertility treatment using intra-cytoplasmic sperm injection (ICSI).

The review is slightly out of date, as several trials have been published since. From our brief assessment of these trials it appears that their findings are largely in line with those of the review with regard to IVF treatment.

Given that rFSH appears more effective than uFSH for IVF and that rFSH is more expensive, a cost-effectiveness analysis could be an important component in any decision making process.

Request Carried Out: September 2002

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Bariatric procedures

Synopsis

Question:	What is the evidence that gastric bypass is better than gastric banding in reducing obesity related co-morbidities?
Evidence Identified:	Picot J, Jones J, Colquitt JL, Gospodarevskaya E, Loveman E, Baxter L, Clegg AJ. The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation. Health Technology Assessment. 2009; 13(41) Colquitt JL, Picot J, Loveman E, Clegg AJ. Surgery for obesity. Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD003641. DOI: 10.1002/14651858.CD003641.pub3.
Comments:	Currently, there is a paucity of evidence on the effectiveness of gastric bypass in reducing co-morbidities, compared with gastric banding. Very limited data from a small RCT (n = 51) with uncertainty in the methodological quality of the study suggested that co-morbidities were few and similar in both laparoscopic Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding procedures.
Date Completed:	September 2010

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Bariatric procedures

Request completed: September 2010

Question

What is the evidence that gastric bypass is better than gastric banding in reducing obesity related co-morbidities?

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol (www.arif.bham.ac.uk/strategy.shtml). Text and index terms were used to represent the population and the intervention. Sources were searched from their inception to August 2010. No language restriction was applied to the searches. As an example the MEDLINE search can be found in Appendix A. The following inclusion criteria were used for study selection:

Population	People with obesity who are eligible for bariatric procedure
Intervention	Gastric bypass
Comparator	Gastric banding
Outcome	Obesity related co-morbidities
Study design	Systematic reviews and health technology assessments

Results

Full search results can be found in Appendix B.

One health technology assessment (HTA) report[1] was identified as being most recent, comprehensive and relevant to the question posed.

This well-conducted HTA report, published in 2009, was an update of a previously published systematic review and economic evaluation. The systematic review of clinical effectiveness, by the same group of authors, was also published as a Cochrane review in 2009.[2]

The aim of the HTA report[1] was to assess the clinical effectiveness and cost-effectiveness of bariatric surgery for obesity. The clinical effectiveness review sought to identify randomised controlled trials (RCTs) comparing different surgical procedures and controlled clinical trials and prospective cohort studies (with a control cohort) comparing surgery with non-surgical interventions. The population of interest was adult patients with body mass index (BMI) of 30 or over and young

people who fulfil the definition of obesity for their age, sex and height. The intervention was open or laparoscopic surgical procedures. The comparator was surgical procedures in comparison with one another or non-surgical interventions. The main outcomes were weight change, quality of life (QoL), preoperative and postoperative mortality and morbidity, and obesity related co-morbidities. Follow up duration was a minimum of 12 months.

The review's searches were conducted up to 2008. Twenty RCTs comparing different surgical procedures and six trials comparing surgery with non-surgical interventions were included.

The 20 RCTs that compared different surgical procedures were all two-armed and in total contained the following nine comparisons:

1. Gastric bypass vs. vertical banded gastroplasty: 7 trials
2. Laparoscopic Roux-en-Y gastric bypass vs. laparoscopic adjustable gastric banding: 1 trial
3. Laparoscopic Roux-en-Y gastric bypass vs. laparoscopic sleeve gastrectomy: 1 trial
4. Laparoscopic adjustable gastric banding vs. laparoscopic isolated sleeve gastrectomy: 1 trial
5. Gastric bypass (non-banded) vs. banded gastric bypass: 1 trial
6. Vertical banded gastroplasty vs. adjustable gastric banding: 3 trials
7. Open gastric bypass vs. laparoscopic gastric bypass: 4 trials
8. Open vertical banded gastroplasty vs. laparoscopic vertical banded gastroplasty: 1 trial
9. Open adjustable silicone gastric banding vs. laparoscopic adjustable silicone gastric banding: 1 trial

Of the 20 RCTs only five reported outcomes on co-morbidities. Outline characteristics of the five trials are listed below in Table 1.

Table 1 Outline characteristics of the five RCTs that reported co-morbidities*

Study	Comparison	Follow-up
Angrisani 2007 (Italy)	• Laparoscopic Roux-en-Y gastric bypass (n = 27) • Laparoscopic adjustable gastric banding (n = 24)	60 months
Himpens 2006 (Belgium)	• Laparoscopic adjustable gastric banding (n = 40) • Laparoscopic isolated sleeve gastrectomy (n = 40)	36 months
Bessler 2007 (USA)	• Banded gastric bypass (n = 46) • Gastric bypass (non-banded) (n = 44)	Up to 36 months
van Dielen 2005 (Netherlands)	• Vertical banded gastroplasty (n = 50) • Laparoscopic adjustable gastric banding (n = 50)	24 months and 84 months
Puzziferri 2006 (USA)	• Open gastric bypass (n = 76) • Laparoscopic gastric bypass (n = 79)	36 months

* For definition of the surgical procedures see Appendix C.

As it can be seen, only one trial (Angrisani 2007), which compared laparoscopic Roux-en-Y gastric bypass (LRYGBP) with laparoscopic adjustable gastric binding (LAGB) and reported co-morbidities, is relevant to the question posed above.

This trial targeted participants with a body mass index (BMI) between 35 and 50 and at an age between 16 years and 50 years. Twenty-seven participants were recruited to the LRYGBP group and 24 to the LAGB. Follow-up was 60 months. There were a number of similarities at baseline between the LRYGBP group and the LAGB in terms of age, gender, BMI and co-morbidity (see Table 2 for details). However, it was unclear whether the similarity was due to the small sample size.

Table 2 Baseline characteristics (Angrisani 2007)

	LRYGBP	LAGB
Number of participants	27	24
Mean age (SD)	34.1 (8.9)	33.8 (9.1)
Gender (male : female)	4 : 20	5 : 22
BMI [mean ± SD (range)]	43.8 ± 4.1 (38.9 - 48.9)	43.4 ± 4.2 (38.1 - 49.2)
Co-morbidity (no. of patients):		
Hyperlipaemia	2	0
Hypertension	1	3
Type 2 diabetes	1	0
Sleep apnoea	0	1

The review authors assessed the quality of the study and highlighted that there was uncertain risk of bias regarding allocation sequence generation, allocation concealment, whether the trial was free of selective reporting and free of other bias. Thus the methodological quality of the trial was poor. As to the study results, at a five year follow up diabetes and hyperlipaemia in the LRYGBP group and sleep apnoea in the LAGB group resolved. The review authors concluded that this small study showed that co-morbidities were few and similar in the comparison groups; the risk of bias for this study is uncertain, although the risk of bias for co-morbidities is likely to be low.

A further ARIF search for primary studies from 2008 to date was conducted but identified no relevant studies.

Conclusions

Currently, there is a paucity of evidence on the effectiveness of gastric bypass in reducing co-morbidities, compared with gastric banding. Very limited data from a small RCT (n = 51) with uncertainty in the study methodological quality suggested that co-morbidities were few and similar

in both laparoscopic Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding procedures.

References

1. Picot J, Jones J, Colquitt JL, Gospodarevskaya E, Loveman E, Baxter L, Clegg AJ. The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation. [Review] [197 refs] Health Technology Assessment (Winchester, England). 2009; 13(41):1-190, 215-357

2. Colquitt JL, Picot J, Loveman E, Clegg AJ. Surgery for obesity. Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD003641. DOI: 10.1002/14651858.CD003641.pub3.

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 gastric band$.mp.
2 lap band$.mp.
3 or/1-2
4 gastric bypass$.mp.
5 3 and 4

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Appendix B – Literature search results

Systematic reviews

Source – Cochrane Library (CDR) 2010 Issue 8

Oude Luttikhuis Hiltje, Baur Louise, Jansen Hanneke, Shrewsbury Vanessa A, O'Malley Claire, Stolk Ronald P, Summerbell Carolyn D. Interventions for treating obesity in children. Cochrane Database of Systematic Reviews: Reviews 2009 Issue 1 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD001872.pub2

Fernandes Marcos AP, Atallah Álvaro N, Soares Bernardo , Saconato Humberto, Guimarães Sandra M, Matos Delcio, Carneiro Monteiro Larissa R, Richter Bernd. Intragastric balloon for obesity. Cochrane Database of Systematic Reviews: Reviews 2007 Issue 1 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD004931.pub2

Colquitt Jill L, Picot Joanna, Loveman Emma, Clegg Andrew J. Surgery for obesity. Cochrane Database of Systematic Reviews: Reviews 2009 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD003641.pub3

Curioni Cintia, André Charles, Veras Renato. Weight reduction for primary prevention of stroke in adults with overweight or obesity. Cochrane Database of Systematic Reviews: Reviews 2006 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD006062.pub2

Source – Cochrane Library (DARE) 2010 Issue 3

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Clegg A J,Colquitt J,Sidhu M K, Royle P, Loveman E, Walker A. The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation (Structured abstract). Health Technology Assessment 2002; 6 (12): 1-153

Whitlock E P, O'Connor E A, Williams S B, Beil T L, Lutz K W. Effectiveness of weight management programs in children and adolescents (Structured abstract). Agency for Healthcare Research and Quality 2008.

Tice JA, Karliner L, Walsh J, Petersen AJ, Feldman MD. Gastric banding or bypass: a systematic review comparing the two most popular bariatric procedures (Structured abstract). American Journal of Medicine 2008; 121 (10): 885-893

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Lefevre F. Laparoscopic adjustable gastric banding for morbid obesity (Provisional abstract). Blue Cross and Blue Shield Association, Technology Evaluation Center; 2007

Lefevre F. Newer techniques in bariatric surgery for morbid obesity: laparoscopic adjustable gastric banding, biliopancreatic diversion, and long-limb gastric bypass (Provisional abstract). Blue Cross and Blue Shield Association, Technology Evaluation Center; 2005

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Buchwald H, Estok R, Fahrbach K, Banel D, Sledge I. Trends in mortality in bariatric surgery: a systematic review and meta-analysis (Structured abstract). Surgery 2007; 142 (4); 621-635

Source – Cochrane Library (HTA database) 2010 Issue 3

Chen J, McGregor M. The gastric banding procedure: an evaluation (Structured abstract). Montreal: Technology Assessment Unit of the McGill University Health Centre (MUHC); 2004

Institute for Clinical Systems Improvement. Gastric restrictive surgery for clinically severe obesity in adults (Structured abstract). Bloomington MN: Institute for Clinical Systems Improvement (ICSI); 2005

Blue Cross Blue Shield Association. Laparoscopic adjustable gastric banding for morbid obesity (Structured abstract). Chicago IL: Blue Cross Blue Shield Association (BCBS); 2007

Medical Services Advisory Committee. Laparoscopic adjustable gastric banding for morbid obesity (Structured abstract). Canberra: Medical Services Advisory Committee (MSAC); 2003

Guo B, Harstall C. Laparoscopic adjustable gastric banding for the treatment of clinically severe (morbid) obesity in adults: an update (Structured abstract). Edmonton: Alberta Heritage Foundation for Medical Research (AHFMR); 2005

Comite d'Evaluation et de Diffusion des Innovations Technologiques. Laparoscopic adjustable gastric banding - systematic review, expert panel (Brief record). Paris: Comite d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT); 2003

HAYES Inc. Laparoscopic bariatric surgery: Roux-en-Y gastric bypass, vertical banded gastroplasty and adjustable gastric banding (Structured abstract). Lansdale, PA: HAYES, Inc; 2007

Blue Cross Blue Shield Association. Newer techniques in bariatric surgery for morbid obesity: laparoscopic adjustable gastric banding, biliopancreatic diversion, and long-limb gastric bypass (Structured abstract). Chicago IL: Blue Cross Blue Shield Association (BCBS); 2005

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HAYES Inc. Open restrictive bariatric surgery: gastroplasty and gastric banding (Structured abstract). Lansdale, PA: HAYES, Inc; 2007

Blue Cross Blue Shield Association. Special report: the relationship between weight loss and changes in morbidity following bariatric surgery for morbid obesity (Structured abstract). Chicago IL: Blue Cross Blue Shield Association (BCBS); 2003

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Pichon Riviere A, Augustovski F, Ferrante D, Garcia Marti S, Glujovsky D, Lopez A. Usefulness of surgical treatments for obesity (Brief record). Ciudad de Buenos Aires: Institute for Clinical Effectiveness and Health Policy (IECS);2004

Day P. What is the evidence for the safety and effectiveness of surgical and non-surgical interventions for patients with morbid obesity? (Structured abstract). Christchurch: New Zealand Health Technology Assessment (NZHTA); 2005

Source – MEDLINE (Ovid) 1950 – Aug week 1 2010

De Groot NL. Burgerhart JS. Van De Meeberg PC. de Vries DR. Smout AJ. Siersema PD. Systematic review: the effects of conservative and surgical treatment for obesity on gastro-oesophageal reflux disease. [Review] [61 refs]. Alimentary Pharmacology & Therapeutics 2009; 30(11-12):1091-102

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Pratt JS. Lenders CM. Dionne EA. Hoppin AG. Hsu GL. Inge TH. Lawlor DF. Marino MF. Meyers AF. Rosenblum JL. Sanchez VM. Best practice updates for pediatric/adolescent weight loss surgery. [Review] [83 refs]. Obesity 2009; 17(5):901-10

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Treadwell JR. Sun F. Schoelles K. Systematic review and meta-analysis of bariatric surgery for pediatric obesity. [Review] [89 refs]. Annals of Surgery 2008; 248(5):763-76

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Levy P. Fried M. Santini F. Finer N. The comparative effects of bariatric surgery on weight and type 2 diabetes. [Review] [58 refs]. Obesity Surgery 2007; 17(9):1248-56

Chaston TB. Dixon JB. O'Brien PE. Changes in fat-free mass during significant weight loss: a systematic review. [Review] [63 refs]. International Journal of Obesity 2007; 31(5):743-50

O'Brien PE. McPhail T. Chaston TB. Dixon JB. Systematic review of medium-term weight loss after bariatric operations. [Review] [53 refs]. Obesity Surgery 2006; 16(8):1032-40

Pannala R. Kidd M. Modlin IM. Surgery for obesity: panacea or Pandora's box?. [Review] [100 refs]. Digestive Surgery 2006; 23(1-2):1-11

Maggard MA. Shugarman LR. Suttorp M. Maglione M. Sugerman HJ. Livingston EH. Nguyen NT. Li Z. Mojica WA. Hilton L. Rhodes S. Morton SC. Shekelle PG. Meta-analysis: surgical treatment of obesity.[Summary for patients in Ann Intern Med. 2005 Apr 5;142(7):I55; PMID: 15809458]. Comments. Comment in: ACP J Club. 2005 Sep-Oct;143(2):51; PMID: 16134925]. Annals of Internal Medicine 2005; 142(7):547-59

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O'Brien PE. Dixon JB. Lap-band: outcomes and results. Journal of Laparoendoscopic & Advanced Surgical Techniques. Part A. 2003; 13(4):265-70 Abstract

Gomez Escudero O. Herrera Hernandez MF. Valdovinos Diaz MA. [Obesity and gastroesophageal reflux disease]. [Review] [31 refs] [Spanish]. Revista de Investigacion Clinica 2002; 54(4):320-7

Gentileschi, P. Kini, S. Catarci, M. Gagner, M. Evidence-based medicine: open and laparoscopic bariatric surgery. [Review] [134 refs]. Surgical Endoscopy 2002; 16(5):736-44.

Source - EMBASE (Ovid) 1980 to 2010 Week 32

Boudouris O. Obesity Surgery. Conference: International Federation for the Surgery of Obesity and metabolic disorders. XIV World Congress Paris France. 19 (8) (pp 1042-1043), 2009.

Cabra H.A, Zanela O.O, Anaya P, Rodriguez S. Value in Health. Conference: ISPOR 12th Annual European Congress Paris France.. 12 (7) (pp A491), 2009. Date of Publication: October 2009.

Buchwald H, Estok R, Fahrbach K, Banel D, Jensen M.D, Pories W.J. Weight and Type 2 Diabetes after Bariatric Surgery: Systematic Review and Meta-analysis. American Journal of Medicine 2009; 122 (3) 248-256.e5

Systematic review in progress

Source – Cochrane Library (CDR) 2010 Issue 8

Oyesanya Olufunso A, van Wely Madelon, Clarke Mike J. Life-style modification, non-pharmacological and pharmacological strategies for obese subfertile women. Cochrane Database of Systematic Reviews: Protocols 2009 Issue 1 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD007616

Other reviews

Source – National Obesity Observatory

Dent M, Chrisopoulos S, Nulhall C, Ridler C. Bariatric surgery for obesity. Oxford; National Obesity Observatory; 2010.

Guideline

Source – NICE web site

National Institute for Health and Clinical Effectiveness. Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children. NICE Clinical Guideline CG43. London: NICE; 2006.
http://www.nice.org.uk/nicemedia/live/11000/30365/30365.pdf
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Appendix C – Sources of definitions of the surgical procedures

Adjustable gastric banding, **vertical banded gastroplasty** and **Roux-en-Y gastric bypass**: http://www.athealth.com/consumer/disorders/gastric.html

Sleeve Gastrectomy: http://www.healthierweight.co.uk/obesity-surgery/sleeve-gastrectomy/how-is-the-operation-performed/

Laparoscopic Adjustable Gastric Banding: http://www.streamline-surgical.com/procedures-gastric-band.htm

Vertically Banded Gastric Bypass: http://www.johnhustedmd.com/vert_banded.htm [
Open Bariatric Surgery and **Laparoscopic Bariatric Surgery:**
http://www.docshop.com/education/bariatrics/types/

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Gastrointestinal Infections
Respiratory Infections
School Children

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence on the effectiveness of interventions to prevent or reduce transmission of gastrointestinal and respiratory infections in schools in young children?

Reviews Identified

No systematic reviews were identified.

Trials Identified

Source - Cochrane Library 2001 Issue 3 (CCTR)

- Niffenegger JP. Proper handwashing promotes wellness in child care. Journal of Pediatric Health Care 1997;11(1):26-31
- Ulione MS. Effectiveness of a health promotion program in Head Start. Missouri Nurse 1996;65(1):16
- Kotch JB, Weigle KA, Weber DJ, Clifford RM, Harms TO, Loda FA, Gallagher PN Jr, Edwards RW LaBorde D, McMurray MP et al. Evaluation of an hygienic intervention in child day-care centers. Pediatrics 1994;94(6):991-4
- Roberts CR, Imrey PB, Turner JD, Hosokawa MC, Alster JM. Reducing physician visits for colds through consumer education. JAMA 1983;250 (15):1986-9
- Kimel LS. Handwashing education can decrease illness absenteeism. Journal of School Nursing 1996 ;12(2):14-16,18
- Master D, Hess Longe SH, Dickson H. Scheduled hand washing in an elementary school population Family Medicine 1997;29(5): 336-9
- Roberts L, Jorm L, Patel M, Smith W, Douglas RM, McGilchrist C. Effect of infection control measures on the frequency of diarrheal episodes in child care: a randomized, controlled trial Pediatrics 2000 ;105 (4 Pt 1) :743-6
- Roberts L, Smith W, Jorm L, Patel M, Douglas RM, McGilchrist C Effect of infection control measures on the frequency of upper respiratory infection in child care: a randomized, controlled trial. Pediatrics 2000;105 (4 Pt 1) :738-42
- Uhari M, Mottonen M. An open randomized controlled trial of infection prevention in child day-care centers. Pediatric Infectious Disease Journal 1999 ;18(8):672-7

Source - Medline search 1966 - 2001

- Early E, Battle K, Cantwell E, English J, Lavin JE, Larson E. Effect of several interventions on the frequency of handwashing among elementary public school children (Clinical trial) American Journal of Infection Control 1998;26(3):263-9.

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Comments

Our searches identified no relevant systematic reviews on this topic. Extending our searches to look for primary studies, we identified a number of trials. As we have only searched Medline and the Cochrane Library controlled trials register for these primary studies, the list should not be viewed as comprehensive.

Most of the studies were randomised controlled trials. Some of the studies encompass the setting (schools), population (children 3-7years) and outcomes (prevention/reduction in GI and respiratory infections) relevant to the question. Others encompass different settings (day care centres) and populations (children under 3 years, mixed child-adults population), which may or may not provide relevant information. At present, we have not undertaken a critical appraisal of these trials.

A systematic review on this topic is currently being undertaken by the West Midlands Health Technology Assessment Collaboration (formerly the Development and Evaluation Service (DES).

Request Carried Out: December 2001

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Imatinib
Gastrointestinal Stromal Tumours

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of imatinib (Glivec®) in the treatment of patients with gastrointestinal stromal tumours?

Reviews Identified

No systematic reviews were identified.

Primary Studies Identified

- Demetri GD, von Mehren M, Blanke CD, van den Abbeele AD, Eisenberg B et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumours. New England Journal of Medicine 2002; 347(7):472-80

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Comments

No systematic reviews were identified.

From the key trial by Demetri et al, imatinib appears to be a promising treatment for GIST, particularly for patients for whom the prognosis is very poor. Unfortunately, in our view the length of follow-up in the above study is not long enough nor is there sufficient information on the prognostic factors in the included patients to definitely say that imatinib truly confers survival benefits substantially better than what would be expected from the natural history of the disease.

Other trials are in progress and NICE is preparing guidance on this topic.

The topic is prone to require updating as new information becomes available.

Request Carried Out: December 2002

Updated: November 2004 - NICE has issued guidance on this topic.

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Archived ARIF Request

Gastroplasty
Morbid Obesity

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Is banded gastroplasty a safe, effective and cost effective treatment for morbid obesity?

Reviews Identified

RCTs only

- Andersen T et al. Long-term (5-year) results after either horizontal gastroplasty or very-low-calorie diet for morbid obesity. International Journal of Obesity 1988;12:277-84
- Andersen T. Horizontal or vertical banded gastroplasty after pretreatment with very-low-calorie formula diet: a randomized trial. International Journal of Obesity 1987;11:295-304

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Comments

No systematic reviews were identified.

The two randomised trials give useful insights into aspects of the effectiveness of gastroplasty:

- That very-low-calorie diets can be effective in treating morbid obesity.
- That vertical banded gastroplasty is more effective than horizontal gastroplasty.
- That dietary and surgical interventions should be seen as complementary.
- That the short term effects of horizontal gastroplasty and possibly vertical banded gastroplasty, are poorly maintained over five years.

Account does need to be taken in the interpretation of the two trials that there may be discordant results from other trials examining the same question. In this situation there is a need to undertake a systematic review of all available research.

Request Carried Out: July 1996

Updated: May 1997 - The NHS Centre for Reviews & Dissemination have produced an Effective Health Care Bulletin on, "The Prevention & Treatment of Obesity" (April 1997, Vol3 No2) which largely

supercedes the information which ARIF provided in relation to this request. However, no specific comments are made on the likely complementary nature of very low calorie diets and gastroplasty, and the difference in effects of horizontal and vertical gastroplasty. ARIF continues to believe these are important issues in considering surgical treatments for the morbidity/severely obese.

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Archived ARIF Request

Gender Reassignment Surgery

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in April 1997 and Update in July 2004.

The Problem Submitted for ARIF to Advise Upon:

What are the effects of gender reassignment surgery, and does the balance of positive and negative effects suggest that this procedure is clinically effective overall?

Question Reformulated

A detailed consideration of the main elements of the question was undertaken:

- INTERVENTION: Do different surgical procedures have different effects and has the technical skill with which the procedure is generally performed improved over time?
- POPULATION: Does the nature of the effects depend on characteristics of the person submitted for surgery? It would be expected that the following would have an important bearing:
- Whether the original biological sex is male or female.
- The degree of certainty about the diagnosis, distinguishing between the general condition of gender dysphoria and recognised causes of this such as transvestitism, homosexuality and primary transsexualism.
- Other characteristics of the patient beyond the primary diagnosis, such as previous treatment and coexisting conditions.
- OUTCOMES: In the case of gender reassignment the following outcomes would be expected to be important:
- Immediate success of surgery - complications of surgery, cosmetic/aesthetic effect, requirement for reoperation.
- Health outcomes for the individual - especially suicide.
- Psychological outcomes for the individual - measures of adjustment, happiness, regret or satisfaction with the operation.
- Social outcomes for the individual - ability to work, maintain relationships and generally contribute to society.
- Health/psychological/social outcomes for other family members.
- Societal outcomes - especially use of health care resources.

Reviews Identified

An extensive bibliography of relevant studies was compiled; the list below represents those references most pertinent to the comments section.

- Brown GR. A review of clinical approaches to gender dysphoria. Journal of Clinical Psychiatry 1990; 51: 57-64

Other Literature Identified

- Snaith P et al. Sex reassignment surgery. A Study of 141 Dutch transsexuals. British Journal of Psychiatry 1993; 162: 681-5
- Meyer JK, Reter DJ. Sex reassignment: follow up. Archives of General Psychiatry 1979; 36: 1010-1015
- Abramowitz SI. Psychosocial outcomes of sex reassignment surgery. Journal of Consulting and Clinical Psychology 1986; 54: 183-189
- Williams G. Gender reassignment today. British Medical Journal 1987; 295: 1348
- Mate-Kole KC et al. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. British Journal of Psychiatry 1990; 157: 261-4
- Kuiper B, Cohen-Kettenis P. Sex reassignment surgery: a study of 141 Dutch transsexuals. Archives of Sexual Behaviour 1988; 17: 349-457

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Comments

The overall conclusion reached by ARIF was:

The degree of uncertainty about any of the effects of gender reassignment is such that it is impossible to make a judgement about whether the procedure is clinically effective.

This was based on the following observations on the literature identified:

- There is no systematic review of the available research literature, thus even the better reviews identified (Brown GR, 1990) do not give sufficient detail about the review method to assure that bias has been avoided. Making a judgement about the clinical effectiveness of gender reassignment surgery is immediately made difficult without unbiased review of the available research.
- There seem to have been at least 30 research assessments of the effects of gender reassigment surgery (Brown GR, 1990). The number of these particularly dictates that some sort of systematic review is necessary to make a balanced judgement about what the effects actually are. Further, the development of research in the field suggests that criticisms of early studies have only been reacted to more recently (Snaith P et al, 1993). This emphasizes that any reviews must not only be systematic, but up-to-date.
- Although the research published generally states that the effects are beneficial, it would be incorrect to say that this finding has been universal (Meyer JK, Reter DJ, 1979). This study has been heavily criticised on grounds of method, but given that most of the research designs used to answer the question are highly susceptible to bias, its results cannot be easily discounted on this basis (Abramowitz SI, 1986). Further, individuals involved in providing gender reassignment surgery have actually voiced their concern that the results of available research are misleading (Williams G, 1987). One should not overstate the importance of an opinion, but a challenge to the "face validity" of the results should prompt closer scrutiny of whether there are grounds to suspect that the "researchers might have got it wrong".
- Most research designs employed to investigate the effects of gender reassignment surgery have not employed a control group. This means that it is very difficult to ascribe any effects identified to the surgery performed. The alternative explanation that improvements would have occurred anyway, because as time passes the individual adjusts better to their circumstances, is plausible and has received support from a study which did contain a control group (Meyer JK, Reter DJ, 1979). The results of this on its own are not sufficient to overturn the results of other studies performed, but it does raise doubts about the true nature of the effect of gender reassignment surgery, which should at least have been more intensively investigated than has been the case. The only study (Mate-Kole et al, 1990) to have taken up this challenge compared outcomes in 20 patients having immediate

surgery with 20 patients awaiting surgery. Its results seem to reinforce the existence of benefit observed in the studies without controls, but the correct comparison is between one small controlled study (Meyer JK, Reter DJ, 1979) which showed little effect of surgery against another similarly small study (Mate-Kole et al, 1990) showing benefit. Further, the latter study is also not without flaws. A particular concern is bias in the assessment of outcome. It would have been clear to both the participants and the investigators whether they were in the treatment or control group and in such circumstances it is highly likely that questions using the options, "more active/same/less active" could have received biased responses. Results obtained for those in the treatment group will have a tendency to overestimate the effect of the surgery, and results for those in the control group will have a tendency to underestimate the effect of "usual" treatment.

- The final basis for the assertion that there is considerable uncertainty about the effects of gender reassignment surgery is the high rates of loss to follow-up in many studies, over 50% in some cases (Kuiper B, Cohen-Kettenis P, 1988). Although loss is inevitable to some degree, high rates are important sources of bias, particularly where there is no control group. The reason for this is that it may be the surgery itself and the consequences of it, e.g dissatisfaction or even suicide, causing the drop-outs. Thus those patients who are examined to obtain the results are self-selected towards those who have better outcomes.

The points above, by raising significant problems in the conduct of much of the research claiming to show that gender reassignment surgery is beneficial, suggests that the true conclusion from the available research is that we genuinely cannot be certain about what its effects are. A systematic review could help reduce this uncertainty, but because of the flawed nature of the majority of the research it is likely that the only way to reduce the level of uncertainty is to undertake more research using more rigorous designs with a control group, ideally randomly assigned, and blind independent assessment of outcomes (Abramowitz SI, 1986).

Request Carried Out: April 1997

Updated: July 2004

The search for literature conducted in 1997 was up-dated following media interest in this topic, and direct contact concerning our original request.

We re-ran searches on the Cochrane Library, MEDLINE and PsycINFO as well as interrogating web-sites of key organisations involved in health technology assessment such as NICE, CCOHTA, AHRQ and NZHTA. [Further details of locations searched and search terms used are available on request].

The search was conducted on 5/7/04.

Although many narrative reviews have been published since 1997, there were only two satisfying criteria for being systematic e.g. statement of sources searched:

- Best L, Stein K. Surgical gender reassignment for male to female transsexual people. Development and Evaluation Committee Report No 88. Southampton: Wessex Institute for Health Research & Development, 1998
- Day P. Trans-gender reassignment surgery. NZHTA Tech Brief Report 2002 Vol 1 No 1. Christchurch: New Zealand Health Technology Assessment (NZHTA), 2002

These identified no randomised controlled trials or controlled trials to the end of 2001 and mostly based their conclusions on cohort studies and case-series.

Both reviews while recognising net benefits to carefully selected individuals remained concerned about the quality of evidence on effectiveness (particularly adverse outcomes) and the biases to which available studies were open. [In particular see discussion in section 5.2 of the report by Best and Stein.]

Our searches confirm absence of randomised controlled trials and controlled trials to December 2001, and have identified none since then to the end of June 2004.

Further cohort studies and case-series appear to have been published eg Lawrence AA. Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. Archives of

Sexual Behavior 2003;32(4):299-315. We have not assessed in detail whether all these studies are open to the level of bias which gave rise to the uncertainty in the DEC and NZHTA reports, although the concerns about loss to follow-up do apply to the specific article quoted where only 232 out of 727 persons undergoing surgery were represented in the main results.

If a parallel control group is not feasible, as proponents of gender reassignment surgery suggest, follow-up studies must convince readers that they have identified a representative cohort of individuals (particularly with respect to likelihood of experiencing benefits or disbenefits) and represented all of these in the final results. The logistics of following patients up over long periods and achieving a cohort which is not influenced by the immediate results (i.e. individuals with good/very poor outcomes most likely to remain in touch with surgeon) strongly suggest that the cohort studies should also be conducted prospectively (study planned and organised before data collection begins).

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General Management Oesophageal Cancer

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The Problem Submitted for ARIF to Advise Upon:

Is there any evidence on the effectiveness of different interventions for cancer of the oesophagus?

Reviews Identified

- Bhansali MS, Vaidya JS, Bhatt PK et al. Chemotherapy for carcinoma of the oesophagus: A comparison of evidence from meta-analyses of randomised controlled trials and historical control studies. Annals of Oncology 1996;7:355-359
- Blazeby JM and Alderson D. Review: Chemotherapy, irradiation and their roles in the management of oesophageal cancer. Journal of Gastroenterology and Hepatology 1997;12:612-619

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Comments

We identified no general reviews on the management of oesophageal cancer. The only relevant systematic review identified was that by Bhansali which is a reasonably reliable review of the literature on the role of chemotherapy, specifically cisplatinum-based combination chemotherapy. It provides a useful summary of the effect on survival of adjuvant and neoadjuvant chemotherapy for this condition, which according to the RCT data is small. The main limitation of this review in relation to the question is its failure to address other aspects of the management of oesophageal cancer, and in this sense the review by Blazeby and Alderson is more helpful.

This is not a systematic review, but is a good narrative overview of the roles of chemotherapy and irradiation in the management of oesophageal cancer. It starts from the assumption that surgery is the standard treatment and that other treatments should be used as adjuvents to surgery, or when surgery is inappropriate, but provides no evidence to support this. Although the reliability of the review is uncertain, it concludes that at this stage there is no clear evidence of any survival benefit associated with neoadjuvant therapy.

In summary, there appear to be considerable uncertainties around the effectiveness of different interventions for cancer of the oesophagus. Surgery appears to be the standard treatment at the moment, with other treatments being used in addition to this or as alternatives when patients are

unsuitable for surgery, although the evidence base for this is unclear.

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Archived ARIF Request

Imiquimod
Genital Warts

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of imiquimod in the treatment of genital warts?

Reviews Identified

- Moore RA, Edwards JE, Hopwood J, Hicks D. Imiquimod for the treatment of genital warts: a quantitative systematic review. BMC Infectious Diseases 2001; 1(3) 1-21. http://www.biomedcentral.com/1471-2334/1/3

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Comments

Our search only identified one systematic review. In general the review appears to be well conducted and its findings can probably be relied upon, although aspects of our appraisal were limited by under reporting of some parts of the methodology employed. Six double blind randomised placebo controlled trials were included in the review. The review did not identify any trials comparing imiquimod to other interventions for genital warts.

The results indicate that compared to placebo imiquimod is an effective treatment for genital warts. Treatment may not be quite as successful in HIV-positive patients.

Further research is required to assess whether imiquimod is more or less effective than other established treatments for genital warts.

This topic is prone to require updating as new information becomes available.

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Mucolytic Agents
Glue Ear

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The Problem Submitted for ARIF to Advise Upon:

What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Question Reformulated

Due to the breadth of this question, we focused our attention on groups of interventions. The groups of interventions were antimicrobial drugs, steriods, antihistamines and decongestants, mucolytic agents, and auto-inflation.

This web page details our findings on mucolytic agents. Links to pages on the other groups of interventions can be found at the bottom of this page.

Reviews Identified

- Williamson I. Otitis media with effusion. In: Clinical Evidence 3. London: BMJ Publishing Group, 2000. Pp248-254
- Pignataro O, Pignataro L D, Gallus G, Calori G, Cordaro C I. Otitis media with effusion and s-carboxymethylcysteine and/or its lysine salt: a critical overview. International Journal of Pediatric Otorhinolaryngology 1996, 35(3), pp.231-241.

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Comments

The review by Williamson is a systematic overview of treatments for glue ear and appears a concise and accurate synthesis of the evidence presented in other systematic reviews.

We identified one systematic review, by Pignataro et al (1996), on the use of a mucolytic agent (carboxymethylcysteine and/or its salt) to treat glue ear and this was the same review identified and included in the overview review by Williamson. The review by Pignataro et al appears to contain a number of errors in some of the odds ratio diagrams/Forest plots, although the tabulated summary statistics given in the review are correct. The review does identify a number of issues with the existing primary research including small samples sizes, heterogeneity of clinical endpoints and the need for

standardised guidelines for assessment and reporting of outcomes. To some extent the analysis in the review attempts to take into account these limitations and the methods employed seem appropriate. The meta-analyses were performed for s-carboxymethylcysteine and/or its salt treatment versus placebo for two endpoints, one based on overall clinical improvement and the other dictated by reversion to a normal tympanogram. The findings demonstrated a trend towards carboxymethylcysteine and/or its salt being more effective than placebo, however the limitations of the available evidence prevent a definitive assessment of effectiveness.

In the overview review by Williamson a conservative slant is placed on the findings of the review and this seems appropriate given the limitations outlined above, however, it could be argued that it may not present the whole picture.

Additional information relevant to this topic is available in the other web pages on glue ear and these are on the following interventions: antimicrobial drugs, steroids, antihistamines and decongestants, and autoinflation.

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Prevention
Glue Ear

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The Problem Submitted for ARIF to Advise Upon:

What interventions are effective for the prevention of glue ear (otitis media with effusion)?

Reviews Identified

- Williamson I. Otitis media with effusion. In: Clinical Evidence 3. London: BMJ Publishing Group, 2000. Pp248-254

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Comments

We identified no reviews on interventions aimed at modifying risk factors or preventing glue ear.

A systematic review of reviews on glue ear, by Williamson, came to the same finding. In addition, this review did not identify any RCTs of interventions aimed at preventing glue ear.

Additional information relevant to this topic is available in the other web pages on glue ear and these are on the following groups of interventions for the treatment of glue ear : antimicrobial drugs, steroids, antihistamines and decongestants, mucolytic agents and autoinflation.

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Steroids
Glue Ear

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The Problem Submitted for ARIF to Advise Upon:

What treatments, other than surgical procedures, have been shown to be effective in the treatment of glue ear (otitis media with effusion)?

Question Reformulated

Due to the breadth of this question, we focused our attention on groups of interventions. The groups of interventions were antimicrobial drugs, steriods, antihistamines and decongestants, mucolytic agents, and auto-inflation.

This web page details our findings on steroids. Links to web pages on the other groups of interventions can be found at the bottom of this page.

Reviews Identified

- Williamson I. Otitis media with effusion. In: Clinical Evidence 3. London: BMJ Publishing Group, 2000. Pp248-254
- Butler CC, van der Voort JH. Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children (Cochrane Review). In: The Cochrane Library, Issue 4, 2000. Oxford: Update Software.

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Comments

The review by Williamson is a systematic overview of treatments for glue ear and appears a concise and accurate synthesis of the evidence presented in other systematic reviews.

The review by Butler and van der Voort is a more recent Cochrane review specifically on treatment with steroids. This is a well conducted review which concludes that there is limited and imperfect evidence that oral steroids combined with antibiotics lead to quicker resolution of glue ear in the short term (2 weeks) than control plus antibiotics. However, there is no evidence of long term benefit from treatment. All other comparisons of either oral or topical steroids versus control with or without antibiotics were either not statistically significant or not measurable due to insufficient information from the included

trials. The review highlights a number of important limitations with the existing primary research in this area. The authors conclude that based on current evidence steroid treatment cannot at present be recommended.

Although, too recent to be included, this review does not appreciably alter the findings of the overview review by Williamson.

Additional information relevant to this topic is available in the other web pages on glue ear and these are on the following interventions: antimicrobial drugs, antihistamines and decongestants, mucolytic agents, and autoinflation.

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Growth Hormone
Growth Hormone Deficiency

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness/cost effectiveness of growth hormone treatment of growth hormone deficient adults?

Reviews Identified

- Anthony D, Milne R. Growth hormone for growth hormone deficient adults. Southampton: Wessex Institute for Health Research and Development, 1997 (DEC Report 75).
- Payne JN et al. The use of growth hormone in adults. Sheffield: Trent Institute for Health Services Research, 1997 (Guidance Notes for Purchasers: 97/08)

Trials Identified

Contact ARIF for reference list.

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Comments

We identified a systematic review (Anthony and Milne 1997) and an economic evaluation (Payne et al 1997). The review has robust methodology and therefore its findings can probably be relied upon. The main conclusions of this review are that the most significant benefits of GH treatment in GH deficient adults are seen in improvement in exercise capacity, increased bone mineral density, increased lean body mass, reduction in fat mass and improvement in cardiac structure and function. Although GH treatment can produce significant improvements in cardiovascular markers, the consequences for morbidity and mortality are unknown.

The economic evaluation takes the Wessex Institute DEC report as a starting point and extrapolates to determine the cost benefit implications of adopting GH treatment. It gives estimated costs of the uptake of this treatment at the health authority level. It also models the degree of improvement in quality of life and mortality that would be required for GH treatment to be cost effective to the NHS. Due to deficiency of evidence, the authors had to make a number of assumptions and these obviously weaken the impact of some of the findings and therefore they will not be reiterated here.

In summary, GH treatment for GH deficient adults appears to be effective in increasing exercise capacity, bone mineral density, lean body mass, reducing fat mass and improving cardiac structure and function. At the time of publication of the DEC report, there was insufficient evidence from high quality studies to determine the effect of GH on quality of life, nor to determine cost effectiveness.

A large number of studies have been published since publication of the above reports, however the findings of these new studies do not alter the main conclusions above. Information on these studies is available on request.

This is an area prone to need for regular updating as new information is continually becoming available.

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Recombinant Factor VIII (rFVIII) Haemophilia A

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What are the effects/effectiveness of rFVIII in individuals with Haemophilia A, relative to existing plasma derived FVIII (pdFVIII) preparations?

ARIF was asked to participate in a West Midlands regional group advising on whether rFVIII should be made available in the region. A report of this group's complete findings is available via the ARIF office on request.

Question Reformulated

The critical outcome was identified as risk of viral transmission.

Other outcomes included:

- Prevention/amelioration of haemorrhage
- Long term morbidity/disability
- Development of antibodies to FVIII
- Patient/carer anxiety
- Clinician anxiety

Cost of any benefits was also important, although advising on the available research evidence on this was not part of ARIF's brief

Reviews Identified

- Anthony D. On-demand recombinant factor VIII for people with haemophilia A. Winchester: Wessex Institute for Health Research and Development, 1997 DEC Report No. 71
- United Kingdom Haemophilia Centre Directors Organisation Executive Committee. Guidelines on therapeutic products to treat haemophilia and other hereditary coagulation disorders. Haemophilia 1997;3:66-77
- Association of Hemophilia Clinic Directors of Canada. Clinical practice guidelines. Hemophilia and von Willebrand's Disease: 2. Management. Canadian Medical Association Journal 1995;153(2):147-157

Other Literature Identified

Additional sources of information used by ARIF included:

- Advice of clinicians with responsibility for care of haemophiliacs within the West Midlands on availability of research.
- Recombinant Factor VIII - Report of a multi-professional group. North West Regional Office (NHSE), 1997.
- Abstracts to presentations at the XVI Congress of the International Society on Thrombosis and Haemostasis via the Internet.

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Comments

Although none of the reviews identified was completely systematic in approach, the DEC report and the report of the UK Haemophilia Directors were well structured and generally explicit about the methods used to identify relevant research. All the reviews provided useful background and taken together with the other sources of information interrogated, we believe that the working group was aware of the majority of relevant research, of reasonably robust design, available at the time the group met.

Unfortunately, with respect to the effect of critical importance, the reduction in risk of serious transmitted infection e.g. by hepatitis A,B,G, HIV and parvovirus, the available empirical research is of very limited assistance in guiding a decision. The main problem is a lack of research of adequately robust design to reliably confirm that the very small reduction in risk that might occur with a change from pdFVIII to rFVIII, actually occurs. To demonstrate such a reduction would require a comparative study with large numbers of subjects observed over a period of many years. Such a study does not appear to exist, nor does it appear to be in progress. In the absence of such, we have to rely on observations of different cohorts or case-series exposed to different FVIII preparations. Interpreting comparisons of the incidence of infection in such cohorts or case-series, compiled at different times in different countries, is fraught with difficulty because we can never be assured that the baseline characteristics of the groups observed are equivalent; such differences might account for all or some of the observed incidence of infection. This is further compounded by the fact that in general the quality of surveillance of cohorts exposed to the pdFVIII products has been so much less detailed than for rFVIII products.

It was for this reason that the group, in making their decision on what the likely effects of changing from pdFVIII to rFVIII were, had to consider carefully other types of evidence, particularly that from the basic clinical sciences such as virology.

The eventual conclusion of the group, with which ARIF concurred, was that even taking the theoretical considerations into account the expected benefits of a change from pdFVIII to rFVIII was likely to be very small, so small as to be impossible to quantify.

However, the searches revealed that much research is in progress and there was a need to keep any advice under regular review.

This is an area particularly prone to need for regular updating as new information is continually becoming available.

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Prophylactic versus Intermittent FVIII Haemophilia A

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The Problem Submitted for ARIF to Advise Upon:

What are the effects/effectiveness of continuous versus intermittent FVIII in treatment of Haemophilia A - including the effect of different prophylactic dosage regimes?

Reviews Identified

- Berntrop E. The treatment of haemophilia, including prophylaxis, constant infusion and DDAVP. Ballieres Clinical Haematology 1996; 9: 259-271

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Comments

Although this review is not systematic it is useful in making clear:

- Uncertainty about the extent of overall benefit that actually accrues from use of FVIII prophylactically
- Uncertainty about the optimal dose
- The high cost of any benefits arising

Ideally, additional randomised trials should be commissioned to reduce this uncertainty, but this seems unlikely on ethical grounds. Thus, making purchasing decisions on this topic, on the basis of research evidence alone, will remain difficult.

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Vitamin K
Haemorrhagic Disease of the Newborn (HDNB)

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence for the effectiveness and safety of giving vitamin K to newborns to prevent Haemorrhagic Disease of the Newborn (HDNB), and what is the best means of administration?

Question Reformulated

The specific question we addressed was around the relative effectiveness of different administration methods of Vitamin K supplementation in the prevention of haemorrhagic disease of the newborn (HDNB).

Reviews Identified

- Brousson MA, Klein MC. Controversies surrounding the administration of Vitamin K to infants to prevent haemorrhagic disease of the newborn (HDNB) and the safest method, in the light of preliminary evidence suggesting that intramuscular administration of Vitamin K is associated with childhood cancer. Canadian Medical Association Journal 1996;154(3):307-315

Trials Identified

- Greer FR, Marshall FP, Severson RR et al. A new mixed micellar preparation for oral vitamin K prophylaxis: randomised controlled comparison with an intramuscular formulation in breast fed infants. Archives of Disease in Childhood 1998;79:300-305

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Comments

The review is not a systematic review and it is open to various biases, particularly publication and foreign language bias. Its conclusions are not clearly supported by the data it presents. As such, its conclusion that intramuscular administration is more effective than oral administration is unfounded. The conclusion that intramuscular administration probably does not increase the risk of childhood cancer, but that the possibility cannot be discounted, is more balanced and consistent with other epidemiological studies.

Given the limitations of the review we went on to look at some of the primary studies. The cited study is

a reliable randomised trial. Its conclusion, that a new oral preparation, when given in multiple doses, is at least as effective as the standard intramuscular preparation, is probably justified.

The evidence base on this topic is difficult to interpret for a number of reasons. Firstly, there are many different treatment options available and most studies address only one. Secondly, most studies are small and the key outcomes are rare, reducing their ability to detect clinically important differences. Thirdly, complex and important issues around compliance, acceptability and cost exist around many of the different options. Some, if not all, of these issues may well be addressed by a Cochrane review that is expected soon.

Request Carried Out: June 2000

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Stapling Haemorrhoidectomy Haemorrhoids

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of the stapling technique versus conventional surgery for grade III haemorrhoids not suitable for non-resective surgery?

Trials Identified

- Rowsell M, Bello M, Hemingway DM. Circumferential mucosectomy (stapled haemorrhoidectomy) versus conventional haemorrhoidectomy: randomised controlled trial. Lancet 2000;355:779-81
- Mehigan BJ, Monson JRT, Hartley JE. Stapling procedure for haemorrhoids versus Milligan-Morgan haemorrhoidectomy: randomised controlled trial. Lancet 2000;355:782-85

Case-Series Identified

- Beattie GC, Lam JPH, Louden. A prospective evaluation of the introduction of circumfrential stapled anoplasty in the management of haemorrhoids and mucosal prolapse. Colorectal Disease 2000;2:137-142
- Altomore D, Rinaldi M, Chiumarulo C, Palasciano N. Treatment of external anorectal mucosal prolapse with circular stapler. Diseases of the colon and rectum 1999; 42: 1102-1105
- Kohlstadt CM, Weber J, Prohm P. Stapler hemorrhoidectomy A new alternative to conventional methods. Zentralbl Chir 1999;124(3):238-243
- Longo A. Treatment of hemorrhoids disease by reduction of mucosa and hemorrhoidal prolapse with a circular suturing device: a new procedure. Proceedings of the 6th World Congress of Endoscopic Surgery. Mundozzi Editore 1998; 777-784.

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Comments

Our searches identified no systematic reviews on this subject. On searching for primary studies we identified two RCTs. Both studies were similar with regard to design, execution and reporting, and compared stapling haemorrhoidectomy with conventional haemorrhoidectomy. Both studies appear to have robust methodology and were well reported. Similar patients were enrolled in each study although some patients with grade IV haemorrhoids were included in the study by Mehigan et al. The numbers of

patients randomised in each study was fairly small (22 & 40) and the postoperative follow-up period in both was fairly short at only 6-10 weeks.

With regard to their findings both studies reported patients undergoing stapling haemorrhoidectomy experienced significantly less pain and returned to normal activities in a significantly shorter period than patients treated by conventional haemorrhoidectomy. The study by Rowsell et al reported small but significantly shorter in-patient stay with the stapling technique but Mehigan et al found no difference when compared to conventional therapy. Both studies report similar clinical outcomes and adverse events between both treatments.

Some believe that the large case-series study by Longo (1998) identified above already provides an adequate evidence base for the effectiveness of this intervention. ARIF is concerned about the biases to which case-series are susceptible and that these studies may be accepted as evidence of effectiveness over RCTs.

In summary, stapling haemorrhoidectomy is a promising new technique which may have advantages to the patient over existing conventional haemorrhoidectomy; however, the technique has only been rigorously evaluated in a small number of patients and with a limited follow-up period. ARIF's view is that this new technology should only be commissioned in the context of an RCT.

This is an area prone to need for regular updating as new information becomes available.

Request Carried Out: August 2000

Updated: April 2001 - A systematic review on this topic is currently being undertaken by the West Midlands Development and Evaluation Service.

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Archived ARIF Request

Health Checks Immigration

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence base for asking GPs to carry out health checks on new immigrants, in particular full blood count, Malaria blood film and stool microbiology?

Reviews Identified

None.

Trials Identified

None.

Other Literature Identified

Retrospective cohort (audit)

- Persson A, Rombo L. Intestinal parasites in refugees and asylum seekers entering the Stockholm area, 1987-88: Evaluation of routine stool screening. Scandinavian Journal of Infectious Diseases 1994;26:199-207

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Comments

On the basis of our search one can only conclude that the evidence base of this practice is weak. In particular we could find no empirical research on the overall effects/effectiveness of a screening programme or alternatively information on test performance (sensitivity/specificity etc) of stool microscopy/FBC/Malaria film and the impact of treatment on individuals identified as positive and any consequences of inappropriate treatment/non treatment.

The article above provides useful background information on the yield of positive findings on stool examination, broken down by country of origin and organism. It emphasises that the overall effectiveness of a screening programme is likely to be highly dependent on the main countries of origin of those immigrating to a particular area.

An article on the separate topic of post-tropical screening is of interest in the wider context of this

request:

- Carroll B, Dow C, Snashall D et al. Post-tropical screening: how useful is it? British Medical Journal 1993;307:541

Again, although the article by giving the prevalence of abnormalities identified, indicates the potential benefits of such screening, it gives little information on what the impact of screening is unless we assume that all abnormalities are correctly identified, none are missed, and the treatments available produce cure without any side-effects or have no adverse effects where the disease "detected" was not actually present.

Coincidentally, we noted that a number of Cochrane Reviews on aspects of treatment of diseases prevalent in those entering from overseas are becoming available eg giardiasis and schistosomiasis haematobium.

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Archived ARIF Request

Lamivudine
Hepatitis B

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of lamivudine in the treatment of chronic hepatitis B?

Reviews Identified

- MTRAC. Lamivudine (Zeffix). Keele: Dept of Medicines Management, Keele University, 2000. http://www.keele.ac.uk/depts/mm/MTRAC/ProductInfo/summaries/L/LAMIVUDINEs.html

Trials Identified

- Tassopoulos NC, Volpes R, Pastore G. Efficacy of lamivudine in patients with hepatitis B e antigen-negative/hepatitis B virus DNA-positive (precore mutant) chronic hepatitis B. Lamivudine Precore Mutant Study Group. Hepatology 1999;29:889-96
- Dienstag JL, Schiff ER, Wright TL. Lamivudine as initial treatment for chronic hepatitis B in the United States. New England Journal of Medicine 1999;341:1256-63
- Lai CL, Chien RN, Leung NW. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. New England Journal of Medicine 1998;339:61-8

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Comments

We identified three RCTs, all of which were included in the MTRAC report and thus the comments below are based on our assessment of the MTRAC report.

Although the format of the MTRAC report does not facilitate assessment of the methodology employed to identify and review the evidence, the report does provide a good summary of the RCTs. The findings of the report suggest that lamivudine significantly improves liver histology and suppresses viral replication in patients with chronic hepatitis B and compensated liver disease. The maximum follow-up of patients in the RCTs is one year and thus the long-term benefits with regard to reduction in cirrhosis and/or development of carcinoma are not known. The incidence of adverse events appears similar to that of placebo groups.

There are three points that should be noted. First, variants of hepatitis B virus with reduced susceptibility to lamivudine have been identified in up to a third of patients after one year of lamivudine treatment. Potentially this may limit how long lamivudine can be effectively utilised as a treatment for chronic hepatitis B in individual patients and in the future this may possibly reduce the efficacy of lamivudine altogether. Second, all the studies are of fairly short duration/follow-up and as such long-term effects and adverse events are unknown. Third, the cost effectiveness of lamivudine is at present unknown due to the above and the lack of knowledge about the likely duration of treatment.

In summary, based on studies of relatively short duration, lamivudine appears to be an effective treatment for chronic hepatitis; however, the duration and long-term efficacy of treatment are unknown.

This is an area prone to need for regular updating as new information is continually becoming available.

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Inguinal hernia repair versus watchful waiting in asymptomatic or minimally symptomatic men

Synopsis

Question:	To assess the clinical and cost effectiveness of surgical inguinal hernia repair versus watchful waiting, in asymptomatic or minimally symptomatic men.
Evidence Identified:	Fitzgibbons RJ, Jr., Giobbie-Hurder A, Gibbs JO, Dunlop DD, Reda DJ, McCarthy M, Jr. et al. Watchful waiting vs. repair of inguinal hernia in minimally symptomatic men: a randomized clinical trial. JAMA 2006;295(3):285-292 Stroupe KT, Manheim LM, Luo P, Giobbie-Hurder A, Hynes DM, Jonasson O et al. Tension-free repair versus watchful waiting for men with asymptomatic or minimally symptomatic inguinal hernias: a cost-effectiveness analysis. Journal of the American College of Surgeons 2006;203(4):458-468 O'Dwyer PJ, Norrie J, Alani A, Walker A, Duffy F, Horgan P et al. Observation or operation for patients with an asymptomatic inguinal hernia: a randomized clinical trial. Annals of Surgery 2006;244(2):167-173
Comments:	Two RCTs were identified and both have similar findings i.e. that in men who present with an asymptomatic hernia (one that is not painful), there is no difference in outcome of pain and quality of life scores between the strategy of watchful waiting and surgery. Surgery is the more expensive option, but the differences between the two strategies may reduce over time as patients following a watchful waiting strategy may eventually require surgery. Fitzgibbons and colleagues concluded that there is no difference between the two treatment strategies, therefore surgery should not be performed until it is clinically necessary i.e. the hernia becomes painful. O'Dwyer and colleagues recommended that as there is no difference between the two strategies, that surgery should not be delayed as a patient's general health may deteriorate, making the surgery more dangerous from an anaesthetic point of view. This probably reflects the uncertainty around the data, in that only 2 years of follow up have been obtained. This may also be a reflection of the different mean ages in the two trials, i.e. the mean age in the O'Dwyer trial was 71 years compared to 55 years in the Fitzgibbons trial therefore the patients in the O'Dwyer trial were more likely to present an anaesthetic risk if surgery is delayed.
Date Completed:	July 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Clinical and cost effectiveness of asymptomatic or minimally symptomatic inguinal hernia repair versus watchful waiting.

Request completed: July 2010

Question

What is the clinical and cost effectiveness of inguinal hernia repair? Issues to be explored were: which patients were likely to benefit the most from surgical repair; were there any patients who were not likely to benefit from surgical repair; what is the natural history of inguinal hernia; what are the long term effects of surgery; what are the costs?

Question clarification

In consultation with the requester, the question was focused on the clinical and cost effectiveness of inguinal hernia repair compared to watchful waiting in asymptomatic or minimally symptomatic patients.

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol (www.arif.bham.ac.uk/strategy.shtml). Further searches of MEDLINE, EMBASE and CENTRAL were run to target any relevant randomised controlled trials (RCTs). Text and index terms were used to represent the population and the intervention. Sources were searched from their inception to July 2010. No language restriction was applied to the searches. As an example the MEDLINE search can be found in Appendix A. The following inclusion criteria were used for study selection:

Population	Patients with an inguinal hernia
Intervention	Surgical inguinal hernia repair
Comparator	Watchful waiting
Outcome	Effectiveness, cost effectiveness. (including any subgroup analysis, short and long term outcomes – looking at pain reduction, reduction in adverse events related to hernia e.g. strangulation, also QoL measures. Recurrence and revision statistics for group with surgical inguinal hernia repair)
Study design	Systematic reviews and health technology assessments, primary studies.

Results

Full search results can be found in Appendix B.

No systematic reviews for inguinal hernia repair compared to watchful waiting were identified. The searches did identify two RCTs[1,2] which are described below.

Fitzgibbons RJ, Giobbie-Hurder A, Gibbs JO, Dunlop DD, Reda DJ, McCarthy M et al. Watchful waiting vs. repair of inguinal hernia in minimally symptomatic men a randomized clinical trial *JAMA* 2006;295:285-292

This was the largest of the two trials (n = 724), and was conducted in the USA, which may limit generalisability to the UK setting. Patients were men aged 18 years or older who had an asymptomatic or minimally symptomatic inguinal hernia, defined as the absence of hernia related pain or discomfort when undertaking usual activities. Hernias could be primary or recurrent, unilateral or bilateral. Most men had had their hernia for more than 6 weeks duration. Men were excluded if they had undetectable hernias or had local or systemic infection. Patients who presented with an anaesthetic risk were also excluded.

Surgical repair had to be undertaken using the "standard Lichtenstein open tension-free method" and participating surgeons underwent training in this method.[3] Patients randomised to watchful waiting (WW), were given a written list of instructions about when to seek help and lifestyle advice.[3]

The primary outcome was pain and discomfort that interfered with usual activities reported at 2 years. This was measured using a visual analogue score where 1 = no pain or discomfort, 2 = mild pain not interfering with usual activities, 3 = moderate pain interfering with usual activities and 4 = severe pain. Quality of life was also measured as a primary outcome, using the physical component score of the SF-36 health related quality of life measure. Surgical patients were also assessed for post operative complications, at 2 weeks and 3 months post op, and patients in the WW were examined 6 months post enrolment and yearly thereafter.[1]

The study has been reported over five publications. The first describes in detail the study methodology,[3] the second reports the main clinical results,[1] the third reports additional work investigating whether delay of repair had consequences on the type and extent of future procedures,[4] the fourth examines the effect of delay on the patients' family[5] and the fifth is a cost effectiveness analysis.[6]

The study was generally well conducted, with appropriate randomisation and concealment of allocation methodology utilised. There may be some selection bias that occurred during recruitment of the sample prior to randomisation i.e. some patients were recruited by radio advert as well as through clinics and 903 of those invited to participate refused at the point of randomisation, but it would be difficult to predict what affect this has had on the trial results. Intention to treat analysis and an on treatment sensitivity analysis were undertaken.

At two years, 5.1% of the WW group had pain and discomfort that interfered with usual activity compared to 2.2% for surgical repair (difference 2.86%: 95%CI -0.04%, 5.77% p=0.52). Regarding the SF-36 physical component score, differences between the two groups were negligible, with patients in the WW group registering a mean rise of 0.29 (of 100) increase from baseline compared to 0.13 (of 100) for the surgical patients.[1] For patients who underwent surgery there were three intra-operation events; one wound haematoma, one post anaesthetic hypertension, and one ilioinguinal nerve injury. Post operatively there were 90 events in 85 patients. These were mainly haematoma's but there were three life threatening complications: one patient developed a deep vein thrombosis (DVT); one experienced post operative bradycardia; and one patient developed post operative hypertension. At the 3 month check up, 13 patients had groin pain and two had leg pain. A total of five patients had hernia recurrence. The only adverse event reported for the WW group was a patient who had an acute hernia incarceration without strangulation. This outcome may have influenced the trial authors' conclusions: "WW is an acceptable option for men with minimally symptomatic inguinal hernia. Delaying surgical repair until symptoms increase is safe because acute hernia incarcerations occur rarely".

Regarding the other publications, no difference in operation time and other outcomes occurred in patients who delayed hernia repair.[4] Similarly the effect on delay to the patients' family was not viewed as a major issue.[5]

The cost effectiveness analysis[6] was reasonably well conducted according to the Drummond checklist.[7] However, to fully evaluate the validity of the economic evaluation a thorough assessment by a health economist is required. Three questions were posed: how many patients have the operation and how long have they waited since diagnosis; do patients on WW require more nonsurgical care to manage their hernia; do patients who delay surgery require more costly procedures. Costs were calculated from verified patient reports of healthcare received, including inpatient and outpatient care episodes, physician costs and prescription costs. Taken from a healthcare perspective, the costs were based on the USA health system (Medicare costs adjusted to 2004 USA dollars using the Consumer Price Index). The authors stated that 10 months into the trial, the data collection became less precise as patient recall of events seemed to deteriorate,

although recall regarding high cost events such as hospital visits appeared good. This could underestimate the costs in the WW group, if for example, GP visits are not reported. Effectiveness was measured using the physical component score of the SF-36, which was then converted into a utility score.

Table 1. Results of Cost Effectiveness Analysis.

Follow up at 2 years	**TFR (n = 317)**	**WW (n = 324)**	**Difference (TFR-WW) [ICER] (95% CI)**
Utility scores	0.875	0.868	p value 0.29
Mean costs ($)	7,875	6,044	1,831 (409, 3,044)
Mean QALY	1.724	1.693	0.031 (0.001, 0.058)
ICER, $ per QALY			[59,065 (1,358, 322,765)]

QALY = quality adjusted life year, ICER = incremental cost effectiveness ratio.

At two years patients randomised to surgery had a slightly higher QALY (difference 0.031), but they also had higher mean costs than the WW group (difference $1,831). The incremental cost per QALY was estimated to be $59,065 but this could be as low as $1,358 or as high as $322, 765[*]. The main problem is that this estimate is based on just 2 years of patient follow up. If longer term data and a longer time horizon were used then it would be likely that more patients in the WW group would have had surgery, therefore the differences in cost between the two strategies may be smaller, reducing the incremental cost per QALY for the surgery group. The authors concluded that "At 2 years, WW was a cost effective treatment option for men with minimal or no hernia symptoms".

O'Dwyer PJ, Norrie J, Alani A, Walker A, Duffy F, Horgan P. Observation or operation for patients with an asymptomatic inguinal hernia a randomized clinical trial. *Annals of Surg*ery 2006;244(2):167–173

This was a smaller trial (n=160) but was based in the UK. It aimed to compare surgical repair of an asymptomatic inguinal hernia to WW. Patients were men aged 55 years and over. Men were excluded if they had undetectable hernias or presented with an anaesthetic risk.

Surgical repair was undertaken using tension free mesh. Patients randomised to WW, were given a telephone number to call if the hernia became symptomatic or complicated. Surgical repair in this

[*] Using the 2010 retail price index and exchange rate this would be £46,467.41 (£ 905.33 to £215176.66), however, it should be borne in mind that this conversion does not take into account health service differences between the UK and USA.

group was undertaken if the hernia became acutely irreducible, developed pain or increased in size and interfered with work or leisure activities

The primary outcome was pain and quality of life, measured using a visual analogue score for the pain and the SF-36 health related quality of life measure. Measurements were taken at six months and one year. The primary endpoint was pain at one year.

Out of 232 eligible patients, 160 agreed to randomisation. Of those not participating, 58 refused because they did not want to be randomised to surgery and 14 refused because they did not want to be randomised to WW. The mean duration that the patient had had a hernia was three years.

Pain scores and SF-36 were similar between the two groups at 1 year. Utility scores were 0.772 for the WW group and 0.769 for the surgical group, QALY calculations were not undertaken. Patients in the surgical group at median follow up (574 days) cost £401.90 more than patients in the WW group taking into account clinic, operative and costs of complications.

Poor reporting reduces assessment of the validity of the study methods, with randomisation, concealment of allocation and blinding of outcome assessors not described. There also seems to be a discrepancy between the number of patients in the surgical group who received surgery (reported as 75 out of 80), and the number who crossed over to WW (reported to be 8). Intention to treat analysis and an on treatment sensitivity analysis were undertaken. The main results had been adjusted for baseline characteristics of pain and quality of life scores.

In the surgical group, one patient died of cancer before surgery, one had a serious cardiac event, and cancelled surgery, while three refused the surgery dates offered. Time to surgery was on average 102 days (3 months). Fifteen patients (20%) had crossed over from WW to receive surgery by one year. Amongst the reasons for surgery were an increase in pain (11 patients), hernia size (8 patients), detrimental affect of the hernia on work and leisure pursuits (3 patients), and an acute hernia presentation (1 patient). One of these patients had a post operative cardiac event and died and one patient who remained in the WW group had a stroke. These adverse events in the WW group may have influenced the trial authors' conclusion that: "Repair of an asymptomatic inguinal hernia does not affect the rate of long-term chronic pain and may be beneficial to patients in improving overall health and reducing potentially serious morbidity".

Conclusions

No systematic reviews or health technology assessments were identified. Two RCTs[1,2] were identified and both have similar findings i.e. that in men who present with an asymptomatic hernia (one that is not painful), there is no difference in outcome of pain and quality of life scores between the strategy of watchful waiting and surgery. Surgery is the more expensive option, but the differences between the two strategies may reduce over time as patients following a watchful waiting strategy may eventually require surgery. Fitzgibbons and colleagues[1] concluded that as there is no difference between the two treatment strategies, therefore surgery should not be performed until it is clinically necessary i.e. the hernia becomes painful. O'Dwyer and colleagues[2] recommended that as there is no difference between the two strategies, that surgery should not be delayed as patients general health may deteriorate, making the surgery more dangerous from an anaesthetic point of view. This probably reflects the uncertainty around the data, in that only 2 years of follow up have been obtained. It may also reflect a difference in patient characteristics, for instance the mean age in the O'Dwyer trial was 71 years compared to 55 years in the Fitzgibbons trial therefore the patients in the O'Dwyer trial were more likely to present an anaesthetic risk if surgery is delayed.

References

1 Fitzgibbons RJ, Jr., Giobbie-Hurder A, Gibbs JO, Dunlop DD, Reda DJ, McCarthy M, Jr., *et al*. Watchful waiting vs. repair of inguinal hernia in minimally symptomatic men: a randomized clinical trial.[Erratum appears in JAMA. 2006 Jun 21;295(23):2726]. *JAMA* 2006;**295**(3):285-292

2 O'Dwyer PJ, Norrie J, Alani A, Walker A, Duffy F, Horgan P, *et al*. Observation or operation for patients with an asymptomatic inguinal hernia: a randomized clinical trial. *Annals of Surgery* 2006;**244**(2):167-173

3 Fitzgibbons RJ, Jonasson O, Gibbs J, Dunlop DD, Henderson W, Reda D, *et al*. The development of a clinical trial to determine if watchful waiting is an acceptable alternative to routine herniorrhaphy for patients with minimal or no hernia symptoms. *Journal of the American College of Surgeons* 2003;**196**(5):737-742

4 Thompson JS, Gibbs JO, Reda DJ, McCarthy M, Jr., Wei Y, Giobbie-Hurder A, *et al*. Does delaying repair of an asymptomatic hernia have a penalty? *American Journal of Surgery* 2008;**195**(1):89-93

5 Gibbs JO, Giobbie-Hurder A, Edelman P, McCarthy M, Jr., Fitzgibbons RJ, Jr., Gibbs JO, *et al*. Does delay of hernia repair in minimally symptomatic men burden the patient's family? *Journal of the American College of Surgeons* 2007;**205**(3):409-412

6 Stroupe KT, Manheim LM, Luo P, Giobbie-Hurder A, Hynes DM, Jonasson O, *et al*. Tension-free repair versus watchful waiting for men with asymptomatic or minimally symptomatic inguinal hernias: a cost-effectiveness analysis. *Journal of the American College of Surgeons* 2006;**203**(4):458-468

7 Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Critical Assessment of Economic Evaluation. Methods for the Economic Evaluation of Health Care Programmes. Oxford: Oxford University Press; 1997 p.27-45

Appendix A – Literature search

The following search strategy was used to search for systematic reviews and primary studies in MEDLINE and was adapted for use in the other information sources:

1 inguinal hernia$.mp. or exp Hernia, Inguinal/
2 watchful waiting.mp.
3 (watch$ or wait$ or delay$ or postpon$).mp.
4 2 or 3
5 1 and 4

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Appendix B – Literature search results

Primary studies

Source – MEDLINE (Ovid) 1950 to June Week 4 2010

Fitzgibbons RJ, Giobbie-Hurder A, Gibbs JO, Dunlop DD, Reda DJ, McCarthy M et al Watchful Waiting vs. Repair of Inguinal Hernia in Minimally Symptomatic Men A Randomized Clinical Trial *JAMA.* 2006; **295:** 285-292. http://jama.ama-assn.org/cgi/content/abstract/295/3/285

O'Dwyer PJ, Norrie J, Alani A, Walker A, Duffy F, Horgan P Observation or Operation for Patients With an Asymptomatic Inguinal Hernia A Randomized Clinical Trial *Ann Surg* 2006 August; **244(2)**: 167–173 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1602168/

Gibbs JO, Gobbie-Hurder A, Edelman P. McCarthy M, Fitzgibbons RJ. Does delay of hernia repair in minimally symptomatic men burden the patient's family? *J Am Coll Surg* 2007; 205(3):409-12. http://www.ncbi.nlm.nih.gov/pubmed/17765156?dopt=AbstractPlus

Systematic Reviews

Source – Cochrane Library (Wiley) 2010 Issue 2 (CDSR)

McCormack Kirsty, Scott Neil, Go Peter M.N.Y.H, Ross Sue J, Grant Adrian, Collaboration the EU Hernia Trialists. Laparoscopic techniques versus open techniques for inguinal hernia repair. Cochrane Database of Systematic Reviews: Reviews 2003 Issue 1 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD001785 YR: 2003 NO: 1 PB: John Wiley & Sons, Ltd http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001785/frame.html

Source – Cochrane Library (Wiley) 2010 Issue 2 (DARE)

Gholghesaei M, Langeveld H R, Veldkamp R, Bonjer H J. Costs and quality of life after endoscopic repair of inguinal hernia vs. open tension-free repair: a review (Provisional abstract) *Surgical Endoscopy* 2005; **19(6)**: 816-821
http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12005001278/frame.html

McCormack K, Wake B, Perez J, Fraser C, Cook J, McIntosh E et al. Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation (Provisional abstract) *Health Technology Assessment* 2005; **9(14)**: 1-203

Source - Cochrane Library (Wiley) 2010 Issue 2 (HTA)

L'Agence Nationale d'Accreditation d' Evaluation en Sante (ANAES) Clinical and economic evaluation of laparoscopic surgery in the context of inguinal hernia repair (Brief record) Paris: L'Agence Nationale d' Accreditation d' Evaluation en Sante (ANAES); 2000
http://www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-32000001807/frame.html

Galician Agency for Health Technology Assessment (AVALIA-T) Inguinal hernia: clinical practice guideline (Structured abstract) Santiago de ComPostela: Galician Agency for Health Technology Assessment (AVALIA-T); 2007
http://www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-32008100173/frame.html

National Institute for Clinical Excellence. Laparoscopic surgery for inguinal hernia repair (Structured abstract) London: National Institute for Clinical Excellence (NICE); 2004: 33
http://www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-32004000796/frame.html

Gerhardus A, Jalilvand N, Heintze C, Krauth C. The open versus laparoscopic methods in surgery of inguinal hernias - a systematic review (Brief record) Cologne: German Agency for Health Technology Assessment at the German Institute for Medical Documentation and Information (DAHTA DIMDI); 2003 http://www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-32005000581/frame.html

Gerhardus A, Jalilvand N, Heintze C, Krauth C. The open versus laparoscopic methods in surgery of inguinal hernias - a systematic review (Brief record) Hannover: Hannover Medical School, Medizinische Hochschule Hannover (MHH); 2003 http://www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-32005000394/frame.html

Source - MEDLINE (Ovid) 1950 to June Week 4 2010

van Hanswijck de Jonge P, Lloyd A, Horsfall L, Tan R, O'Dwyer PJ. The measurement of chronic pain and health-related quality of life following inguinal hernia repair: a review of the literature. *Hernia* 2008; **12(6):**561-9

Vale L, Ludbrook A,Grant A. Assessing the costs and consequences of laparoscopic vs. open methods of groin hernia repair: a systematic review. *Surgical Endoscopy*. 2003; **17(6)**:844-9

Stylopoulos N, Gazelle GS, Rattner DW. A cost-utility analysis of treatment options for inguinal hernia in 1,513,008 adult patients. *Surgical Endoscopy* 2003; **17(2)**:180-9

Zib M, Gani J. Inguinal hernia repair: where to next? Comment in: ANZ J Surg. 2003 May; 73(5):352-3; PMID: 12752295], Comment in: ANZ J Surg. 2003 May; 73(5):352; author reply 352-3; PMID: 12752296] *ANZ Journal of Surgery*. 2002; **72(8):**573-9

Other reviews

Source – MEDLINE (Ovid) 1950 to June Week 4 2010

Nelson AL, Cohen JT, Greenberg D, Kent DM. Much cheaper, almost as good: decrementally cost-effective medical innovation. [Review] [51 refs] *Annals of Internal Medicine*. 2009; **151(9)**:662-7

Economic evaluations

Source – Cochrane Library (Wiley) 2010 Issue 2 (EED)

Stroupe K T, Manheim L M, Luo P, Giobbie-Hurder A, Hynes D M, Jonasson O et al. Tension-free repair versus watchful waiting for men with asymptomatic or minimally symptomatic inguinal hernias: a cost-effectiveness analysis (Provisional abstract) *Journal of the American College of Surgeons* 2006; **203(4)**: 458-468 http://www.mrw.interscience.wiley.com/cochrane/cleed/articles/NHSEED-22006002009/frame.html

Khan R A, Bhutiani R P The walk in walk out hernia clinic: a study of its cost effectiveness (Brief record) *Ambulatory Surgery* 2008; **14(2)** http://www.mrw.interscience.wiley.com/cochrane/cleed/articles/NHSEED-22008102217/frame.html

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Archived ARIF Request

Hernia Repair Laparoscopic

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in April 1996 and update in April 2001.

The Problem Submitted for ARIF to Advise Upon:

Should laparoscopic treatment of inguinal hernias be purchased in the light of the evidence on its effectiveness?

Question Reformulated

Particular attention needs to be directed at the range of outcomes considered important:

- Operative mortality and morbidity especially post-operative pain and infection rates
- Time in hospital
- Time off work/normal activities
- Recurrence rate
- Costs to health service and individual

Comments

Request Carried Out: April 1996

Updated: April 2001 - Our original comments and subsequent update on this request have been superseded by guidance issued by the National Institute for Clinical Excellence (NICE). This guidance can be found on the NICE website.

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Archived ARIF Request

Hernia Repair
Mesh (partially absorbable or non-absorbable)
Inguinal Hernias

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in March 2006.

The Problem Submitted for ARIF to Advise Upon:

What is the relative effectiveness of partially absorbable mesh in comparison with non-absorbable mesh in the repair of inguinal hernias?

The use of synthetic mesh in inguinal hernia repair reduces the risk of hernia recurrence and appears to reduce the chance of persisting pain in comparison with sutured repair. However, for some patients, severe chronic pain remains a problem and this may be caused by the type of mesh used. The standard non-absorbable mesh (made of polypropylene) can induce a foreign tissue reaction. As the extent of this reaction depends on the amount and structure of the incorporated material it has been hypothesized that reducing the amount of mesh left in situ (by using a partially absorbable mesh) may reduce long term pain.

Reviews Identified

No systematic reviews were identified.

Randomised Controlled Trials

- Bringman S, Heikkinen TJ, Wollert S, Osterberg J, Smedberg S, Granlund H, Ramel S, Fellander G, Anderberg B. Early results of a single-blinded, randomized, controlled, Internet-based multicenter trial comparing Prolene and Vypro II mesh in Lichtenstein hernioplasty. Hernia. 2004;8(2):127-34
- Post S, Weiss B, Willer M, Neufang T, Lorenz D. Randomized clinical trial of lightweight composite mesh for Lichtenstein inguinal hernia repair. British Journal of Surgery. 2004;91(1):44-8
- O'Dwyer PJ, Kingsnorth AN, Molloy RG, Small PK, Lammers B, Horeyseck G. Randomized clinical trial assessing impact of a lightweight or heavyweight mesh on chronic pain after inguinal hernia repair. British Journal of Surgery. 2005;92(2):166-70

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Comments

Three well-conducted RCTs were identified. All compared the effectiveness of partially absorbable mesh (composed of polypropylene fibres mixed with absorbable polyglactin threads) with non-

absorbable mesh for patients undergoing tension-free open surgery (Lichtenstein technique) to repair an inguinal hernia. Whilst trial length varied (follow-up ranged from 8 weeks to 12 months) the three RCTs all assessed postoperative pain, quality of life and postoperative complications.

The results reported by the three RCTs were mixed. The evidence identified indicated partially absorbable mesh may be associated with less chronic pain but that the impact on recurrence rates was unclear.

To-date there seems insufficient evidence to either fully support or refute the routine use of partially absorbable rather than non-absorbable mesh for inguinal hernia repairs. Further larger RCTs conducted over longer periods would be beneficial.

Request Carried Out: March 2006

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Clinical measurement tools and referrals for hip replacement

Synopsis

Question:	Which clinical measurement tools that measure referral threshold for hip replacement are evidence based and of these, which is the best?
Reviews Identified:	No systematic reviews or health technology assessments were identified that directly answered the question. Two national guidelines and a systematic review investigating the usefulness of clinical pathways were examined, which may inform the decision process.
Comments:	Two national guidelines that make recommendations on referral for hip replacement surgery were identified, however, neither is based on patient assessments using clinical measurement tools.
Date Completed:	April 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Clinical measurement tools that measure referral threshold for hip replacement

Request completed: April 2010

Question

Which clinical measurement tools that measure referral threshold for hip replacement are evidence based and of these, which is the best?

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol http://www.arif.bham.ac.uk/strategy.shtml. Text and index terms were used to represent the population and the intervention. Sources were searched from their inception to March 2010. No language restriction was applied to the searches. The MEDLINE search can be found in Appendix A. The following inclusion criteria were used for study search and selection:

Population	Patients who may need a hip replacement
Intervention	Clinical assessment tools used to measure referral threshold for hip replacement
Study design	Systematic reviews, health technology assessments

Results

No systematic reviews or health technology assessments were identified that directly answered the question. However, two clinical guideline documents[1,2] that give recommendations on referral of patients for hip replacement and one systematic review[3] that examines the effectiveness of clinical pathways in the treatment of patients with hip pathology were identified and are described below, to inform debate around the question. Full search results can be found in Appendix B.

Of the guidelines, one was issued by the National Institute for Health and Clinical Excellence (NICE).[1] The authors conducted a systematic review with literature searches up to 2007. There was a paucity of good quality evidence, therefore the recommendations on referral criteria for hip and knee joint replacements (see page 296 of the publication) were mainly informed by expert opinion (see page 269 to 296). The recommendations were based on the holistic assessment of a patient, i.e. joint symptoms together with quality of life and willingness for replacement surgery etc, rather than an assessment using specific clinical measurement tools. The authors acknowledged that there are tools using orthopaedic scores and questionnaires assessing pain, functional impairment and radiographic damage, the most common being the New Zealand score and the

Oxford hip or knee score, but none have been validated for the assessment of appropriateness of referral.

The second guideline was produced by the Osteoarticular Research Group at University of Edinburgh, UK.[2] The authors conducted a systematic review of existing guidelines for the management of hip and knee osteoarthritis (OA). Literature searches were up to 2006. The methodological quality of the review was good. The recommendation for joint replacement for hip or knee OA was based on 14 existing treatment guidelines that used evidence from observational studies. The recommendation was presented within a clinical pathway framework i.e. overall consideration of the condition, pain relief, functional improvement and previous and current treatment, rather than an assessment using specific disease measurement tools (see page 150 of the publication).

The systematic review by Barbieri and colleagues[3] aimed to evaluate the effectiveness of clinical pathways for hip and knee joint replacements when compared with standard medical care. Literature searches were from 1975 to 2007. The methodology of the review was good, with a wide systematic search strategy and appropriate data extraction process, however, most of the included studies were cohort studies with the majority using historical controls. Out of 22 included studies, only six looked at hip replacement and four examined both hip and knee replacement. Meta-analysis was also limited as only around half of the included studies were in a format that could be meta-analysed, therefore the results should be viewed with caution. The authors found that the clinical pathway groups had significantly fewer patients suffering postoperative complications, shorter length of stay in hospital and lower costs during hospital stay compared with standard medical care. However, recommendations regarding when patients should be offered replacement surgery were not given.

Conclusions

No systematic reviews or health technology assessments were identified that had investigated clinical measurement tools to help treatment decisions regarding hip replacement. Two national guidelines that make recommendations on referral for hip replacement surgery were identified, however, neither is based on patient assessments using clinical measurement tools.

References

1. National Collaborating Centre for Chronic Conditions. Osteoarthritis. National clinical guideline for care and management in adults. London: Royal College of Physicians; 2008. [NICE Clinical Guideline CG59]. Available at http://www.nice.org.uk/nicemedia/pdf/CG059FullGuideline.pdf [Accessed on 25-03-2010]

2. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis and Cartilage 2008;16:137-162. Available at http://www.oarsi.org/pdfs/oarsi_recommendations_for_management_of_hip_and_knee_oa.pdf [Accessed on 25-03-2010]

3. Barbieri A, Vanhaecht K, Van Herck P, Sermeus W, Faggiano F, Marchisio S, et al. Effects of clinical pathways in the joint replacement: a meta-analysis. BMC Medicine 2009, 7:32

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 Osteoarthritis, Hip/
2 Arthroplasty, Replacement, Hip/
3 hip replacement.tw.
4 hip arthroplasty.tw.
5 patient selection/
6 severity of illness index/
7 eligibility determination/
8 guideline.pt.
9 practice guideline.pt.
10 (guideline$ or recommend$ or consensus or standard$).tw.
11 1 or 2 or 3 or 4
12 5 or 6 or 7 or 8 or 9 or 10
13 11 and 12
14 5 or 6 or 7
15 2 or 3 or 4
16 14 and 15
17 8 or 9 or 10
18 or/1-4
19 17 and 18
20 limit 19 to "reviews (specificity)"

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Appendix B – Literature search results

Systematic Reviews and Guidelines

Source – NICE web site

National Collaborating Centre for Chronic Conditions. Osteoarthritis. National clinical guideline for care and management in adults. London: Royal College of Physicians; 2008. [NICE Clinical Guideline CG59]. http://www.nice.org.uk/nicemedia/pdf/CG059FullGuideline.pdf

Source – NHS Evidence

Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis and Cartilage 2008; 16: 137-162 http://www.oarsi.org/pdfs/oarsi_recommendations_for_management_of_hip_and_knee_oa.pdf

Source – MEDLINE (Ovid) 1950 – March week 2 2010

Barbieri A, Vanhaecht K, Van Herck P, Sermeus W, Faggiano F, Marchisio S et al. Effects of clinical pathways in the joint replacement: a meta-analysis. BMC Medicine 2009; 7:32.

Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N. et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. Osteoarthritis & Cartilage 2007; 15(9):981-1000.

Zhang W, Doherty M. EULAR recommendations for knee and hip osteoarthritis: a critique of the methodology. British Journal of Sports Medicine 2006; 40(8):664-9.

Terwee CB, Mokkink LB, Steultjens MP, Dekker J.
Performance-based methods for measuring the physical function of patients with osteoarthritis of the hip or knee: a systematic review of measurement properties.
Rheumatology 2006; 45(7):890-902.

Zhang W, Doherty M, Arden N, Bannwarth B, Bijlsma J, Gunther KP, et al.
EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT).
EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT).
Annals of the Rheumatic Diseases 2005; 64(5):669-81.

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Archived ARIF Request

Laser Therapy Unwanted Hair Hirsutism

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in December 2005.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of laser therapy for unwanted hair?

Reviews Identified

- Ball C. Laser treatment for unwanted hair STEER 2003; 3(13) http://www.wihrd.soton.ac.uk/projx/signpost/steers/STEER_2003(13).pdf
- Clayton WJ, Lipton M, Elford J, Rustin M, Sherr L. A randomized controlled trial of laser treatment among hirsute women with polycystic ovary syndrome. The British Journal of Dermatology 2005 ; 152(5): 986-92 http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/176/CN-00513176/frame.html

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Comments

This is a well conducted review which suggested that laser treatment with various lasers (ruby, alexandrite and Nd:YAG) were effective. However, the evidence was case-series which are open to bias.

Since the STEER report an RCT has been published providing further evidence supporting effectiveness. It should however be clearly noted this RCT was not identified as part of a systematic review and publication bias may be operating.

Request Carried Out: December 2005

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Archived ARIF Request

Sperm Washing
HIV Discordant Couples

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence of effectiveness of sperm washing in reducing the risk of HIV transmission in couples where the man is HIV+ve and the woman HIV-ve?

Sperm washing is a technique that aims to remove the HIV virus from the sperm of HIV+ve men prior to its use in the assisted fertilisation of HIV-ve women.

Reviews Identified

No systematic reviews were identified.

Primary Studies

- Marina S, Marina F, Alcolea R et al Human immunodeficiency virus type 1 - serodiscordant couples can bear healthy children after undergoing intrauterine insemination. Fertility and Sterility 1998; 70(1):35-39
- Semprini AE, Levi-Setti P, Bozzo M et al Insemination of HIV-negative women with processed semen of HIV-positive partners. The Lancet 1992; 340(28):1317-1319

Other

- Marina S, Marina F, Alsolea et al Pregnancy following intracytoplasmic sperm injection from an HIV-1-seropositive man. Human Reproduction 1998;13(11) :3247-3249
- Semprini AE, Fiore S, Pardi G Reproductive counselling for HIV-discordant couples (letter). The Lancet 1997;349:1401-1402
- Gilling-Smith C, Smith JR, Semprini AE HIV and infertility: time to treat (editorial). BMJ 2001;322: 566-567

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Comments

Our searches revealed no systematic reviews on this topic. However, we did identify a number of primary studies, editorials and letters to journals.

Many of the primary studies we identified were laboratory-based and assess the presence of HIV in washed sperm obtained from HIV+ve men to determine the success of the intervention. As such, these studies did not measure any patient-centred outcomes (i.e. seroconversions in women or HIV status of children conceived using washed sperm), and therefore their usefulness is limited to methodological development and providing data for theoretical modelling of HIV transmission.

Published articles refer to there being a large cohort of HIV discordant couples who have undergone insemination with washed sperm without HIV infection occurring in the woman or any resulting child. However, we have only identified a couple of case series (Semprini et al 1992, Marina et al 1998) on the effectiveness of sperm washing to reduce the risk of HIV transmission in discordant couples and these enrolled less than 100 couples in total. These studies indicate that sperm washing is a promising technique, although the results should be treated with caution due to the small population studied and the uncontrolled study designs. However, it seems unlikely that studies with more robust design (prospective controlled studies) will be undertaken for ethical reasons especially.

Although sperm washing is aimed at removing associated HIV, it is important to consider that washed sperm is tested to ensure that is free of the presence of HIV before insemination occurs. A question that we have not addressed is that of the diagnostic accuracy of the tests used to determine this status. The presence of false negative results will have serious implications for the mother and child as well as health economic and medico-legal implications for the health care provider.

Request Carried Out: January 2002

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ARIF Archived Request

Homebirths
Low Obstetric Risk Women

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The Problem Submitted for ARIF to Advise Upon:

What is the comparative safety of home births compared to hospital births for women classified as being of low obstetric risk?

Reviews Identified

- Olsen O, Jewell MD. Home versus hospital birth (Cochrane Review). In: The Cochrane Library, Issue 1, 2001. Oxford: Update Software.
- Hodnett ED. Home-like versus conventional institutional settings for birth (Cochrane Review).
- In: The Cochrane Library, Issue 1, 2001. Oxford: Update Software.
- Olsen O. Meta-analysis of the safety of home birth. Birth. 24(1):4-13; discussion 14-6, 1997 Mar

Background Review

- Campbell R, MacFarlane A. Where to be born? The debate and the evidence. Oxford: National Perinatal Epidemiology Unit, 2nd edition; 1994

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Comments

Olsen and Jewell, (2001), compared the outcomes in controlled trials of women who had given birth in either hospital or at home. However there was only one trial of 11 women, which was too small to draw any conclusions.

A systematic, good quality meta-analysis of six controlled observational studies by Olsen (1997) revealed no significant difference in perinatal mortality between home and hospital birth. Another review (Hodnett, 2001) evaluated the outcomes of women assigned to give birth in either conventional hospital wards or home-like settings intended to mimic the home setting. There was a non-statistically significant trend towards higher perinatal mortality in the home-like birth setting. Both reviews found that for women who gave birth in the home or home-like setting, there was less intrapartum analgesia administered, less augmentation of labour, fewer foetal heart rate abnormalities, and the women were more mobile during labour. Possible reasons for this are outlined in our feedback to the requestor.

In conclusion, there is no evidence to suggest that either home births or hospital births are safer for women evaluated as being of low obstetric risk. In addition the comparison of results across a variety of countries is difficult because of the likely differences of organisation of delivery services in these countries.

Request Carried Out: June 2001

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Hormone Replacement Therapy Osteoporosis

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The Problem Submitted for ARIF to Advise Upon:

A policy for treating osteoporosis is to be developed, therefore: Is there a defined group of women who should receive prolonged Hormone Replacement Therapy (HRT) and what role does bone density scanning have in assessing these women?

Reviews Identified

- Grady D et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Annals of Internal Medicine 1992;117:1016-1037
- Udoff L et al. Combined continuous hormone replacement therapy: a critical review. Obstetrics and Gynecology 1995;86(2):306-316

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Comments

The two reviews identified, Grady D et al and Udoff L et al are both systematic in approach, in that we have a clear indication of the methods used to undertake the review and can make judgement about any bias introduced by the reviewing process. They are both limited by the fact that most of the studies included employ methods which are particularly susceptible to bias, especially case-control studies. Nonetheless, interpretated carefully, the paper by Grady D et al gives a good summary of the research evidence relating to the older styles of HRT and the paper by Udoff L et al to the new formulations.

One of the difficulties is integrating the research information on the magnitude of the several main identified risks/benefits associated with HRT, compounded still further by the problem of trying to individualise those risks. The paper by Grady D et al is useful in giving a board indication of the relative balance of the risks and benefits in particular situations, although the figures provided can only be regarded as guestimates, because the overall estimates of risk or benefit are themselves imprecise. However, in the context of a decision about whether bone densitometry would help women make decisions about whether to take HRT, it is quite clear that any individual decisions should be weighted towards avoidance of IHD and/or increased risk of breast cancer based on the size of that risk or the likely individual importance of the risk, respectively. In consequence if we were serious about improving knowledge of individual risk as a method of maximising benefit from HRT, it would seem logical to propose tests which helped predict IHD or breast cancer ahead of initiatives to improve prediction of

risk of hip fracture associated with osteoporosis.

Request Carried Out: June 1996

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Archived ARIF Request

Rehousing
Housing Clearances
Psychological and Physical Health Impact

Table of Contents

WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the health impact of housing clearances, and in particular the psychological and physical health impact on those people who have been rehoused following housing clearance?

Reviews Identified

- Thomson H, Petticrew M, Morrison D. Housing improvement and health gain: a summary and systematic review. MRC Social and Public Health Sciences Unit: 2002: 45
- Thomson H, Petticrew M, Morrison D. Health effects of housing improvement: systematic review of intervention studies. British Medical Journal 2001;323(7306):187-190

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Comments

The two articles above are both reports of the same generally well-conducted systematic review.

Due to the nature, quality and heterogeneity of the primary studies, the review was limited to a narrative overview of studies with the most robust design (prospective and controlled). This overview suggests that some improvements may be observed in residents' mental health and small improvements may be seen in their general health following rehousing. The potential for adverse health effects was also identified. However as the reviewers intimate, the findings should be treated with caution because all of the robust studies were old (1930s - 1980s). As such the generalisability of the findings to current and future regeneration/rehousing programmes is limited due to advances in health care and social and welfare reforms.

The bottom line is that there is insufficient robust evidence available to draw clear conclusions regarding the health effects of rehousing. New prospective and controlled studies are currently being undertaken and the review is due to be updated.

Therefore, as new information is likely to become available on this topic, care should be taken if this advice is accessed more than 6 months after this request was undertaken.

Request Carried Out: December 2003

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Archived ARIF Request

Hyaluronic Acid Viscosupplements
Osteoarthritis
Knee

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness the hyaluronic acid viscosupplements (Synvisc® (Hylan G-F20) and Hyalgan®) in the treatment of osteoarthritis (OA) of the knee?

Reviews Identified

- Towheed TE, Hocberg MC. A systematic review of randomised controlled trials of pharmacological therapy in osteoarthritis of the knee, with an emphasis on trial methodology. Seminars in Arthritis and Rheumatism 1997;26(5):755-770

Reviews in Progress:

- Bellamy N, Campbell J, Wells G , Bourne R. Viscosupplementation for osteoarthritis of the knee (Protocol for a Cochrane Review). In: The Cochrane Library, Issue 4, 2001. Oxford: Update Software.
- Viscosupplementation with hylan G-f 20 for patients with osteoarthritis of the knee - systematic review (project). Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS), Montreal (Quebec), Canada (http://www.aetmis.gouv.qc.ca)

Primary Studies

Contact ARIF for a list

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Comments

The only available completed systematic review that covers viscosupplementation for OA of the knee is out of date as it only includes studies up to 1994.

Two systematic reviews are currently in-progress and these should include trials that are more recent and therefore should provide an up to date assessment of the effectiveness of the intervention.

Our further searches identified a number of trials. Unfortunately, the findings appear inconsistent across the trials. For example, in those trials that compared viscosupplementation to placebo a statistically significant benefit of supplementation was seen for some outcomes in some trials, but no significant benefit in the same outcome measure was seen in other trials.

In summary, although viscosupplementation appears to be a promising technique no robust assessment of the available literature is currently available. This is essential given our problems trying to interpret the available trials informally. Two in-progress systematic reviews should help.

Request Carried Out: February 2002

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Archived ARIF Request

Hydrotherapy

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The Problem Submitted for ARIF to Advise Upon:

What are the effects/effectiveness of hydrotherapy?

Reviews Identified

- Goldby LJ, Scott DL. The way forward for hydrotherapy. British Journal of Rheumatology 1993;32(9):771-3

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Comments

The review cited is not systematic but does provide useful background to the problem stated.

The main problems in making an evidence based purchasing decision in this area are:

- The large number of conditions for which hydrotherapy has been suggested to be of benefit
- The paucity of rigorous evaluations

Since this request was first conducted, ARIF has had correspondence with a physiotherapist who is actively involved in trials of hydrotherapy in the West Midlands. Readers interested in this topic may benefit from contact with her, which should in the first instance be via the ARIF office.

Request Carried Out: July 1996

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Archived ARIF Request

Hyperbaric Oxygen Osteoradionecrosis

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of hyperbaric oxygen for the prevention and treatment of osteoradionecrosis?

Osteoradionecrosis is a process in which radiation, often given as part of treatment for head and neck cancer, leads to damage to the blood supply of areas of bone in the path of the x-ray beam. This in turn leads to open wounds which do not heal properly.

Hyperbaric oxygen treatment is the breathing of 100% oxygen under high pressure in specially designed chambers, also used for treating decompression sickness in divers. In the context of osteoradionecrosis:

- treatment of a wound which has developed spontaneously should be contrasted with
- prevention of a wound forming in damaged bone exposed to injury, such as dental extraction

Reviews Identified

- Wang C, Schwaitzberg S, Berliner E, Zarin DA, Lau J. Hyperbaric oxygen for treating wounds: a systematic review of the literature. Archives of Surgery 2003;138(3):272-9
- Ward SE, Thomas N, Mander C, Brook I. The use of hyperbaric oxygen in the management of patients with oral cancer. Trent Institute for Health Services Research; 2000. Guidance Note for Purchasers 00/03

These are two examples of a number of well conducted reviews, which generally conclude that there is evidence for the effectiveness of hyperbaric oxygen therapy in osteoradionecrosis. However, with the exception of an RCT with 74 subjects, the majority of this is from case-series which are highly susceptible to confounding and bias.

Randomised Controlled Trials

- Annane D, Depondt J, Aubert P, Villart M, Gehanno P, Gajdos P et al. Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomised, placebo-controlled, double-blind trial from the ORN96 Study Group. J Clin Oncol 2004;22(24):4893-4900
- Depondt J, Annane D, Delanian S, Barry B, Baujat B, Guedon C et al. Oxygenotherapie hyperbare pour le traitement des osteo-radionecroses mandibulaires, resultats d'une etude prospective

randomisee en double insu. Annales d'Otolaryngologie & de Chirurgie Cervico-Faciale 2003;120(2):123

These are two reports of a new RCT of the treatment of mild to moderate osteoradionecrosis of the jaw comparing hyperbaric oxygen with placebo in 68 subjects. It does not appear in any of the systematic reviews identified and appears to be well conducted particularly with respect to allocation concealment and blinding. At 1 year it shows no benefit for hyperbaric oxygen in terms of recovery, time to treatment failure and time to pain relief.

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Comments

Given that the existing evidence was finely poised, the new RCT suggests commissioning hyperbaric oxygen as a routine therapy for osteoradionecrosis may need to be reconsidered. Commissioners should promote further research, particularly large scale RCTs.

Request Carried Out: December 2004

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Clinical measurement tools and referrals for hysterectomy

Synopsis

Question:	Which clinical measurement tools that measure referral threshold for hysterectomy are evidence based and of these, which is the best?
Reviews Identified:	No systematic reviews or health technology assessments were identified that answered the question. One NICE guidance on heavy menstrual bleeding was identified, which contained recommendations on referral of patients with heavy menstrual bleeding for hysterectomy, thus may be informative: National Collaborating Centre for Women's and Children's Health. Heavy menstrual bleeding. London: Royal College of Obstetricians and Gynaecology; 2007. NICE Clinical Guideline CG44. http://www.nice.org.uk/nicemedia/live/11002/30401/30401.pdf
Comments:	One clinical guideline that contained recommendations on referral of women with heavy menstrual bleeding for hysterectomy was identified, however, the recommendations were not based on patient assessments using clinical measurement tools.
Date Completed:	May 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Clinical measurement tools that measure referral threshold for hysterectomy

Request completed: May 2010

Question

Which clinical measurement tools that measure referral threshold for hysterectomy are evidence based and of these, which is the best?

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol http://www.arif.bham.ac.uk/strategy.shtml. Text and index terms were used to represent the population and the intervention. Sources were searched from their inception to May 2010. No language restriction was applied to the searches. The MEDLINE search can be found in Appendix A. The following inclusion criteria were used for study search and selection:

Population	Patients who may need a hysterectomy
Intervention	Clinical assessment tools used to measure referral threshold for hysterectomy
Study design	Systematic reviews, health technology assessments

Results

No systematic reviews or health technology assessments were identified that answered the question.

One clinical guideline document on heavy menstrual bleeding issued by the National Institute for Health and Clinical Excellence (NICE) in 2007 was identified, which contained recommendations on referral of patients with heavy menstrual bleeding (HMB) for hysterectomy. It may be informative to the decision process thus is described. Full search results can be found in Appendix B.

The guideline made recommendations on a range of treatment options for HMB, including hysterectomy. Evidence searches were comprehensive and up to 2006. The evidence statements on indications for hysterectomy included one systematic review and five observational studies (chapter 12.1.1 - 12.1.2 on page 89 - 90 of the publication). The authors recommended that hysterectomy for HMB should be considered only when (page 99 -100 of the publication):

- *"Other treatment options have failed, are contraindicated or are declined by the woman*
- *There is a wish for amenorrhoea*

- *The woman no longer wishes to retain her uterus and fertility"*

However, no clinical measurement tools that were used as referral threshold assessment were stated.

Conclusions

No systematic reviews or health technology assessments were identified that had investigated clinical measurement tools to help treatment decisions regarding hysterectomy. One clinical guideline that contained recommendations on referral of women with heavy menstrual bleeding for hysterectomy was identified, however, the recommendations were not based on patient assessments using clinical measurement tools.

References

National Collaborating Centre for Women's and Children's Health. Heavy menstrual bleeding. London: Royal College of Obstetricians and Gynaecology; 2007. NICE Clinical Guideline CG44. Available at http://www.nice.org.uk/nicemedia/live/11002/30401/30401.pdf [Accessed: 11-05-2010]

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 patient selection/
2 severity of illness index/
3 eligibility determination/
4 guideline.pt.
5 practice guideline.pt.
6 (guideline$ or recommend$ or consensus or standard$).tw.
7 hysterectomy.mp.
8 1 or 2 or 3 or 4 or 5 or 6
9 7 and 8 (2593)
11 limit 10 to "reviews (specificity)"

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Appendix B – Literature search results

Systematic Reviews and Guidelines

Source – NICE web site

National Collaborating Centre for Women's and Children's Health. Heavy menstrual bleeding. London: Royal College of Obstetricians and Gynaecology; 2007. NICE Clinical Guideline CG44. http://www.nice.org.uk/nicemedia/live/11002/30401/30401.pdf

Source – MEDLINE (Ovid) 1950 – April week 4 2010

Kovac S R. Which route for hysterectomy? Evidence-based outcomes guide selection. Postgraduate Medicine 1997; 102(3):153-8.

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Archived ARIF Request

Hysterectomy and Sub-Total Hysterectomy

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The Problem Submitted for ARIF to Advise Upon:

For non-malignant cases, which produces the best outcomes; hysterectomy or sub-total hysterectomy?

Reviews Identified

- Hasson HM. Cervical removal at hysterectomy for benign disease. Risks and benefits. Journal of Reproductive Medicine 1993; 38: 781-790

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Comments

The review identified is not completely systematic and as a result we cannot judge how much the reviewing process has compounded any biases inherent in the original studies making up the review. Despite this the review provides a rich source of background information. It also identifies a number of comparative studies which would be a good starting point for a more detailed consideration of the issue.

Request Carried Out: September 1996

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Archived ARIF Request

Photodynamic Therapy
Idiopathic Sub-Foveal Choroidal Neovascularisation

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in October 2002.

The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of photodynamic therapy for idiopathic sub-foveal choroidal neovascularisation?

Photodynamic therapy (PDT) is a newly developed type of treatment combining

- injection of a light-sensitive dye which concentrates in areas of “abnormality”
- low power laser

The rationale is that abnormal cells can be destroyed without damage to nearby normal cells.

PDT has applications in a number of areas, particularly cancer. However, requests to ARIF have focused on the use of this technology in treatment of eye disease. In this application the only currently commercially available light sensitive dye is verteporfin.

Idiopathic subfoveal choroidal neovascularisation occurs in patients without evidence of age-related macular degeneration (AMD) although it shares the same common feature of vision loss and the growth of new fragile blood vessels which are leaky and tend to cause scarring. The condition is relatively rare compared to AMD and tends to occur at a younger age.

Reviews Identified

No reviews were identified.

Primary Studies Identified

- Spaide RF et al. Treatment of idiopathic subfoveal choroidal neovascularisation lesions using photodynamic
- therapy with verteporfin. Am J Ophthalmol 2002; 134:62-68

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Comments

We identified no systematic reviews and no randomised controlled trials.

The only study found was on the treatment of a series of only 8 cases. Being an uncontrolled study it is highly likely to be subject to bias and confounding and as such the findings should be treated with caution.

Given these limitations the study seems to indicate that PDT may be a useful technique for treating idiopathic idiopathic sub-foveal choroidal neovascularisation as visual acuity appears to significantly improve after treatment and no treatment related adverse events were reported over the duration of follow up.

The authors acknowledge the limitations in study design and indicate that this is preliminary data requiring further study using robust controlled trials. We would concur with this conclusion.

It is important to distinguish this use of PDT from its use as a treatment for sub-foveal choroidal neovascularisation in age related macular degeneration on which NICE guidance is pending.

See related requests on:-

Age-Related Macular Degeneration (AMD/ARMD)/Sub-foveal Predominantly Classic Choroidal Neovascularisation (CNV)/Photodynamic Therapy

Age-Related Macular Degeneration (AMD/ARMD)/Sub-foveal Occult Choroidal Neovascularisation (CNV)/Photodynamic Therapy

Pathological Myopia/Choroidal Neovascularisation/Photodynamic Therapy

Request Carried Out: October 2002

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Archived ARIF Request

Immunoglobulin Replacement Therapy Immunodeficiency - Primary

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness and cost-effectiveness of immunoglobulin replacement therapy for common variable immunodeficiency (CVID).

Primary or secondary immunodeficiency are conditions where there is deficiency of gamma-globulins, proteins which help the body fight infection. Immunodeficiency is sometimes referred to as hypogammaglobulinaemia.

Primary immunodeficiency is where the problem occurs from birth – there are two main types, common variable immunodeficiency (CVID) and X-linked hypogammaglobulinaemia; secondary immunodeficiency occurs when another disease affects the body's ability to produce gamma-globulins. Chronic lymphocytic leukaemia (CLL) is such a disease.

The main health outcomes associated with hypogammaglobulinaemia are increased susceptibility to infections particularly of the lung, airways and sinuses. Repeated lung infections in this condition have in the past led to serious long-term lung damage such as bronchiectasis.

Reviews Identified

Background reviews - The following set out clearly a number of key issues concerning the use of immune replacement therapy in primary immunodeficiency:-

- Haeney M. Intravenous immune globulin in primary immunodeficiency. Clinical and Experimental Immunology 1994;97(S1):11-15

Systematic Reviews - There were no systematic reviews of RCTs examining the effectiveness of immunoglobulin replacement therapy.

Primary Studies Identified

a) the comparative effectiveness of intramuscular, intravenous and subcutaneous immunoglobul replacement e.g.

- Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy.

Journal of Clinical Immunology 2000; 20(2):94-100

b) the comparative effectiveness of different doses of intravenous immunoglobulin e.g.

- Pruzanski W, Sussman G, Dorian W, Van T, Ibanez D, Redelmeier D. Relationship of the dose of intravenous gammaglobulin to the prevention of infections in adults with common variable immunodeficiency. Inflammation 1996;20(4):353-9

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Comments

The place of immunoglobulin replacement therapy for primary immunodeficiency appears to be well established in the Handbook for Transfusion Medicine (3rd Edition), Chapter 8, available on-line www.transfusionguidelines.org.uk . The basis of this appears to be a strong rationale and the perceived dramatic impact on infections when intramuscular immunoglobulin first became available in the 1950's. There are no RCTs comparing immunoglobulin replacement therapy with supportive care not involving immunoglobulin replacement, and arguably such studies would no longer be ethical. Given this, it is unlikely that we will ever be able to precisely quantify whether the net clinical benefit is worth the costs of the treatment, generally several thousands of pounds per year (but depending considerably on patient weight, type of preparation and dose chosen).

Request Carried Out: September 2004

Update: May 2006 - A Regional Evaluation Panel (REP) Report was completed in October 2005.

The systematic review of effectiveness in this report confirmed the absence of RCTs comparing immunoglobulin replacement therapy without immunoglobulin replacement therapy. RCTs comparing different types of immunoglobulin replacement do exist.

The economic model in the report, which used non-RCT data to estimate the effect of introducing immunoglobulin replacement therapy on serious infections and survival, suggested that immunoglobulin therapy was cost-effective.

The recommendation of the West Midlands panel to commissioners of healthcare based on the REP report was "supported - borderline evidence".

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Archived Web Page

Revision Total Hip Arthroplasty
Impacted Cancellous Allografts and Cement

Table of Contents

WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the strength of evidence in favour of this technique over existing total hip revision in terms of quality and cost-effectiveness?

Is there any information whether these should be carried out at tertiary centres? Is there a minimal level of activity/experience of operator needed to ensure good quality surgery?

Reviews Identified

None.

Other Literature Identified

- Elting JJ et al. Preliminary report of impaction grafting for exchange femoral arthroplasty. Clinical Orthopaedics and Related Research 1995;319:159-167
- Gie GA. Impacted cancellous allografts and cement for revision total hip arthroplasty. Journal of Bone and Joint Surgery 1993;75B:14-21

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Comments

The primary research in this area is fairly scanty and not robust enough at this stage to provide a valid answer to the question. The two case series cited are of good size (68 and 67 cases) and both suggest that the technique may be the most promising to emerge so far in what, at the moment, represents a considerable challenge for the orthopaedic surgeon. The evidence also suggests that the technique is most successful in younger patients, patients with poor bone stock and those who have undergone repeated versions.

Unfortunately, none of the work we identified directly addresses the questions about effectiveness/cost-effectiveness and whether it should be carried out in specialist centres. Neither did it compare the results of the technique with those of alternative procedures.The primary research in this area is fairly scanty and not robust enough at this stage to provide a valid answer to the question. The two case series cited are of good size (68 and 67 cases) and both suggest that the technique may be the most

promising to emerge so far in what, at the moment, represents a considerable challenge for the orthopaedic surgeon. The evidence also suggests that the technique is most successful in younger patients, patients with poor bone stock and those who have undergone repeated versions.

It appears that this procedure is in the early stages of its development and it may well be some time before some more robust research is available. Purchasers could support the development of this service in the context of a more rigorous evaluation of the technique.

Request Carried Out: August 1997

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Archived ARIF Request

Impotence

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in May 1997.

The Problem Submitted for ARIF to Advise Upon:

What is the research evidence on the epidemiology, diagnosis and treatment of male impotence?

Question Reformulated

The main target of this broad request, was to identify good background reviews on the topic.

Reviews Identified

- Handelsman H. Diagnosis and treatment of impotence. Rockville, MD: Agency for Health Care Policy and Research, 1990. Pp 22
- Dawson C, Whitfield H. Subfertility and male sexual dysfunction. BMJ 1996;312:902-905

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Comments

Both reviews above provide well structured considerations of the topic, making them useful for background.

Beyond this, the AHCPR report is also systematic in approach, suggesting that any conclusions drawn on the actual effects/effectiveness may have a high degree of validity. However, readers should note that the review was published in 1990 and is likely to be out-of-date, a fact which ARIF confirmed by identifying relevant trials in the Cochrane Library's Register of Controlled Clinical Trials (1997, Issue 1).

Request Carried Out: May 1997

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Provision of incentives to motivate smokers to quit

Synopsis

Question:	What is the clinical and cost-effectiveness of providing incentives to motivate smokers to quit?
Reviews Identified:	Cahill K, Perera R. Competitions and incentives for smoking cessation. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD004307. DOI: 10.1002/14651858.CD004307.pub3. Lumley J, Chamberlain C, Dowswell T, Oliver S, Oakley L, Watson L. Interventions for promoting smoking cessation during pregnancy. Cochrane Database of Systematic Reviews 2009, Issue 3, Art. No.: CD001055. DOI: 10.1002/14651858.CD001055.pub3. Cahill K, Perera R. Quit and Win contests for smoking cessation. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD004986. DOI: 10.1002/14651858.CD004986.pub3.
Other Evidence:	O'Connor R, Fix B, Celestino P, Carlin-Menter S, Hyland A, Cummings KM. Financial incentives to promote smoking cessation: evidence from 11 quit and win contests. *Journal of Public Health Management and Practice* 2006;12(1):44-51
Comments:	Material and financial incentives appear effective in motivating smokers in both workplace and community settings to quit in the shorter term but early successes tend to dissipate when rewards cease. Incentives appear effective in promoting smoking cessation during pregnancy but their longer-term impact is unclear. Cost-effectiveness has not been determined. 'Quit and Win' contests involving a modest investment of resources may help some smokers to quit but their longer term impact has not been assessed and evidence to-date suggests their impact on community smoking rates is low.
Date Completed:	June 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Provision of incentives to motivate smokers to quit

Request completed: June 2010

Question

What is the clinical and cost-effectiveness of providing incentives to motivate smokers to quit?

Question clarification

Financial and material incentives are used in many smoking cessation programmes in support of the quitting process. They are used to encourage programme recruitment or reward cessation achieved at predefined stages. They may include cash payments, salary bonuses, promotional items (i.e. T-shirts and pens), lottery tickets, raffles, holidays, and luxury goods (i.e. cars). Rewards may be provided for attendance, irrespective of subsequent performance (i.e. guaranteed), or paid relative to the participant's success within a programme (i.e. contingent). 'Quit and Win' contests were developed in the 1980s by the Minnesota Heart Health Programme and have since been widely used as population-based smoking interventions at local, national and international levels. Key features include the offer of a large prize, a pledge by smokers to quit for a set period of time (generally around 30 days) on the target quit date, validation of smoking status prior to entry, and biochemical validation of quitting amongst potential winners.

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol www.arif.bham.ac.uk/strategy.shtml Text and index terms were used to represent the population and the intervention. Sources were searched from inception to May 2010. No language restriction was applied to the searches. The MEDLINE search can be found in Appendix A. The following inclusion criteria were used for study search and selection:

Population	smokers
Intervention	incentives (financial or material)
Comparator	no intervention/standard care
Outcome	smoking cessation
Study design	systematic reviews and health technology assessments

Results

Full search results can be found in Appendix B.

This report is based on evidence from three systematic reviews focusing solely, or in part, on the clinical effectiveness of incentives in motivating smokers to quit and one, cost-effectiveness study. Of the three systematic reviews, one focuses on competitions and incentives for smoking cessation;[1] one looks at a broad range of interventions for promoting smoking cessation during pregnancy (including the use of rewards);[2] and one assesses 'Quit and Win' contests.[3] The cost effectiveness study assesses the cost-effectiveness of 'Quit and Win' contests.[4] Details of the four papers can be found in Appendices C, D, E and F.

In overall summary, evidence from one generally well-conducted systematic review by Cahill and Perera[1] indicates at six months follow-up, and notably whilst rewards are still being paid, competitions and incentives are effective in increasing cessation rates amongst adults in workplace and community settings. However these early successes tend to dissipate when rewards cease. This review indicates there is some evidence that the offer of rewards encourages higher attendance rates which may, by virtue of this greater pool of participants, increase the number of quitters (in absolute terms). However, once in a programme, cessation rates were similar, in the longer term, amongst those offered rewards in comparison with those not. As the efficacy of the intervention was not established the reviewers felt a cost-effectiveness analysis was redundant.

The Cahill and Perera review[1] included RCTs and controlled studies with baseline and post-intervention measures published up to December 2007 and a caveat is the possibility that studies published since this time might alter the validity of its conclusions. Further scoping searches undertaken for this report identified a further 19 potentially relevant studies published from 2007 to 2010. Details can be found in Appendix G Most of these studies appear to assess relatively small samples over a short time-frame. However one large (n=878) RCT[5] assesses the provision of incentives to employees of a multinational US based company in comparison with information only. This study[5] reports significantly higher rates of smoking cessation amongst the incentive group at 15 or 18 months after enrolment. Any interpretation of these positive results however needs to take into account that a large reward package was paid over a longer time-frame than that reported in earlier studies ($100 for completion of a smoking cessation programme, $250 for cessation of smoking within six months after study enrolment and $400 for abstinence for an additional six months after the initial cessation).

Focusing specifically on smoking cessation during pregnancy, evidence from one generally well-conducted review by Lumley et al[2] indicates that, of the different types of smoking interventions assessed, the provision of incentives appeared to be the most effective. A meta-analysis of four

generally small studies of variable quality indicated there was a significant reduction in smoking amongst groups offered incentives in comparison with those not (risk ratio (RR): 0.76, 95% CI: 0.71 to 0.81, p<0.00001). This compares with the reviews' main meta-analysis of 65 studies (n=21,258) which indicated there was a significant reduction in smoking in late pregnancy following interventions in general (RR; 0.94, (95% CI: 0.93 to 0.96). The intervention was notably restricted to pregnancy and its effectiveness in the longer term in the absence of financial or material incentives was not considered. The cost-effectiveness of the intervention was not assessed.

Focusing specifically on 'Quit and Win' contests, evidence from one generally well-conducted review by Cahill & Perera[3] indicates contests may help some smokers quit, but their impact on community smoking rates is low. This conclusion is however based on only five studies targeting relatively local populations (city/county) in which the likelihood of selection bias cannot be discounted. Furthermore the identified evidence indicates the contests may be subject to levels of deception which could undermine their validity. Regarding the efficacy of international 'Quit and Win' contests the authors concluded that whilst these are often well supported, especially in developing countries, an absence of well designed comparative studies prevents firm conclusions. The review authors stated only one of the included studies reported information about the cost-effectiveness of the intervention. The study estimated the cost per quitter for the 'Quit and Win' contestants was US$130 vs. US%179 for the free NRT users, but the authors suggested this should be interpreted cautiously as the two groups were self selected and demographically different from each other. Finally evidence from one plausible cost-effectiveness study of 11 'Quit and Win' contests in the USA conducted by O'Connor et al[4] concluded that for a relatively modest investment of resources thousands of smokers can be recruited to make a serious quit attempt and many will remain non-smokers months later. However programme impact in the longer term was not assessed.

Conclusions

Material and financial incentives appear effective in motivating smokers in both workplace and community settings to quit in the shorter term. However these early successes tend to dissipate when rewards cease. Incentives may encourage smokers to take part in cessation programmes thereby increasing the number of potential quitters in absolute terms. However once recruited cessations amongst those offered rewards in comparison with those not appear similar. There is some evidence from small controlled trials that incentives are effective in promoting smoking cessation during pregnancy. However the longer-term impact after women have given birth and incentives are withdrawn has not been determined. 'Quit and Win' contests involving a relatively modest investment of resources may help some smokers to quit but their longer term impact has

not been adequately assessed and evidence to-date suggests their impact on community smoking rates is low.

References

1. Cahill K, Perera R. Competitions and incentives for smoking cessation. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD004307. DOI: 10.1002/14651858.CD004307.pub3.

2. Lumley J, Chamberlain C, Dowswell T, Oliver S, Oakley L, Watson L. Interventions for promoting smoking cessation during pregnancy. Cochrane Database of Systematic Reviews 2009, Issue 3, Art. No.: CD001055. DOI: 10.1002/14651858.CD001055.pub3.

3. Cahill K, Perera R. Quit and Win contests for smoking cessation. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD004986. DOI: 10.1002/14651858.CD004986.pub3.

4. O'Connor R, Fix B, Celestino P, Carlin-Menter S, Hyland A, Cummings KM. Financial incentives to promote smoking cessation: evidence from 11 quit and win contests. *Journal of Public Health Management and Practice* 2006;**12**(1):44-51

5. Volpp K, Troxel A, Pauly M, Glick H, Puig A, Asch D et al. A randomised, controlled trial of financial incentives for smoking cessation. *N Engl J Med* 2009;**360**:677-709

6. Lando HA, Pirie PL, McGovern PG, Pechacek TF, Swim J, Loken B. A comparison of self-help approaches to smoking cessation. *Addictive Behaviours* 1991;**16**:83-93

7. Bains N, Pickett W, Laundry B, Mecredy D. Predictors of smoking cessation in an incentive-based community intervention. *Chronic Diseases in Canada* 2000;21(2):54-61

8. McAlister AL, Gumina T, Urjanheimo E-L, Laatikainen T, Uhanov M, Oganov R, et al. Promoting smoking cessation in Russian Karelia: a 1-year community based program with quasi-experimental evaluation. *Health Promotion International* 2000;**15**:(2):109-112

9. Hahn EJ, Rayens MK, Warnick TA, Chirila C, Rasnake RT, Paul TP, et al. A controlled trial of a quit and win contest. *American Journal of Health Promotion* 2005;**20**(2):117-126

10. Hawk LW, Higbee C, Hyland A, Alford T, O'Connor R, Cummings KM, Concurrent Quit & Win and nicotine replacement therapy voucher giveaway programs: participant characteristics and predictors of smoking abstinence. *Journal of Public Health Management and Practice* 2006;**12**(1):52-59

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 incentive$.mp. or exp Motivation/
2 reward$.mp.
3 contest$.mp.
4 competition$.mp.
5 prize$.mp. or exp "Awards and Prizes"/
6 payment$.mp.
7 contract$.mp.
8 (win or winner$).mp.
9 (quit and win).mp.
10 or/1-9
11 exp Smoking/ or smoking.mp. or exp Smoking Cessation/
12 smoker$.mp.
13 Tobacco/ or tobacco.mp.
14 cigarette$.mp.
15 or/11-14
16 10 and 15
17 limit 16 to "reviews (specificity)"

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Appendix B – Literature search results

Systematic reviews

Source - Cochrane Library (Wiley) 2010 Issue 2 (CDSR)

Cahill K, Perera R. Competitions and incentives for smoking cessation. Cochrane Database of Systematic Reviews: Reviews 2008 Issue 3 John Wiley & Sons, Ltd Chichester, UK. DOI: 10.1002/14651858.CD004307.pub3 YR: 2008 NO: 3 PB: John Wiley & Sons, Ltd.
http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004307/frame.html
DOI: 10.1002/14651858.CD004307.pub3

Cahill K, Perera R. Quit and Win contests for smoking cessation. Cochrane Database of Systematic Reviews: Reviews 2008 Issue 4 John Wiley & Sons, Ltd Chichester, UK. DOI: 10.1002/14651858.CD004986.pub3 YR: 2008 NO: 4 PB: John Wiley & Sons, Ltd.
http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004986/frame.html
DOI: 10.1002/14651858.CD004986.pub3

Reda AA, Kaper J, Fikretler H, Severens JL, van Schayck CP. Healthcare financing systems for increasing the use of tobacco dependence treatment. Cochrane Database of Systematic Reviews: Reviews 2009 Issue 2 John Wiley & Sons, Ltd Chichester, UK. DOI: 10.1002/14651858.CD004305.pub3 YR: 2009 NO: 2 PB: John Wiley & Sons, Ltd.
http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004305/frame.html
DOI: 10.1002/14651858.CD004305.pub3

Cahill K, Moher M, Lancaster T. Workplace interventions for smoking cessation. Cochrane Database of Systematic Reviews: Reviews 2008 Issue 4 John Wiley & Sons, Ltd Chichester, UK. DOI: 10.1002/14651858.CD003440.pub3 YR: 2008; NO: 4 PB: John Wiley & Sons, Ltd.
http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003440/frame.html
DOI: 10.1002/14651858.CD003440.pub3

Source - cited in Cahill K, Perera R. Competitions and incentives for smoking cessation. Cochrane Database of Systematic Reviews: Reviews 2008 Issue 3 John Wiley & Sons, Ltd Chichester, UK

Lumley J, Chamberlain C, Dowswell T, Oliver S, Oakley L, Watson L. Interventions for promoting smoking cessation during pregnancy. Cochrane Database of Systematic Reviews 2009, Issue 3, John Wiley & Sons, Ltd Chichester, UK. DOI: 10.1002/14651858.CD003440.pub3 YR: 2009; NO: 3 PB: John Wiley & Sons, Ltd.
http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001055/frame.html
DOI: 10.1002/14651858.CD001055.pub3

Source - Cochrane Library (Wiley) 2010 Issue 2 (DARE)

Smedslund G, Fisher K J, Boles S M, Lichtenstein E. The effectiveness of workplace smoking cessation programmes: a meta-analysis of recent studies (Structured abstract). *Tobacco Control* 2004; **13(2)**: 197-204
http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12004008412/frame.html

Bains N, Pickett W, Hoey J. The use and impact of incentives in population-based smoking cessation programs: a review (Structured abstract). *American Journal of Health Promotion* 1998; **12(5)**: 307-320
http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-11998005650/frame.html

Eriksen M P, Gottlieb N H. A review of the health impact of smoking control at the workplace (Structured abstract). *American Journal of Health Promotion* 1998; **13 (2)**: 83-104
http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-11999005223/frame.html

Source – MEDLINE (Ovid) 2010 1950 to May Week 3 2010

Leeks KD, Hopkins DP, Soler RE, Aten A, Chattopadhyay SK. Task Force on Community Preventive Services. Worksite-based incentives and competitions to reduce tobacco use. A systematic review. *American Journal of Preventive Medicine* 2010; **38(2 Suppl)**:S263-74

Hey K, Perera R. Quit and Win contests for smoking cessation. Update in Cochrane Database Syst Rev. 2008;(4):CD004986; PMID: 18843674 Cochrane Database of Systematic Reviews. (2):CD004986, 2005.

Hey K, Perera R. Competitions and incentives for smoking cessation. [Review] [68 refs] [Update in Cochrane Database Syst Rev. 2008;(3):CD004307; PMID: 18646105]
SO Cochrane Database of Systematic Reviews. (2):CD004307, 2005.

Other reviews

Source – MEDLINE (Ovid) 2010 1950 to May Week 3 2010

Fang WL, Goldstein AO, Butzen AY, Hartsock SA, Hartmann KE, Helton M et al. Smoking cessation in pregnancy: a review of postpartum relapse prevention strategies. *Journal of the American Board of Family Practice* 2004 ;**17(4)**: 264-75,

Schubiner H, Herrold A, Hurt R. Tobacco cessation and youth: the feasibility of brief office interventions for adolescents *Preventive Medicine* 1998; **27(5 Pt 3**):A47-54,

Matson DM, Lee JW, Hopp JW. The impact of incentives and competitions on participation and quit rates in worksite smoking cessation programs. *American Journal of Health Promotion* 1993; **7(4)**:270-80

Source – TRIP database

Eriksen MP, Gottlieb NH. A review of the health impact of smoking control at the workplace *Am J Health Promot* 1998; **13(2)**: 83-104

Source – ARIF database

Bains N. Use of incentives to promote smoking cessation: a review. Toronto, Ontario: Ontario Tobacco Research Unit 1995;(1):1-31.

Economic evaluations

Source – Cochrane Library 2010 Issue 7 (NHS EED)

Salize HJ, Merkel S, Reinhard I, Twardella D, Mann K, Brenner H. Cost-effective primary care-based strategies to improve smoking cessation: more value for money (Provisional abstract). *Archives of Internal Medicine* 2009; **169(3)**: 230-235
http://www.mrw.interscience.wiley.com/cochrane/cleed/articles/NHSEED-22009100601/frame.html

O'Connor R, Fix B, Celestino P, Carlin-Menter S, Hyland A, Cummings KM. Financial incentives to promote smoking cessation: evidence from 11 quit and win contests (Structured abstract). *Journal of Public Health Management and Practice* 2006; **12(1)**: 44-51
http://www.mrw.interscience.wiley.com/cochrane/cleed/articles/NHSEED-22006001644/frame.html

Haile M J, Wiggers JH, Spigelman AD, Knight J, Considine RJ, Moore K. Novel strategy to stop cigarette smoking by surgical patients: pilot study in a preadmission clinic (Structured abstract). *ANZ Journal of Surgery* 2002; **72(9)**: 618-622
http://www.mrw.interscience.wiley.com/cochrane/cleed/articles/NHSEED-22002001718/frame.html

Hoeflmayr D, Hanewinkel R. Do school-based tobacco prevention programmes pay off? The cost-effectiveness of the 'Smoke-free Class Competition' (Structured abstract). *Public Health* 2008; **122(1):** 34-41
http://www.mrw.interscience.wiley.com/cochrane/cleed/articles/NHSEED-22008000203/frame.html

Shipley RH, Hartwell TD, Austin WD, Clayton AC, Stanley LC. Community stop-smoking contests in the COMMIT trial: relationship of participation to costs (Structured abstract). *Preventive Medicine* 1995; **24(3)**: 286-292
http://www.mrw.interscience.wiley.com/cochrane/cleed/articles/NHSEED-21995000712/frame.html

Johansson PM, Tillgren PE, Guldbrandsson KA, Lindholm LA. A model for cost-effectiveness analyses of smoking cessation interventions applied to a quit-and-win contest for mothers of small children (Structured abstract). *Scandinavian Journal of Public Health* 2005; **33(5):** 343-352
http://www.mrw.interscience.wiley.com/cochrane/cleed/articles/NHSEED-22005007701/frame.html

Source – CRD databases

O'Connor R, Fix B, Celestino P, Carlin-Menter S, Hyland A, Cummings K M. Financial incentives to promote smoking cessation: evidence from 11 quit and win contests. *Journal of Public Health Management and Practice* 2006; **12(1)**: 44-51
http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=22006001644

Background information

Source – NICE website

Should incentives be used to encourage healthy living? Report of meeting of NICE's citizens council May 2010
http://www.nice.org.uk/newsroom/features/HealthyLivingIncentives.jsp

Source – TRIP database

Troughton A, Kavanagh J, Oakley A, Harden A, Powell C. A summary of ongoing activity in the use of incentives schemes to encourage positive behaviours in young people. Social Science Research Unit, Institute of Education, University of London. London: EPPI Centre; 2005
http://eppi.ioe.ac.uk/EPPIWebContent/hp/reports/incentives/Incentives_ongoing_schemes.pdf

Kavanagh J, Troughton A, Oakley A, Powell C. A systematic review of the evidence for incentives schemes to encourage positive health and other social behaviours in young people. Social Science Research Unit, Institute of Education, University of London. London: EPPI Centre; 2006
http://eppi.ioe.ac.uk/EPPIWebContent/hp/reports/incentives/Incentives_systematic_review.pdf

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Appendix C – Critical appraisal of :

Cahill K, Perera R. Competitions and incentives for smoking cessation. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD004307. DOI: 10.1002/14651858.CD004307.pub3.

This comprehensive, generally well-conducted and relatively up-to-date (searches to December 2007) review aimed to determine whether competitions and incentives led to higher long-term quit rates and examine the relationship between incentives and participation rates.

The review included RCTs, allocating individuals (adult smokers), workplaces, groups within workplaces, or communities to experimental or control conditions, along with controlled studies with baseline and post-intervention measures. Trials aimed at pregnant smokers were excluded given coverage of this group in another Cochrane review.[2] Quit and Win contests were not considered as they were the subject of a companion review.[3]

Seventeen studies were identified. Twelve were based in the USA, three in the UK, one in Australia, and one in the USA and Canada. Seven studies were set in clinics or health centres, and ten in worksites. All 17 studies rewarded smoking cessation either alone or in combination with recruitment and/or participation. Incentives included lottery tickets (n=2); cash payments (n=6); cash payments for individual quitters plus worksite-wide prize draws (n=3); cash payments to individuals based on their team's performance within the worksite (n=2); and deposits refunded for abstinence (n=4).

The review authors commented the studies were often underpowered (study size, where reported, ranged from 49 to 2,402) and of variable quality. Eleven studies were described as randomised (of which six used a cluster-randomised design), two were described as 'quasi experimental', and four were non-randomised controlled studies. Only three studies reported any attempt to blind participants, trialists or assessors. Ten of the included studies treated programme drop-outs and losses to follow-up as continuing smokers, and conducted analyses on an intention-to-treat basis. Six studies followed up participants for a maximum of six months, two for between six and twelve months, six for 12 months, and three for 24 months.

A meta-analysis of nine studies (RCTs with extractable data) was conducted. Odds ratios (ORs) were adjusted to take account of cluster randomisation using an intraclass correlation of 0.01049. At six months follow-up the intervention effect was marginally significant (adjusted OR: 1.44, 95% confidence interval (CI): 1.01 to 2.01, p=0.042). However as the two studies reporting significant effects both paid their final reward to coincide with the six-month follow-up it was felt this may have introduced bias. A sensitivity analysis excluding these studies reduced the adjusted OR to 0.93

(95% CI: 0.59 to 1.47, p>0.05). At the 12-month and later follow-ups the adjusted ORs were not significant for these or any other studies.

The authors concluded incentives and competitions have not been shown to enhance long-term cessation rates, as early success tends to dissipate when rewards cease. They stated there was some evidence that recruitment rates can be improved by rewarding participation. This may then, potentially, increase the number of quitters (in absolute terms). However, once in a programme, cessation rates were similar amongst those offered rewards in comparison with those not. The type of reward, and whether or not smokers pledged their own money to take part, made no difference to the number of successful quitters. As the efficacy of the intervention was not established a cost-effectiveness analysis was not felt appropriate.

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Appendix D – Critical appraisal of:

Lumley J, Chamberlain C, Dowswell T, Oliver S, Oakley L, Watson L. Interventions for promoting smoking cessation during pregnancy. Cochrane Database of Systematic Reviews 2009, Issue 3, Art. No.: CD001055. DOI: 10.1002/14651858.CD001055.pub3.

This comprehensive, generally well conducted and relatively up-to-date (searches to June 2008) review aimed to assess the effects of smoking cessation interventions during pregnancy on smoking behaviour and perinatal health outcomes.

The review included RCTs and quasi-randomised controlled trials where smoking cessation during pregnancy was a primary aim of the intervention. A wide range of interventions were considered including: cognitive behavioural therapy, educational and motivational interviewing strategies; interventions based on stages of change; feedback of foetal health status or measurement of by-products of tobacco smoking to the mother; provision of rewards and incentives; provision of pharmacotherapies; and other strategies including hypnosis.

Of the 72 studies identified by the review, four studies assessed the effectiveness of rewards and incentives. All four studies were based in the USA. Incentives included vouchers (n=3) and a monthly lottery conducted amongst abstinent participants (n=1). Three studies, those assessing vouchers, assessed relatively small samples (53, 77 and 220 participants). One larger study, of a monthly lottery, recruited 935 participants. Two of the four studies were described as RCTs. Allocation methods for the remaining two studies were unclear. Study quality was variable. The review authors stated allocation concealment was either not undertaken or difficult to determine. Participants, trialists and assessors do not appear to have been blinded to the intervention. Three studies appeared to analyse results based on intention to treat.

A meta-analysis of the four studies indicated there was a significant reduction in smoking amongst groups offered incentives in comparison with those not (risk ratio (RR): 0.76, 95% CI: 0.71 to 0.81, $p<0.00001$).

The review authors commented that, of the different types of smoking cessation interventions assessed, the provision of incentives appeared to be the most effective. This compares with the reviews main meta-analysis of 65 studies (n=21,258) which indicated there was a significant reduction in smoking in late pregnancy following interventions in general (RR; 0.94, (95% CI: 0.93 to 0.96).

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Appendix E – Critical appraisal of:

Cahill K, Perera R. Quit and Win contests for smoking cessation. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD004986. DOI: 10.1002/14651858.CD004986.pub3.

The rationale for developing 'Quit and Win' contests was influenced by assumptions that: 1) most quit attempts fail within 30 days; 2) the chance of winning a large prize might offset the discomforts of quitting and motivate large numbers of smokers to make an attempt; and 3) after 30 days of abstinence the intrinsic reinforcements for quitting are more likely to maintain abstinence.

This comprehensive, generally well conducted and relatively up-to-date (searches to November 2007) review aimed to determine whether 'Quit and Win' contests can deliver higher long-term quit rates than baseline community quit rates. To assess programme impact both the quit rates achieved by participants and the population impact (which takes account of the proportion of the target population entering the contest) were considered.

The review included RCTs, allocating individuals (adult smokers) or communities to experimental or control conditions, along with controlled studies with baseline and post-intervention measures.

Five studies were identified.[6-10] Three were based in the USA, one in Canada, and one in Russia. All targeted relatively local populations (city/county). No controlled trials of international 'Quit and Win' contests were identified. Only one RCT was identified.[6] As this trial based in Mankato, Minnesota (USA) focused on the efficacy and acceptability of different self-help cessation materials and did not include the prize element of the full 'Quit and Win' contest, an assessment of the effectiveness of the fully functioning contest was not possible. Follow-up was often over 3-4 months rather than the planned seven months. The remaining four studies were non-randomised controlled studies.[7-10] One study,[7] with 12 months follow-up, compared quit rates amongst entrants to a contest (n=231) in two counties of Eastern Ontario (Canada) with a random sample of non-entrant smokers (n=385) living in the same area or in two adjacent counties. One study[8] evaluated the population impact of a contest held in Pitkaranta (Russia) conducting baseline surveys in this and a neighbouring district and follow-up surveys of a panel of daily smokers in Pitkaranta (n=176) and the control community (n=202) one year later. One study[9] compared 56% of Quit and Win contestants (n=494) in Lexington-Fayette county (USA) with randomly selected smokers outside the contest area (n=512). Abstinence was assessed at three, six and 12 months. One study[10] reported a campaign in Erie and Niagara counties (USA) in which participants could choose to enter a one month 'Quit and Win' contest (n=849), or could receive a free two-week supply of

nicotine patches or gum (n=690), or could combine both options (n=230). Abstinence was assessed at four and seven months.

The review authors commented that the five included studies all reported on relatively small numbers. The review authors stated the interventions were all conducted in communities that had current or prior experience of 'Quit and Win' contests. In contrast, for the most part, the control groups or communities were not attuned to smoking as a public health priority. Amongst contestant participants in comparison with controls a larger proportion were women, younger, better educated, smoked more cigarettes, were in the contemplation or preparation stage of change, and had made more previous quit attempts. The impact of selection bias on study findings therefore remains an important consideration.

Given the heterogeneity of the included studies a meta-analysis was not performed. Three studies[7-9] demonstrated significantly higher quit rates (8% to 20%) for the 'Quit and Win' group in comparison with the control group at the 12-month assessment. However the population impact measure, where reported, indicated the effect of contests on community smoking prevalence was small (less than one in 500 smokers quitting because of the contest). Only one study attempted biochemical validation of all claims of abstinence. This study[9] contrasted self-reported quit rates with confirmed ones. Amongst the intervention group there was a three-fold difference between self-reported (24.6%) and confirmed (7.3%) rates of cessation. The control group disparity was more than thirteen-fold (8.1% vs. 0.6%).

The review authors stated only one of the included studies[10] reported information about the cost-effectiveness of the intervention. The study authors[10] estimated the cost per quitter for the 'Quit and Win' contestants was US$130 vs. US$179 for the free NRT users, but pointed out that such comparisons may be misleading as the two groups were self selected and demographically different from each other.

The review authors concluded whilst controlled trials indicated 'Quit and Win' contests may help some smokers quit, their impact on community smoking rates is low. Furthermore contests may be subject to levels of deception which could undermine their validity. Regarding the efficacy of international 'Quit and Win' contests the authors concluded that whilst these are often well supported, especially in developing countries, an absence of well designed comparative studies prevents firm conclusions.

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Appendix F – Critical appraisal of :

O'Connor R, Fix B, Celestino P, Carlin-Menter S, Hyland A, Cummings KM. Financial incentives to promote smoking cessation: evidence from 11 quit and win contests. *Journal of Public Health Management and Practice* 2006; 12(1): 44-51

The study aimed to assess the cost-effectiveness of 11 'Quit and Win' contests in New York State, comparing quit rates with those observed in a state-wide population telephone survey.

This was a prospective cohort study with a historical control. From 2001 to 2004, an overall sample of 5,504 adult smokers participated in 11 'Quit and Win' contests (ranging from 112 to 1,683). In ten of the eleven contests a $1,000 prize was offered. The remaining contest offered prizes ranging from $500 to $2,000. Over 8,000 adults representative of the New York State population, enrolled in the 2003-2004 Adult Tobacco Survey (ATS), were used as the control group. The study authors stated contest participants were generally similar to those from the general population but tended to be younger and smoke more cigarettes. Follow-up surveys were undertaken four to six months after each contest ended to assess participants' success in quitting. In the counties that enrolled a large number of participants random samples of individuals were selected. Of the initial 5,504 sample, 2,756 were available at follow-up (50.1% response rate).

The analysis of the clinical data was restricted to individuals available at follow-up. The primary outcome measure was the quit rate based on self-reported smoking. The percentages of participants who quit and tried to quit during the contest were also reported. The secondary outcome was programme reach.

The cost analysis was restricted to programme costs and included advertising costs and prizes but did not include personnel costs associated with organising the contest and validating contest winners. Median programme expenditure was $25,928 (ranging from $91,441 to $4,345). Median cost per contestant was $75 (ranging from $30.48 to $125.09). Control group costs were assumed to be zero. Discounting was not performed. The price year was not reported but costs were gathered from 2001 to 2004.

In terms of programme reach, across the 11 communities 0.55% of smokers, on average, participated in the contest. Ninety percent of smokers enrolled in the contest reported attempting to quit, and 53 to 72% reported quitting for the full month of the contest. At four to six months follow-up, average self reported quit rates were 31% (ranging from 22 to 49%). The state-wide population survey indicated for eight of the 11 programmes quit rates were significantly higher than the estimated 21% quit rate seen amongst smokers making a quit attempt in the previous year. An incremental analysis was performed for these eight communities. The cost per attributable quit was

calculated as the cost for promoting the contest divided by the number of quits attributable to the programme. The ranged from $301.07 to $953.72.

The authors concluded that for a relatively modest investment of resources thousand of smokers can be recruited to make a serious quit attempt and many will remain smoke-free months later. However programme impact in the longer term was not assessed.

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Appendix G – Additional Literature Searches

Sources – CENTRAL (Wiley) 2010 Issue 2; MEDLINE (OVID) 1950 – Week 2 2010

Alessi SM, Petry NM, Urso J. Contingency management promotes smoking reductions in residential substance abuse patients. *Journal of applied behavior analysis* 2008; **41**(4):617-622

Chivers LL, Higgins ST, Heil SH, Proskin RW, Thomas CS. Effects of initial abstinence and programmed lapses on the relative reinforcing effects of cigarette smoking. Journal of applied behavior analysis 2008; 41(4):481-497

Dahm JL, Cook E, Baugh K, Wileyto EP, Pinto A, Leone F, et al. Predictors of enrollment in a smoking cessation clinical trial after eligibility screening. Journal of the National Medical Association 2009; 101(5):450-455

Dallery J, Meredith S, Glenn IM. A deposit contract method to deliver abstinence reinforcement for cigarette smoking. Journal of applied behavior analysis 2008; 41(4):609-615

Davidson MM, Cronk NJ, Harris KJ, Harrar S, Catley D, Good GE. Strategies to recruit and retain college smokers in cessation trials. Research in Nursing & Health 2010; 33(2):144-155

Dunn KE, Sigmon SC, Thomas CS, Heil SH, Higgins ST. Voucher-based contingent reinforcement of smoking abstinence among methadone-maintained patients: a pilot study. Journal of applied behavior analysis 2008; 41(4):527-538

Heil SH, Higgins ST, Solomon LJ, Lynch ME, McHale L, Dumeer A, et al. Voucher-based incentives for abstinence from cigarette smoking in pregnant and postpartum women (PA6-1). Society for Research on Nicotine and Tobacco 13th Annual Meeting February 21 24, Austin, Texas 2007;25

Heil SH, Higgins ST, Bernstein IM, Solomon LJ, Rogers RE, Thomas CS, et al. Effects of voucher-based incentives on abstinence from cigarette smoking and fetal growth among pregnant women. Addiction (Abingdon, England) 2008; 103(6):1009-1018

Higgins ST, Heil SH, Badger GJ, Skelly JM, Solomon LJ, Bernstein IM. Educational disadvantage and cigarette smoking during pregnancy. Drug & Alcohol Dependence 2009; 104 Suppl 1:S100-S105

Lamb RJ, Morral AR, Kirby KC, Javors MA, Galbicka G, Iguchi M. Contingencies for change in complacent smokers. Experimental and Clinical Psychopharmacology 2007; 15(3):245-255

Lamb RJ, Kirby KC, Morral AR, Galbicka G, Iguchi MY. Shaping smoking cessation in hard-to-treat smokers. Journal of Consulting and Clinical Psychology 2010; 78(1):62-71

MacKillop J, Kahler CW. Delayed reward discounting predicts treatment response for heavy drinkers receiving smoking cessation treatment. Drug & Alcohol Dependence 2009; 104(3):197-203

Roll JM, Howard JT. The relative contribution of economic valence to contingency management efficacy: a pilot study. Journal of applied behavior analysis 2008; 41(4):629-633

Stoops WW, Dallery J, Fields NM, Nuzzo PA, Schoenberg NE, Martin CA, et al. An internet-based abstinence reinforcement smoking cessation intervention in rural smokers. Drug & Alcohol Dependence 2009; 105(1-2):56-62

Tevyaw TO, Colby SM, Tidey JW, Kahler CW, Rohsenow DJ, Barnett NP, et al. Contingency management and motivational enhancement: a randomized clinical trial for college student smokers. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 2009; 11(6):739-749

Van OL, Lechner L, Reubsaet A, Wigger S, de VH. Relapse prevention in a national smoking cessation contest: effects of coping planning. British Journal of Health Psychology 2008; 13(3):525-535

Van OL, Lechner L, Reubsaet A, Steenstra M, Wigger S, de VH. Optimizing the efficacy of smoking cessation contests: an exploration of determinants of successful quitting. Health Education Research 2009; 24(1):54-63

Volpp KG, Troxel AB, Pauly MV, Glick HA, Puig A, Asch DA, et al. A randomized, controlled trial of financial incentives for smoking cessation. The New England journal of medicine 2009; 360(7):699-709

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Archived ARIF Request

Peri-Urethral Injection Incontinence

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in January 1997.

The Problem Submitted for ARIF to Advise Upon:

What is the cost-effectiveness of peri-urethal collagen injections in the treatment of stress incontinence. Are there short or long term complications that need to be considered?

Reviews Identified

- Fantl JA, Newman DK, Colling J et al. Urinary incontinence in adults: acute and chronic management. Clinical Practice Guideline No2 1996 update. Rockville MD: US Department of Health and Human Services. Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No 96-0682, 1996.

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Comments

This appears to be a systematic review of all the literature on most aspects of incontinence and in this respect the document provides excellent background material. However, the statements made on the use of peri-urethral injections in women are only supported by evidence from uncontrolled case series. There is enormous variation in the results reported and it is impossible to gauge whether this is due to variation in:

- Quality of study particularly completeness of follow-up and independent assessment of outcome.
- Study populations, particuarly prior operation for the condition.
- Outcomes, particularly length of follow-up.
- Intervention, particularly different materials used in the infection. e.g. teflon, collagen and the degree of technical competence of the operator.

Caution must be exercised in implementing any conclusions drawn from this section of the report.

This request demonstrates the importance of considering not just the validity of a review, when on exists, but also the validity of the component studies. Critical appraisal of some of the case-series included in the AHCPR guideline is particularly instructive. Considering in detail one of the primary studies below for this purpose is strongly suggested:

- Monga AK et al. Periurethral collagen injections for genuine stress incontinence and 2 year follow up. British Journal of Urology 1995;76:156-160
- Eckford SD, Abrams P. Para-urethral collagen implantation for female stress incontinence. British Journal of Urology 1991;68:586-589
- Beckingham IJ et al. Long-term follow-up of women treated with peri-urethral teflon injections for stress incontinence. British Journal of Urology 1992; 69: 580-583

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Archived ARIF Request

Infant Mortality Rates (IMR)
Perinatal Mortality Rates (PMR)

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The Problem Submitted for ARIF to Advise Upon:

Suggest an approach to devise an evidence based strategy to reduce high rates of perinatal and infant mortality.

The main role of ARIF in this request was to assist and facilitate a worker from the commissioning authority in question, identify interventions which had been demonstrated to have an effect on perinatal and infant mortality.

Reviews Identified

- Cochrane Pregnancy and Childbirth Database.

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Comments

Although the database above is becoming increasingly out-of-date, searching using terms such as "perinatal deaths", "infant mortality" etc can be a useful starting point in the task set. Increasingly, as more and more reviews are transferred to the Cochrane Database of Systematic Reviews in the Cochrane Library, this database could be used in exactly the same way.

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IVF and GIFT
Infertility

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The Problem Submitted for ARIF to Advise Upon:

Are there any reviews on IVF and GIFT that have been produced since the 1992 Effective Health Care Bulletin, The Management of Subfertility. Leeds: School of Public Health, University of Leeds, 1992. pp24. No 3?

Reviews Identified

- Hughes E, Collins J, Vandekerckhove P. Ovulation induction with urinary follicle stimulating hormone vs human menopausal gonadotropin for clomiphene-resistant polycystic ovary syndrome. In: Lilford R, Hughes E, Vandekerckhove P (eds.) Subfertility Module of The Cochrane Database of Systematic Reviews , [updated 03 December 1996]. Available in The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration; Issue 1. Oxford: Update Software; 1997. Updated quarterly.
- Daya S. Comparison of human follicle-stimulating hormone and human menopausal gonadotropin for ovarian stimulation in in vitro fertilization cycles. In: Lilford R, Hughes E, Vandekerckhove P (eds.) Subfertility Module of The Cochrane Database of Systematic Reviews , [updated 03 December 1996]. Available in The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration; Issue 1. Oxford: Update Software; 1997. Updated quarterly.
- Kotarba D, Kotarba J, Hughes E. et al. Growth hormone in in vitro fertilization. In: Lilford R, Hughes E, Vandekerckhove P (eds.) Subfertility Module of The Cochrane Database of Systematic Reviews , [updated 03 December 1996]. Available in The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration; Issue 1. Oxford: Update Software; 1997. Updated quarterly.
- Daya S, Gunby J, Hughes EG. Follicle-stimulating hormone versus human menopausal gonadotropin for in vitro fertilization cycles: a meta-analysis. Fertility and Sterility 1995;64(2):347-354
- Schenker JG, Ezra Y. Complications of assisted reproductive techniques. Fertility and Sterility 1994;61(3):411-422
- Hughes EG, Fedorkow DM, Daya S. The routine use of gonadotropin releasing hormone agonists prior to in vitro fertilization and gamete intrafallopian transfer: a meta- analysis of randomized controlled trials. Fertility and Sterility 1992;58(5):888-896

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Comments

The list indicates that there are a number of systematic reviews on specific aspects of IVF/GIFT which should be taken into account when considering the Effective Health Care Bulletin on this topic. Purchasers should also be aware that there appear to be large numbers of randomized trials on this topic published since 1992.

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Intra-Cytoplasmic Sperm Injection (ICSI) Infertility

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence for the effectiveness of intra-cytoplasmic sperm injection for assisted conception?

Question Reformulated

ICSI is one of several methods of assisted conception. The question to be addressed was thus defined as follows:

Intervention: Intra-cytoplasmic sperm injection.
Comparator: Other methods of in vitro/assisted fertilisation.
Outcomes: Pregnancy, live birth rates and adverse effects.

Reviews Identified

- van Rumste MME, Evers JLH, Farquhar CM, Blake DA. Intra-cytoplasmic sperm injection versus partial zona dissection, subzonal insemination and conventional techniques for oocyte insemination during in vitro fertilisation (Cochrane Review). In: The Cochrane Library, Issue 3, 1999. Oxford: Update Software.

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Comments

The review identified is both up-to-date and methodologically robust. However, the reliability of the results is limited by methodological weaknesses inherent in the included studies, and also by the fact that the summary analysis relies heavily on sub-group analyses, which can be misleading.

Because the main unit of randomisation is the egg and not the couple, the primary outcome in most studies is the fertilisation rate, not pregnancy and birth rates. It is also important to note that with ICSI, fertilisation is achieved using essentially abnormal sperm, through a technique that could result in trauma to the sperm or the egg. Foetal abnormalities must be a major concern and the review does not adequately address this.

The review findings suggest that ICSI fertilisation rates for couples with poor quality semen are better

than those with conventional IVF, but for couples with normal semen there is no difference between the two. There is insufficient information to draw reliable conclusions for other outcomes and comparisons.

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Vaccination
Influenza

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The Problem Submitted for ARIF to Advise Upon:

What are the effects/effectiveness of different policies on the use of influenza vaccination?

Reviews Identified

- Influenza vaccine and older people. York: NHS Centre for Reviews and Dissemination, 1996. (Effectiveness Matters Vol 2, Issue 1, October 1996.)

ARIF undertook on behalf of the requester a detailed examination of the pieces of research contributing to the review above, particularly:

- Gross PA et al. The efficacy of influenza vaccine in elderly persons: a meta-analysis and review of the literature. Internal Medicine 1995;123:1661-1665

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Comments

The review by Gross P et al is reasonably systematic, although the methods used to identify relevant literature were not completely comprehensive ie there is a risk that some relevant studies will have been overlooked. The included studies were mostly observational cohort studies in which mortality and other outcomes in a vaccinated group were compared with the outcomes in an unvaccinated group. The control groups were not randomly assigned.

Despite the fact that the review by Gross P et al does have short-comings and the findings are based on study designs which are more susceptible to bias than RCTs, the evidence on the effects and effectiveness of influenza vaccination in the elderly is very convincing. Further, health economic data and opinion (Prof J Raftery, University of Birmingham) suggests that influenza vaccination in the elderly is also cost-effective.

On this basis it is ARIF's opinion that:

1. The very least any purchaser should do on the basis of the above, is ensure that influenza vaccination is being received by all those prioritised by the DOH (see CMO's Update 15 - http://www.open.gov.uk/doh/cmo/cmoh.htm). Many audits have suggested that substantial

numbers of those prioritised do not receive influenza vaccination.
2. All purchasers should actively consider other ways to ensure that maximal health gain does accrue from this intervention of proven effectiveness, including extension of vaccination to other older persons who are not designated as "high risk" .

Coincidentally we also note that there is research evidence on the effects/effectiveness of methods to improve influenza vaccination uptake - see Cochrane Library (1997, Issue 2), Cochrane Controlled Trials register:

- Karuza J, Calkins E, Feather J et al. Enhancing physician adoption of practice guidelines. Dissemination of influenza vaccination guideline using a small-group consensus process. Archives of Internal Medicine 1995;155:625-32
- Ives DG, Lave JR, Traven ND et al. Impact of Medicare reimbursement on influenza vaccination rates in the elderly. Preventitive Medicine. 1994; 23: 134-41
- Herman CJ, Speroff T, Cebul RD. Improving compliance with immunization in the older adult: results of a randomized cohort study. Journal of the American Geriatrics Society 1994;42:1154-9
- McDonald CJ, Hui SL, Tierney WM. Effects of computer reminders for influenza vaccination on morbidity during influenza epidemics. MD Comput 1992;9:304-12
- Ohrt CK, McKinney WP. Journal of the American Medical Association 1992;267:1377-80
- Chambers CV, Balaban DJ, Carlson BL et al. The effect of microcomputer-generated reminders on influenza vaccination rates in a university-based family practice center. Journal of the American Board of Family Practice 1991;4:19-26.
- Bloom HG, Bloom JS, Krasnoff L et al. Increased utilization of influenza and pneumococcal vaccines in an elderly hospitalized population. Journal of the American Geriatrics Society 1988;36: 897-901.
- Mullooly JP. Increasing influenza vaccination among high-risk elderly: a randomized controlled trial of a mail cue in an HMO setting. American Journal of Public Health 1987;77:626-7
- Buchner DM, Larson EB, White RF. Influenza vaccination in community elderly. A controlled trial of postcard reminders. Journal of the American Geriatrics Society 1987;35:755-60
- McDowell I, Newell C, Rosser W. Comparison of three methods of recalling patients for influenza vaccination. Canadian Medical Association Journal 1986;135:991-7
- Larson EB, Bergman J, Heidrich F et al. Do postcard reminders improve influenza compliance? A prospective trial of different postcard "cues". Medical Care 1982;20:639-48

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Vaccination of Health Care Workers
Prevention of Influenza

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This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in October 1998.

The Problem Submitted for ARIF to Advise Upon:

Is there any evidence that annual vaccination of health care workers against influenza has health benefits for individuals, patients or organisations?

Reviews Identified

- The Canadian Task Force on the Periodic Health Examination. Clinical preventive health care. Chapter 61. Ottawa, 1994

Trials Identified

- Potter J et al. Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. Journal of Infectious Diseases 1997;175:1-6
- Weingarten S et al. Do hospital employees benefit from the influenza vaccine? A placebo-controlled trial. Journal of General Internal Medicine 1988;3:32-7

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Comments

The review cited is a set of guidelines linked to evidence which recommends vaccination of health care workers.

Appraising the two trials identified, which may not be representative of all the available trial evidence, revelas there is support for vaccination of health care workers, but this evidence is not compelling. Replication of the positive results of effects on health care workers and long stay patients would be valuable.

This is an area prone to need for regular updating as new information is continually becoming available.

Request Carried Out: October 1998

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Integrated Care Pathways

WARNING
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The Problem Submitted for ARIF to Advise Upon:

Are Integrated Care Pathways (ICPs) effective and cost effective, particularly in terms of getting research evidence into practice?

Question Reformulated

We defined an ICP as a structured, multidisciplinary plan of care that provides detailed guidance for each stage in the management of a patient with a specific condition over a given time period.

The main aim of an ICP is to improve the quality of patient care, and specifically to improve the continuity and co-ordination of care across different disciplines and sectors. An important corollary of this is reduced costs.

Thus, our interpretation of the question posed was as follows:
Intervention: Integrated Care Pathways (ICPs).
Population: Any diagnostic group of patients.
Outcomes: Standardisation of care and/or getting research evidence into practice.
Comparator: Other means of ensuring standardisation of care or getting research evidence into practice such as audit, clinical guidelines, or care protocols.

Reviews Identified

- Campbell H, Hotchkiss R, Bradshaw N, Porteous M. Integrated care pathways. BMJ 1998; 316(7125):133-137

Other Literature Identified

- Luther T, Crofts L. Managed care: development of an integrated care pathway in neurosciences. NT Research 1997;2(4):283-291
- Rossiter DA, Edmondson A, al-Shahi R, Thompson AJ. Integrated care pathways in multiple sclerosis rehabilitation: completing the audit cycle. Multiple Sclerosis 1998;4(2):85-89

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Comments

No systematic reviews or other robust evaluations were identified. The cited review is a narrative overview of the evidence on the effectiveness of ICPs. It concludes that there is no robust evidence on their effectiveness in changing practice or improving patient outcomes.

The two primary studies cited are observational case studies of ICPs in different conditions. Neither employs rigorous methods and neither uses an adequate comparison group. Reductions in length of stay were observed in both studies, but the evidence on improved patient outcome was not convincing. There was little direct reference to standardisation of care or getting evidence in practice although adherence to the pathway, which was pretty good in both studies, could clearly act as a proxy for both of these.

In summary, there have been no rigorous evaluations of the effectiveness of ICPs. Any attempt to assess how well they get evidence into practice would have to begin with an assessment of the validity of the guidelines on which the ICP is based. This information could then be used alongside measures of adherence to the ICP over time to give an indication of their success in this area.

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Intravenous Gammaglobulin
Kawasaki Disease

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence that intravenous gammaglobulin prevents the formation of coronary artery aneurysms in children with Kawasaki Disease?

Reviews Identified

- Durongpisitkul K, Gururaj VJ, Park JM et al. The prevention of coronary artery aneurysm in Kawasaki Disease: a meta-analysis on the efficacy of aspirin and immunogloblin treatment. Paediatrics 1995;96(6):1057-1061

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Comments

This meta-analysis appears to be based on a systematic search for prospective and retrospective studies reporting the incidence of coronary artery aneurysm. Our main concern with the review relates to the acceptibility of the method of pooling results from different studies. Other concerns relate to the clinical significance of the differences in incidence between the treatment groups.

Our views coincide, in general terms with those of the CRD reviewers, whose comments on the review can be found in the DARE database.

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Joint Replacement Surgery

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The Problem Submitted for ARIF to Advise Upon:

How effective is simultaneous bilateral joint replacement surgery?

Reviews Identified

Paper supplied by requester:

- Rao JN. Simultaneous Bilateral Joint Replacement Surgery. Paper to Sandwell Health Authority, July 1996. pp4. References 11.

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Comments

ARIF could not identify any reviews relating to the question posed. Nor too could it add significantly to the background paper produced internally by the Authority making the request. On this basis other purchasers may find this document of value; available via the ARIF office.

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Clinical measurement tools and referrals for knee replacement

Synopsis

Question:	Which clinical measurement tools that measure referral threshold for knee replacement are evidence based and of these, which is the best?
Reviews Identified:	No systematic reviews or health technology assessments were identified that directly answered the question. However, three clinical guideline documents that give recommendations on referral of patients for knee replacement and one systematic review that examined the effectiveness of clinical pathways in the treatment of knee pathology were identified, which may inform the decision process.
Comments:	Three clinical guidelines developed recommendations on referral for knee replacement surgery, however, none were based on patient assessments using clinical measurement tools.
Date Completed:	April 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Clinical measurement tools that measure referral threshold for knee replacement

Request completed: April 2010

Question

Which clinical measurement tools that measure referral threshold for knee replacement are evidence based and of these, which is the best?

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol http://www.arif.bham.ac.uk/strategy.shtml Text and index terms were used to represent the population and the intervention. Sources were searched from their inception to April 2010. No language restriction was applied to the searches. The MEDLINE search can be found in Appendix A. The following inclusion criteria were used for study search and selection:

Population	Patients who may need a knee replacement
Intervention	Clinical assessment tools used to measure referral threshold for knee replacement
Study design	Systematic reviews, health technology assessments

Results

No systematic reviews or health technology assessments were identified that directly answered the question. However, three clinical guideline documents[1-3] that give recommendations on referral of patients for knee replacement and one systematic review[4] that examined the effectiveness of clinical pathways in the treatment of knee pathology were identified, which may inform the decision process. Full search results can be found in Appendix B.

Of the guidelines, one was issued by the National Institute for Health and Clinical Excellence (NICE).[1] The second was produced by the Osteoarticular Research Group at University of Edinburgh, UK.[2] They, together with the systematic review,[4] included both hip and knee pathology and have already been described in the previous ARIF feedback - Clinical measurement tools that measure referral threshold for hip replacement.

The third guideline document was produced by the European League Against Rheumatism (EULAR).[3] It aimed to update the existing recommendations for management (including all treatments) of knee osteoarthritis (OA) using evidence based medicine and expert opinion. Its literature search strategy was good but the searches were up to 2002. The authors identified 35

studies on total knee replacement. The studies were all descriptive, with overall quality of the studies ranked using a quality score. However, no further details of the studies were reported. The authors recommended that joint replacement has to be considered in patients with radiographic evidence of knee OA who have refractory pain and disability (page 1150 and page 1153 of the publication).

Conclusions

No systematic reviews or health technology assessments were identified that had investigated clinical measurement tools to help treatment decisions regarding hip replacement. Three clinical guidelines that developed recommendations on referral for knee replacement surgery were identified, however, none were based on patient assessments using clinical measurement tools.

References

1. National Collaborating Centre for Chronic Conditions. Osteoarthritis. National clinical guideline for care and management in adults. London: Royal College of Physicians; 2008. [NICE Clinical Guideline CG59]. Available at http://www.nice.org.uk/nicemedia/pdf/CG059FullGuideline.pdf [Accessed on 25-03-2010]

2. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis and Cartilage 2008;16:137-162. Available at http://www.oarsi.org/pdfs/oarsi_recommendations_for_management_of_hip_and_knee_oa.pdf [Accessed on 25-03-2010]

3. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P et al. Standing committee for international clinical studies including therapeutic trials ESCISIT. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a task force of the standing committee for international clinical studies including therapeutic trials (ESCISIT). Annals of the Rheumatic Diseases 2003,62(12):1145-55.

4. Barbieri A, Vanhaecht K, Van Herck P, Sermeus W, Faggiano F, Marchisio S, et al. Effects of clinical pathways in the joint replacement: a meta-analysis. BMC Medicine 2009, 7:32

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 patient selection/
2 severity of illness index/
3 eligibility determination/
4 guideline.pt.
5 practice guideline.pt.
6 (guideline$ or recommend$ or consensus or standard$).tw.
7 1 or 2 or 3
8 4 or 5 or 6
9 Osteoarthritis, Knee/
10 Arthroplasty, Replacement, Knee/
11 knee replacement.tw.
12 knee arthroplasty.tw.
13 10 or 11 or 12
14 9 or 10 or 11 or 12
15 8 and 14
16 7 and 13
17 limit 15 to "reviews (specificity)"
18 limit 16 to "reviews (specificity)"

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Appendix B – Literature search results

Systematic Reviews and Guidelines

Source – NHS Evidence

Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis and Cartilage 2008; 16: 137-162 http://www.oarsi.org/pdfs/oarsi_recommendations_for_management_of_hip_and_knee_oa.pdf

Source – NICE web site

National Collaborating Centre for Chronic Conditions. Osteoarthritis. National clinical guideline for care and management in adults. London: Royal College of Physicians; 2008. [NICE Clinical Guideline CG59]. http://www.nice.org.uk/nicemedia/pdf/CG059FullGuideline.pdf

Source – MEDLINE (Ovid) 1950 – March week 2 2010

Garratt AM. Brealey S. Gillespie WJ. DAMASK Trial Team.
Patient-assessed health instruments for the knee: a structured review.
Rheumatology 2004; 43(11):1414-23.

Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P et al. Standing Committee for International Clinical Studies Including Therapeutic Trials ESCISIT.
EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Annals of the Rheumatic Diseases 2003; 62(12):1145-55.

Pendleton A, Arden N, Dougados M, Doherty M, Bannwarth B, Bijlsma JW et al.
EULAR recommendations for the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT).
Comment in: Ann Rheum Dis. 2001 Jul;60(7):717; PMID: 11436855]
Annals of the Rheumatic Diseases. 2000; 59(12):936-44.

Barbieri A, Vanhaecht K, Van Herck P, Sermeus W, Faggiano F, Marchisio S. et al
Effects of clinical pathways in the joint replacement: a meta-analysis.
BMC Medicine 2009; 7:32.

Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N. et al.
OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence.
Osteoarthritis & Cartilage 2007; 15(9):981-1000.

Zhang W, Doherty M.
EULAR recommendations for knee and hip osteoarthritis: a critique of the methodology.
British Journal of Sports Medicine 2006; 40(8):664-9.

Terwee CB, Mokkink LB, Steultjens MP, Dekker J.
Performance-based methods for measuring the physical function of patients with osteoarthritis of the hip or knee: a systematic review of measurement properties.
Rheumatology 2006; 45(7):890-902.

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Archived ARIF Request

Laser Therapy
Port Wine Stain

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of laser therapy for port wine stains?

A port wine stain is a type of congenital abnormality of blood vessels just underneath the surface of the skin. They often improve on their own without specific treatment.

Reviews Identified

- Best L. Pulsed dye laser treatment of port wine stains. Southampton: Wessex Institute for Health Research and Development, 1995. (DEC Report 43) Bristol: NHS Executive, South and West.

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Comments

This is a well conducted review which is unfortunately now out-of-date. The review did suggest that pulsed-dye laser treatment was effective, but the evidence was case-series which are open to bias.

A related request looks at the effectiveness of laser therapy (intralesion) for port wine stain.

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Laser Therapy (Intralesion)
Port Wine Stain

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of laser therapy for port wine stains and other subcutaneous vascular disorders (haemangioma and arterio-venous malformations)?

A port wine stain is a type of congenital abnormality of blood vessels just underneath the surface of the skin. They often improve on their own without specific treatment.

Reviews Identified

- Interventional procedure consultation document - Intralesional photocoagulation of subcutaneous congenital vascular disorders. National Institute for Clinical Excellence; June 2003 http://www.nice.org.uk/page.aspx?o=110850

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Comments

The guidance suggests:

“Current evidence on the safety and efficacy of intralesional photocoagulation of sub-cutaneous vascular disorders does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research."

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Routine Health Checks, Primary Care Learning Disabilties

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of regular health checks in the primary care setting for people with learning disability?

Question Reformulated

This question stems from a growing awareness that people with learning disabilities have a high prevalence of health problems relative to the general population, and that these are not being recognised and therefore not adequately addressed. In addition, there is evidence to suggest that people with learning disabilities living in the community consult their GP less often than other vulnerable groups. Regular, proactive health checks have been proposed as one means of addressing this problem.

Reviews Identified

- Kerr M, Fraser W, Felce D. Primary health care for people with a learning disability. A keynote review. British Journal of Learning Disabilities 1996;24:2-8
- Lennox NG, Kerr MP. Primary health care and people with an intellectual disability: the evidence base. Journal of Intellectual Disability Research 1997;41:365-72

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Comments

Two reviews were identified which provide a good overview of the problem. However, neither is systematic in its approach to either the identification, or the summary, of the literature. Together they draw attention to the lack of good evidence on the effectiveness of proactive screening programmes and health education for people with learning disabilities and highlight the need for rigorous evaluations. Our overall impression from the literature we examined is one of an increasing interest in the special health needs of people with learning disabilities, the onset of which coincides with the implementation of "Care in the Community", and a recognition that many of these needs are not met by the current pattern of service provision. Regular primary care health checks are repeatedly recommended, but evidence on their effectiveness is currently scarce.

This topic is one of several currently being reviewed by the West Midlands Development and Evaluation Service.

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Learning Disability

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The Problem Submitted for ARIF to Advise Upon:

Is there evidence of any health promotion interventions that ameliorate the effects of learning disabilities?

Question Reformulated

No specific reviews could be identified on health promotion interventions. The scope of the question which ARIF addressed was in consequence widened to:

Is there evidence of any interventions that have been demonstrated to ameliorate the effects of learning disabilities/previously referred to as "mental deficiency", "mental retardation" or "mental subnormality".

Reviews Identified

- Felce D, Taylor D, Wright K. People with learning disabilities. In Stevens A, Raftery J (eds). Health Care Needs Assessment - The epidemiology based needs assessment reviews. Volume 2. Oxford: Radcliffe Medical Press, 1994.
- Kavale KA, Forness SR. Hyperactivity and diet treatment: a meta-analysis of the Feingold hypothesis. Journal of Learning Disabilities 1983;16(6):324-330
- West Midlands Regional Health Authority. Purchasing briefing: Services for people with a learning difficulty. Birmingham: West Midlands Regional Health Authority, [date of publication unknown]. pp21
- Nye C. Effectiveness of language intervention with the language/learning disabled. Journal of Speech and Hearing Disorders 1987;52:348-357
- Wehmeyer ML. Intra-individual factors influencing efficacy of interventions for stereotyped behaviours: a meta-analysis. Journal of Intellectual Disability Research 1995;39:205-214
- Corrigan PW. Social skills in training adult psychiatric populations: a meta-analysis. Journal of Behavior Therapy & Experimental Psychiatry 1991;22:203-210
- Davis C, Bullis M. The school to community transition of hearing impaired persons with developmental disabilities. A review of the empirical literature. American Annals of the Deaf 1990; 135:352-363
- Lennox DB et al. Decelerative treatment practices with persons who have mental retardation: a review of five years of the literature. American Journal of Mental Retardation 1988;92:492-501

- Casto G, Mastropieri MA. The efficacy of early intervention programs: a meta-analysis. Exceptional Children 1986;52:417-424
- Fuchs LS Fuchs D. Effects of systematic formative evaluation: a meta-analysis. Exceptional Children 1986; 53: 199-208

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Comments

Our search of reviews revealed a surprisingly long list of potentially useful summaries of the available research. We cannot confirm that any of the reviews listed is systematic in approach, but the reviews can be grouped as follows in terms of their potential use as sources for beginning to consider the available research in this area:

Reviews giving a general overview of options which should be considered in purchasing services for those with learning disabilities:

- Felce D et al
- West Midlands Regional Health Authority

Reviews giving information on specific interventions which might be employed to ameliorate learning disabilities:

- Kavate KA (Dietary treatment)
- Nye C (Language intervention - see also ARIF request on speech therapy
- Wehmeyer ML (Interventions for stereotyped behaviour)
- Corrigan PW (Social skills training)
- Davis C (School to community transition - limited information on effects of independent living skills instruction)
- Lennox DB (Decelerative treatment practices)
- Casto G (Early interventions programs)
- Fuchs LS (Systematic formative evaluation)

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Link Worker

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The Problem Submitted for ARIF to Advise Upon:

Research bids have been received to fund "link workers". Is there any research on the effects and effectiveness of these?

Question Reformulated

Link workers is a vague term which required more specific definition. The one used for this request was:

Individuals whose main purpose is to encourage optimal use of existing health services, by providing information about, and encouraging or facilitating access to those services.

This would not include individuals whose main role was to deliver services in the community, e.g. health promotion advice or hypertension screening, who might be better described as "outreach" workers.

Reviews Identified

- NHS Centre for Reviews and Dissemination. Review of the research on the effectiveness of health service interventions to reduce variations in health. CPD Report No 3. York: University of York, NHS Centre for Reviews and Dissemination, 1995. Pp 157

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Comments

This is a systematic review covering the topic of interest and other closely related areas.

A number of evaluations of "link workers" conforming to the above definition exist, but the results are mixed, some suggesting benefit e.g. McAvoy & Raza (1991), others no impact e.g. Hoare et al (1994). In this situation it is impossible to draw categorical conclusions on the overall likelihood of the effect of introducing a "link worker" - this would require a systematic review with a much narrower focus, if possible with some sort of quantitative summary such as a meta-analysis. This would thus be the ARIF suggestion for further research. Any new primary research commissioned should take into account principles emerging from that research already undertaken and listed in the CPD report.

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Low Molecular Weight Heparin (LMWH) Unstable Angina

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The Problem Submitted for ARIF to Advise Upon:

How effective and cost-effective is LMWH relative to other treatments, particularly unfractionated heparin, in the management of unstable angina?

Reviews Identified

- Nicholson T. Low molecular weight heparins (dalteparin and enoxaparin) compared with unfractionated heparin for unstable angina and non Q wave myocardial infarction. Southampton: Wessex Institute for Health Research and Development; 1999. (DEC Report 93)

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Comments

As is typical of many rapid health technology assessment reports, the review does not contain sufficient information on its methods to allow us to reach a judgment on its methodological quality. However, it does contain details of the search strategy it employed, which was adequate, and DEC reports published in recent years generally adhere to certain quality standards. Our reading around the subject indicates that only two large multi-centre RCTs have been undertaken in this area on the two products licensed for use in the UK, both of which are included in the report. On this basis we would suggest that this is a reliable systematic review.

The findings of this review suggest that although this appears to be a promising class of drugs, the superiority of LMWH over unfractionated heparin has not yet been convincingly proven.

This is an area prone to need for regular updating as new information is continually becoming available.

Additional information relevant to this request is available in the requests entitled: LMWH/Deep Venous Thrombosis; LMWH/Treatment of Thromboembolic Disease; LMWH/Prevention and Treatment of Thromboembolic Disease and Management of Unstable Angina; Physical Prophylaxis/Deep Venous Thrombosis

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Low Molecular Weight Heparin (LMWH) Treatment of Thromboembolic Disease

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness and cost effectiveness of LMWH relative to other interventions for the treatment of existing thromboembolic disease?

Reviews Identified

- van den Belt AGM, Prins MH, Lensing AWA, Castro AA, Clark OAC, Attallah AN, Burihan E. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism (Cochrane Review). In: The Cochrane Library, Issue 1, 2000. Oxford: Update Software.
- Gould MK, Dembitzer AD, Doyle RL, Hastie TJ, Garber AM. Low molecular weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. Annals of Internal Medicine 1999;130(10):800-809

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Comments

We identified a number of reviews, all of which compared LMWH with unfractionated heparin and not other interventions or placebo. The two reviews above stood out as being more robust than the rest and they were also the most up to date.

Both reviews are well reported with good internal validity and employ sensitivity analysis of their findings. Both reviews came to the same conclusion that LMWHs are at least as effective as unfractionated heparins in preventing recurrent thromboembolism, bleeding and mortality in existing thromboembolic disease. The review by van den Belt also reported similar findings with respect to thrombus extension.

The predictability of the pharmokinetics of LMWH, and advantages in route of administration over unfractionated heparin, may make LMWHs more suitable for treating selected patients in an outpatient environment. Therefore, true equivalence in effectiveness between these two drug classes in the treatment of existing thromboembolic disease may mean that LMWHs are more cost effective despite their higher price. To this end the review by van den Belt recommends that "LMWH treatment can safely be adopted as the standard therapy in patients with deep venous thrombosis (DVT)", but due to

lack of studies a similar judgment cannot as yet be made for the treatment of patients with pulmonary embolism.

This is an area prone to need for regular updating as new information is continually becoming available.

Additional information relevant to this request is available in the requests entitled: LMWH/Unstable Angina; LMWH/Deep Venous Thrombosis (DVT); LMWH/Prevention and Treatment of Thromboembolic Disease and Management of Unstable Angina; Physical Prophylaxis/Deep Venous Thrombosis

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Archived ARIF Request

Low Molecular Weight Heparin (LMWH)
Treatment of Thromboembolic Disease
Management of Unstable Angina

Table of Contents

WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in March 2000.

The Problem Submitted for ARIF to Advise Upon:

What is known about the relative effectiveness and cost-effectiveness of different LMWH products in the prevention of deep venous thrombosis in orthopaedics; the management of unstable angina; and the treatment of existing thromboembolic disease?

Question Reformulated

Our searches for, and analysis of, systematic reviews on head-to-head comparisons of different LMWH products in the conditions of interest, indicated that very few relevant primary studies of this nature have been undertaken per se. On this basis we expanded the request to search primary research that compared the effectiveness of different LMWH products in any condition.

Reviews Identified

- Anderson DR, O'Brien B, Nagpal S et al. Economic evaluation comparing low molecular weight heparin with other modalities for the prevention of deep vein thrombosis and pulmonary embolism following total hip or knee arthroplasty. Ottawa: Canadian Co-ordinating Office for Health Technology Assessment (CCOHTA); 1998

Trials Identified

- Planes A, Samama MM, Lensing AWA et al. Prevention of deep vein thrombosis after hip replacement. Comparison between two low-molecular-weight heparins, tinzaparin and enoxaparin. Thrombosis & Haemostasis 1999;81(1):22-25
- Planes A, Vochelle N, Fagola M et al. Comparison of two low-molecular-weight heparins for the prevention of postoperative venous thromboembolism after elective hip surgery. Blood Coagulation & Fibrinolysis 1998; 9(6): 499-505

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Comments

We identified no reviews that set out to compare the different LMWHs in the areas of unstable angina

or existing thromboembolic disease. The CCOHTA review addresses the question of prevention in patients undergoing orthopaedic surgery. In our opinion this review is generally a well-conducted systematic review, the findings of which are probably reliable, although certain aspects of the meta-analysis are potentially misleading and should be viewed with caution. Specifically, the practice of generating summary odds ratios from indirect comparisons in the absence of direct comparisons is of questionable validity. The review was unable to provide a valid answer to the question because reliable studies directly comparing different products were not identified.

Our own searches identified only a small number of relevant trials. Readers should note that ARIF searches for primary research never aim to be totally comprehensive. The two trials cited are both large, multi-centre randomised comparisons. Despite a few minor methodological weaknesses, they are both well designed and well conducted. Taken together their results suggest that despite the differences in their chemical make-up, different LMWH products that have been evaluated appear to be largely equivalent in terms of their effectiveness and safety.

This is an area prone to need for regular updating as new information is continually becoming available.

Additional information relevant to this request is available in the requests entitled: LMWH/Unstable Angina; LMWH/Deep Venous Thrombosis (DVT); LMWH/Treatment of Thromboembolic Disease; Physical Prophylaxis/Deep Venous Thrombosis

Request Carried Out: March 2000

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Archived ARIF Request

Lung Cancer - Non-small Cell

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Is there evidence that lung cancer mortality could be substantially reduced by carrying out more surgery?

Reviews Identified

- Lederle FA, Niewoehner DE. Lung cancer surgery: a critical review of the evidence. Archives of Internal Medicine 1994; 154: 2397-2400

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Comments

Although not a sytematic review, the suggested reference provides a well considered assessment of the strengths and weaknesses of the research purporting to demonstrate that surgery for lung cancer is effective. The conclusion that there is uncertainty about the effectiveness of this intervention and the need for more rigorous evaluations seem well-founded.

Request Carried Out: April 1996

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Archived ARIF Request

Testerone Replacement Therapy
Male Menopause

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Is there any evidence as to the effects of testosterone supplementation in middle aged males suffering "andropausal symptoms"?

Reviews Identified

- Testosterone Patch. Birmingham: West Midlands Drug Information Service, 1996 New Product Summary, November 1996
- Testosterone. Midland Therapeutic Review and Advisory Committee, Keele University, Keele, Staffordshire: Midland Therapeutic Review and Advisory Committee, 1997. pp1.

Trials Identified

- Wang C et al. Testosterone replacement therapy improves mood in hypogonadal men - a clinical research centre study. J-Clin-Endocrinol-Metab1996; 81: 3578-3583
- Luisi M et al. Double blind group comparative study of testosterone undecanoate and mesterolone in hypogonadal male patients. J-Endocrin-Invest 1980;3:305-8

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Comments

None of the literature identified directly addressed the use of testosterone replacement therapy (TRT) in the male menopause, but it did consider the use of TRT in the treatment of the symptoms of hypogonadism, many of which concur with those of the andropause. Indeed, the two reviews cited suggest that TRT is only of benefit in men with proven hypogonadism.

The two reviews are not systematic reviews and do not provide any detail on the methods they employed so their results must be viewed with some caution. They demonstrate benefits of TRT for outcomes which largely relate to sexual function. For these reasons we went on to identify the key primary research on the topic.

The study by Wang et al provides a slightly different perspective. It examines the effect of TRT on a

variety of mood parameters and although it is described as a trial, the element relevant to this respect is best described as a before and after comparison. The study by Luisi et al is an early trial which demonstrates a beneficial effect of TRT on sexual activity and mental state.

While none of the studies identified directly consider middle aged men with andropausal symptoms, the subjects of all the studies are men with lower than average testosterone resulting from a variety of causes which are presumed to include the ageing process. It does, however, appear that there is no published evidence which indicates specifically that TRT is of value in the management of the male menopause.

Request Carried Out: August 1997

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Clinical measurement tools and referrals for meniscectomy

Synopsis

Question:	Which clinical measurement tools that measure referral threshold for meniscectomy are evidence based and of these, which is the best?
Evidence Identified:	No systematic reviews or health technology assessments were identified that were relevant to the question
Comments:	Currently, it would appear that there are no systematic reviews, health technology assessments or clinical guidelines that focus on clinical measurement tools that measure referral threshold for meniscectomy.
Date Completed:	July 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Clinical measurement tools and referrals for meniscectomy

Request completed: July 2010

Question

Which clinical measurement tools that measure referral threshold for meniscectomy are evidence based and of these, which is the best?

Method

Systematic reviews and health technology assessments were sought using the ARIF search protocol http://www.arif.bham.ac.uk/strategy.shtml. Text and index terms were used to represent the population and the intervention. Sources were searched from their inception to June 2010. No language restriction was applied to the searches. The MEDLINE search can be found in Appendix A. The following inclusion criteria were used for study search and selection:

Population	Patients who may need a meniscectomy
Intervention	Clinical assessment tools used to measure referral threshold for meniscectomy
Study design	Systematic reviews and health technology assessments

Results

Seven studies including four reviews, two clinical guidelines and one primary study were identified, however, none focused on clinical measurement tools that measure referral threshold for meniscectomy. Full search results can be found in Appendix B.

Conclusions

Currently, it would appear that there are no systematic reviews, health technology assessments or clinical guidelines that focus on clinical measurement tools that measure referral threshold for meniscectomy.

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 patient selection/
2 severity of illness index/
3 eligibility determination/
4 guideline.pt.
5 practice guideline.pt.
6 (guideline$ or recommend$ or consensus or standard$).tw.
7 meniscectomy.mp.
8 1 or 2 or 3 or 4 or 5 or 6
9 7 and 8

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Appendix B – Literature search results

Systematic Reviews and Guidelines

Source – Cochrane Library (DARE) 2010 Issue 2

Ryzewicz M, Peterson B, Siparsky P N, Bartz R L
The diagnosis of meniscus tears: the role of MRI and clinical examination (Structured abstract).
Clinical Orthopaedics and Related Research 2007; 455: 123-133

Source – MEDLINE (Ovid) 1950 – June week 4 2010

Beaufils P, Hulet C, Dhenain M, Nizard R, Nourissat G, Pujol N.
Clinical practice guidelines for the management of meniscal lesions and isolated lesions of the anterior cruciate ligament of the knee in adults.
Orthopaedics & traumatology, surgery & research. 2009; 95(6):437-42

Spahn G, Muckley T, Klinger HM, Hofmann GO.
Whole-Organ Arthroscopic Knee Score (WOAKS).
BMC Musculoskeletal Disorders. 2008; 9:155

Hegedus EJ, Cook C, Hasselblad V, Goode A, McCrory DC.
Physical examination tests for assessing a torn meniscus in the knee: a systematic review with meta-analysis.
Journal of Orthopaedic & Sports Physical Therapy. 2007; 37(9):541-50

Robb G, Reid D, Arroll B, Jackson RT, Goodyear-Smith F.
General practitioner diagnosis and management of acute knee injuries: summary of an evidence-based guideline.
New Zealand Medical Journal. 2007; 120(1249):U2419

Siparsky P, Ryzewicz M, Peterson B, Bartz R.
Arthroscopic treatment of osteoarthritis of the knee: are there any evidence-based indications?. [Review] [22 refs]
Clinical Orthopaedics & Related Research. 2007; 455:107-12

Heckmann TP, Barber-Westin SD, Noyes FR.
Meniscal repair and transplantation: indications, techniques, rehabilitation, and clinical outcome. [Review] [99 refs]
Journal of Orthopaedic & Sports Physical Therapy. 2006; 36(10):795-814

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UNIVERSITY OF BIRMINGHAM

Outcome monitoring tools for hand surgery

Synopsis

Question:	Is there any systematically reviewed evidence on the validity, reliability and responsiveness of clinical measurement tools for monitoring outcomes of hand surgery? Does the evidence from these reviews show how the Disabilities of Arm, Shoulder and Hand (DASH) questionnaire compares with other questionnaires for monitoring outcomes of hand surgery?
Evidence Identified:	No systematic reviews were identified. Three overviews were identified which may provide some useful information: Bindra PR, Dias JJ, Heras-Palau C, Amadio PC, Chung KC, Burke FD. Assessing outcome after hand surgery: the current state. Journal of Hand Surgery British and European Volume 2003;28(4):289-294 Amadio PC. Outcomes assessment in hand surgery. What's new? Clinics in Plastic Surgery 1997;24(1):191-4 Amadio PC. Outcome assessment in hand surgery and hand therapy: an update. Journal of Hand Therapy 2001;14(2):63-7
Comments:	Three overviews were identified, which showed that a number of questionnaires have been used for monitoring outcomes of hand surgery. However, currently there are no systematic reviews that assessed studies investigating measurement properties or comparing the DASH questionnaire with alternative measurements for hand surgery outcomes.
Date Completed:	January 2011

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About ARIF

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ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Outcome monitoring tools for hand surgery

Request completed: January 2011

Original request

What is the most effective tool for monitoring outcomes of hand surgery?

Currently the Disabilities of Arm, Shoulder and Hand (DASH) is being used and we want to test the evidence of systematic reviews about the efficacy of this or alternative tools for measuring outcome of hand surgery.

ARIF refined question

Are there any systematic reviews on the validity, reliability and responsiveness of clinical measurement tools for monitoring outcomes of hand surgery? Does the evidence from these reviews show how the Disabilities of Arm, Shoulder and Hand (DASH) questionnaire compares with other questionnaires for monitoring outcomes of hand surgery?

Method

Systematic reviews were sought using the ARIF search protocol (www.arif.bham.ac.uk/strategy.shtml). Text and index terms were used to represent the population and the intervention. Sources were searched from their inception to November 2010. No language restriction was applied to the searches. As an example the MEDLINE search can be found in Appendix A. The following were the inclusion criteria for study selection:

Population	People undergoing hand surgery
Intervention	Clinical assessment tools used to measure outcomes of hand surgery
Study design	Systematic reviews assessing the validity, reliability and responsiveness of outcome measurement tools for hand surgery

Results

Full search results can be found in Appendix B.

No systematic reviews that evaluated outcome measurement tools for hand surgery were identified. In total, three overviews were identified, which may provide some useful information.

Of the three overviews, one by Brindra and colleagues and published in 2003,[1] reviewed the current (i.e. at the time of conducting the review) status of outcome measurement of hand surgery, with a focus on subjective measurement questionnaires. It introduced stages in developing a questionnaire, essential concepts of a questionnaire (reliability, validity, responsiveness, range, and feasibility), and factors that affect questionnaire completion. It also briefly described existing questionnaires relevant for outcome measurement following hand surgery, and cited the original publication on the development of the questionnaire for most of the questionnaires. A list of the questionnaires covered by the review is presented in Appendix C. The authors stated that, designed for a specific purpose, each of the questionnaires has individual advantages and disadvantages, and suggested recommendations for clinical practice. The review however did not assess the validation of the questionnaires.

The other two reviews, both by Amadio and published in 1997[2] and 2001,[3] discussed issues around outcome measurement of hand surgery, and described the development of the DASH questionnaire. The more recent review[3] also described other measurement tools for hand surgery and hand therapy (including Michigan Hand Questionnaire, Patient-rated Forearm Evaluation Questionnaire, and Carpal Tunnel Syndrome Questionnaire), and discussed issues around questionnaire evaluation, including validity, responsiveness and reliability, internal consistency, sensitivity, and cultural adaptations.

The DASH website (http://www.dash.iwh.on.ca/index.htm) provides a list of all publications related to the DASH questionnaire, which may include primary studies on the validity, reliability and responsiveness of the DASH questionnaire.

Conclusions

Overall, a number of questionnaires have been used to measure outcomes of hand surgery. However, currently there are no systematic reviews that assessed studies investigating the measurement properties of any measurement tools or comparing the DASH questionnaire with alternative measurements for hand surgery outcomes.

References

1. Bindra PR, Dias JJ, Heras-Palau C, Amadio PC, Chung KC, Burke FD. Assessing outcome after hand surgery: the current state. Journal of Hand Surgery British and European Volume 2003;28(4):289-294

2. Amadio PC. Outcomes assessment in hand surgery. What's new? Clinics in Plastic Surgery 1997;24(1):191-4

3. Amadio PC. Outcome assessment in hand surgery and hand therapy: an update. Journal of Hand Therapy 2001;14(2):63-7

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 dash.ti,ab.
2 hand surgery.ti,ab.
3 exp Hand Injuries/su [Surgery]
4 2 or 3
5 "Outcome Assessment (Health Care)"/ or "Outcome and Process Assessment (Health Care)"/ or Treatment Outcome/
6 outcome* or outcome questionnaire* or outcome measure* or outcome* tool*).ti,ab.
7 5 or 6
8 1 or 7
9 4 and 8
10 1 and 4

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Appendix B – Literature search results

Systematic reviews

Source – MEDLINE 1950 - Nov 2010

Naidu SH, Panchik D, Chinchilli VM.
Development and validation of the hand assessment tool.
Journal of Hand Therapy. 22(3):250-6; quiz 257, 2009 Jul-Sep.

Sandqvist G, Johnsson PM, Sturesson AL, Gil M, Geborek P.
Measures and time points relevant for post-surgical follow-up in patients with inflammatory arthritis: a pilot study.
BMC Musculoskeletal Disorders. 10:50, 2009.

Chiari-Grisar C, Koller U, Stamm TA, Wanivenhaus A, Trieb K.
Performance of the disabilities of the arm, shoulder and hand outcome questionnaire and the Moberg picking up test in patients with finger joint arthroplasty.
Archives of Physical Medicine & Rehabilitation. 87(2):203-6, 2006 Feb.

Mink van der Molen AB, Ettema AM, Hovius SE.
Outcome of hand trauma: the hand injury severity scoring system (HISS) and subsequent impairment and disability.
Journal of Hand Surgery - British Volume. 28(4):295-9, 2003 Aug.

Amadio PC.
Outcome assessment in hand surgery and hand therapy: an update.
Journal of Hand Therapy. 14(2):63-7, 2001 Apr-Jun.

Amadio PC.
Outcomes assessment in hand surgery. What's new?
Clinics in Plastic Surgery. 24(1):191-4, 1997 Jan.

Bindra RR, Dias JJ, Heras-Palau C, Amadio PC, Chung KC, Burke FD.
Assessing outcome after hand surgery: the current state.
Journal of Hand Surgery - British Volume. 28(4):289-94, 2003 Aug.

Background references

DASH

The DASH.
http://www.dash.iwh.on.ca/assets/images/pdfs/dash_questionnaire_2010.pdf

Chartered Society of Physiotherapy. Disabilities of the Arm, Shoulder and Hand (DASH)
http://www.csp.org.uk/director/members/practice/clinicalresources/outcomemeasures/searchabledatabase.cfm?item_id=570118519CB4458F4011FCC0991AAFEA

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Appendix C – Questionnaires covered by the Bindra review:

1. **General health questionnaires**
   - The 36-item short-form health survey (SF-36)
   - The 12-item short-form health survey (SF-12)
   - Nottingham Health Profile
   - Sickness Impact Profile
   - Euroqol (EQ-5D)

2. **Region-specific questionnaires**
   - Diasbilities of the arm shoulder and hand (DASH)
   - Outcomes of plastic surgery – hand/arm questionnaire (OPS)
   - Michigan hand questionnaire (MHO)
   - Patient evaluation measure (PEM)
   - Patient related wrist evaluation (PRWE)

3. **Disease-specific questionnaires**
   - Carpal tunnel questionnaire

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Archived ARIF Request

Peer Education
Men Who Have Sex With Men

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of peer education interventions aimed at influencing sexual risk-taking behaviour in men who have sex with men?

Reviews Identified

No systematic reviews were identified. However, a protocol for a systematic was found:

- Johnson W, Peersman G. Interventions to modify sexual risk behaviours for preventing HIV infection in men who have sex with men (Protocol for a Cochrane Review). In: The Cochrane Library, Issue 3, 2001. Oxford: Update Software. Date of most recent substantive amendment: 30 April 1998. Review expected to be published in: Issue 4, 2002

Primary Studies

Source - Cochrane Library 2001 Issue 3 (CCTR)

- Kelly JA, Murphy DA, Sikkema KJ, McAuliffe TL, Roffman RA, Solomon LJ, Winett RA, Kalichman SC, Heckman TG, Perry MJ, Stevenson LY, Hauth AC, Koob JJ, Morgan MG, Norman A, Lemke A, Steiner S, Trenary B, Flynn B, Ayotte DR, Desiderato LL, Lombard DN, Yaffe DM. Randomised, controlled, community-level HIV-prevention intervention for sexual-risk behaviour among homosexual men in US cities. Lancet 1997;350(9090):1500-1505
- Tudiver F, Myers T, Kurtz RG, Orr K, Rowe C, Jackson E, Bullock SL. The talking sex project: Results of a randomized controlled trial of small-group AIDS education for 612 gay and bisexual men. Eval Health Prof 1992;15(1):26-42
- Leviton LC, Valdiserri RO, Lyter DW, Callahan CM, Kingsley LA, Huggins J, Rinaldo CR. Preventing HIV infection in gay and bisexual men: experimental evaluation of attitude change from two risk reduction interventions. AIDS Education & Prevention 1990;2(2):95-108
- Valdiserri RO, Lyter DW, Leviton LC, Callahan CM, Kingsley LA and Rinaldo, CR. AIDS prevention in homosexual and bisexual men: results of a randomised trial evaluating two risk reduction interventions. AIDS 1989;3(1):21-26
- Shepherd J, Weare K, and Turner G. Peer-led sexual health promotion with young gay and bisexual men Results of the HAPEER Project . Health Education 1997;6:204-212

- Elford J, Bolding G, Sherr L Peer education has no significant impact on HIV risk behaviours among gay men in London. AIDS 2001; 15(4): 535-8

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Comments

Given the absence of completed systematic reviews at this time, we focused on the primary studies identified to inform our feedback. All the listed primary studies were either randomised controlled trials or controlled trials. However there was significant heterogeneity in the interventions used, the settings in which the interventions were delivered, the outcomes measured, and the success or otherwise of the peer-education interventions examined. Further caution is required in interpretation because of some methodological limitations of the trials, especially poor follow-up.

In summary, we felt unable to draw meaningful conclusions from existing primary studies on the general effectiveness of peer education interventions in reducing sexual risk-taking behaviours in gay, bisexual and other men who have sex with men outside the context of a systematic review. The on-going review by Johnson and Peersman should help in the future.

Request Carried Out: December 2001

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Archived ARIF Request

Menopause

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What treatments have been shown to be effective to treat symptoms of the menopause?

Question Reformulated

This was a very broad question which essentially asked whether there was good evidence from systematic reviews on the effectiveness of any treatments for the menopause.

Reviews Identified

- Haskell SG, Richardson ED, Horwitz RI. The effect of estrogen replacement therapy on cognitive function in women: a critical review of the literature. Journal of Clinical Epidemiology 1997;50(11): 1249-1264
- Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. Journal of the American Medical Association 1998;279(9): 688-695
- Zweifel JE, O'Brien WH. A meta-analysis of the effect of hormone replacement therapy upon depressed mood. Psychoneuroendocrinology 1997; 22(3): 189-212

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Comments

A large number of relevant systematic reviews were identified and several more relevant Cochrane reviews are expected soon.

Haskell et al and Yaffe et al consider the effects of hormone replacement therapy (HRT) on cognitive function in menopausal women. Both reviews are of reasonable methodological quality. They largely consider the same body of research, concluding that the evidence base for the effectiveness of HRT on cognitive function is inconclusive and has significant methodological limitations.

Zweifel and O'Brien consider the effect of HRT on depressed mood. This is a good systematic review that includes studies of variable methodological quality. Our main criticism of the review is that while it provides good summary tables, it does not present the individual study results, hindering a comprehensive assessment of the validity of the meta-analysis. Nevertheless, the overall pattern of the

results of the meta-analysis is consistent, suggesting that HRT is effective in reducing depressed mood associated with the menopause.

Request Carried Out: July 2000

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Uterine Thermal Balloon Ablation Menorrhagia

Table of Contents

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The Problem Submitted for ARIF to Advise Upon:

What research exists on thermal balloon therapy for women with menorrhagia?

Question Reformulated:

After some discussion with the requester about the background to the request, the question was restated as:

What is known about the effectiveness of endometrial ablation using thermal balloon treatment, under local anaesthetic in the primary care setting, for the treatment of menorrhagia?

Thermal balloon ablation is just one of many methods used to destroy the endometrium and the approach we took was:

a) to evaluate its effectiveness relative to other methods of endometrial destruction, and

b) to consider the effectiveness of endometrial destruction as a broad treatment category relative to other categories such as drug treatment, hormone releasing IUDs and hysterectomy.

Reviews Identified

- Lethaby A, Shepperd S, Cooke I, Farquhar C. Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding (Cochrane Review). In: The Cochrane Library, Issue 2, 1999. Oxford: Update Software.

Trials Identified

- Meyer WR, Walsh BW, Grainger DA et al. Thermal balloon and rollerball ablation to treat menorrhagia: a multicenter comparison. Obstet-Gynecol 1998; 92(1): 98-103.

Other Literature Identified

- Lethaby A, Hickey M. Endometrial destruction techniques for heavy menstrual bleeding (Protocol for a Cochrane Review). In: The Cochrane Library, Issue 2, 1999. Oxford: Update Software.

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Comments

a) With regard to the effectiveness of thermal balloon ablation relative to other endometrial destruction techniques, we identified no published systematic reviews but noted the protocol for the Cochrane review. The trial by Meyer et al is a large, well-designed and conducted, multi-centre RCT that compares thermal balloon ablation with rollerball ablation in the secondary care setting. It demonstrates quite convincingly that the two procedures are comparable at 12 months follow-up in terms of reducing menstrual blood flow and improving quality of life, and that adverse effects were slightly more common in the rollerball group. Our main area of concern, however, is the lack of evidence on the acceptability and tolerability of the treatment when it is employed in the primary care setting under local anaesthesia.

b) In relation to the question on the effectiveness of endometrial destruction relative to other treatment categories, we identified a published Cochrane review. This is a good systematic review, the results of which can probably be trusted, despite the fact that for certain outcomes the use of meta-analytic techniques may have been inappropriate due to the small number of studies recording data on that outcome. The review concludes that hysterectomy is more effective than endometrial destruction, in terms of reducing menstrual blood flow and patient satisfaction, but that endometrial destruction is cheaper and less risky for the patient.

This is an area prone to need for regular updating as new information is continually becoming available.

Request Carried Out: June 1999

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Archived ARIF Request

Physiotherapy Mental Illness

Table of Contents

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of interventions provided by physiotherapists in the treatment of the symptoms of mental illness?

We searched for systematic reviews that include any interventions physiotherapists may provide to mental health patients and that were published since the National Service Framework for Mental Health treatments in Physiotherapy in 2001.

Reviews Identified

- Lawlor DA and Hopker SW. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression of randomised controlled trials. BMJ 2001; 322:1-8
- Cohen-Mansfield J. Non-pharmacologic interventions for inappropriate behaviours in dementia: a review, summary and critique. American Journal of Psychiatry 2001; 9:361-381.

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Comments

Lawlor and Hopker (2001) was a well-conducted, comprehensive systematic review of randomised controlled trials comparing the effectiveness of exercise and other established treatments as an intervention in the management of depression. Although participation in exercise reduced symptoms of depression compared with no treatment, all the studies included in the review had serious methodological weaknesses. It is also not clear if physiotherapists provided the exercise interventions in the studies.

Cohen-Mansfield examined the use of non-pharmacological interventions for inappropriate behaviours (e.g. wandering, disruptive and disturbing behaviours, agitation) in patients with dementia. One RCT (n=36) was identified where patients participated in an exercise programme and the effect of the programme on agitated behaviour was examined. Of the interventions covered in this review, this was the only one physiotherapists would be likely to provide. The trial demonstrated a decrease in agitation in the patients who received the exercise programme. However, it is difficult to draw any conclusions about the effectiveness of exercise for reducing agitation in patients with dementia, because of the

small size of the study and the lack of sufficient information provided on the conduct of the included study.

There is a lack of good quality primary research in these areas.

Request Carried Out: May 2003

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Archived ARIF Request

Prevention
Mental Illness

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Can mental illness be prevented?

See related requests: Can depression be prevented in children and adolescents?, Can postnatal depression be prevented?, Can depression be prevented in adults? , Can eating disorders be prevented?

Reviews Identified

- Cuijpers P, Van Straten A, Smit F. Preventing the incidence of new cases of mental disorders: a meta-analytic review. Journal of Nervous & Mental Disease. 2005 ;193(2):119-25
- Nicholas B, Broadstock M Effectiveness of early interventions for preventing mental illness in young people. A critical appraisal of the literature Christchurch : NZHTA Clearing House NZHTA Report ; August 1999
- Tilford S, Delaney F and Vogels M Effectiveness of mental health promotion interventions: a review London : Health Education Authority, 1997. (Health Promotion Effectiveness Reviews No 4)

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Comments

The most up to date review was critically appraised (Cuijpers P et al 2005). This was a systematic review of reasonable quality. The aim of this review was to assess the effects of preventive interventions on the incidence (new cases) of mental disorders.

The review included 13 trials, with a total of 1,570 subjects. Overall, a statistically significant risk reduction was found in favour of the intervention compared to control with the relative risk across all studies being 0.73 (95% CI 0.56, 0.95).

The review authors advise a cautious interpretation of the results as 2 studies dominated the meta analysis and when removed the result was not statistically significant.

Subgroup analysis found that interventions aimed at depressive disorders were effective, as was

cognitive behaviour therapy and interventions carried out on indicated populations (subclinical groups).

Interestingly, debriefing to prevent Post Traumatic Stress Disorder (PTSD) did not prevent the onset of PTSDs and may increase the risk of getting PTSD, a result consistent with the review on by Rose in 2002.

Request Carried Out: August 2005

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Archived ARIF Request

Total Hip Replacement
Metal to Metal Resurfacing

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Metal-to-metal hip resurfacing has been suggested as an alternative to performing a standard total hip replacement in selected cases, usually in younger patients. The procedure is intended to prevent future need for revisions. What is the evidence for the effectiveness and safety of this procedure?

Reviews Identified

- Rao J. Total hip replacement surgery. Metal to metal resurfacing as a new treatment - the purchaser view. (Unpublished)

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Comments

The only review on this topic that was identified was a short unpublished overview undertaken within the West Midlands Region in 1996. Although brief, this represents a comprehensive summary of the available literature at this time. It concludes that the technique appears promising, but that it is still experimental and requires further evaluation.

Further searches for more recent primary studies failed to identify any new rigorous evaluations, or additional studies, that would alter the findings and conclusions of the review.

Request Carried Out: April 2000

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Archived ARIF Request

Sorafenib
Metastatic Renal Cell Cancer (RCC)

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of sorafenib for metastatic renal cell cancer ?

Sorafenib is one of a new type of anti-cancer drug called multi-kinase inhibitors. At the time of the request (May 2006) the drug was licensed in the USA , but not in Europe and the UK .

Metastatic RCC is a serious condition whose median survival is 6-12 months even with existing treatments such as interferon-alpha.

Reviews Identified

None identified.

Randomised Controlled Trials

- Escudier B, Szczylik C, Eisen T et al. Randomized phase III trial of the multi-kinase inhibitor sorafenib (BAY-43-9006) in patients with advanced renal cell carcinoma (RCC). ECCO 13 – the European Cancer Conference, Paris , France , 30 October – 3 November 2005
- Escudier B, Szczylik C, Eisen T et al. Randomized phase III trial of the multi-kinase inhibitor sorafenib (BAY-43-9006) in patients with advanced renal cell carcinoma (RCC). 2005 ASCO Annual Meeting May 13-17., Orlando , Florida
- FDA web-site http://www.fda.gov/cder/foi/nda/2005/021923_s000_NexavarTOC.htm Accessed 12/05/06

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Comments

There appears to have been one major trial addressing the effectiveness of sorafenib in advanced RCC. The first two references are conference abstracts. The FDA web-site gives full details of the RCT as submitted as part of the licensing process in the USA .

The RCT compares sorafenib with placebo in advanced RCC. Although over 900 patients have been

recruited, the main analysis so far considers data on the first 769 patients. In this the median progression-free survival with sorafenib was 167 days and 84 days with placebo. This difference was highly statistically significant (p<0.000001). An alternative expression of the results is a hazard ratio for progressing of 0.44 [95% CI 0.35 to 0.55] – that is the risk of progressing is much lower in the sorafenib arm.

A subsequent analysis on overall survival in 903 patients randomised, provided further support that sorafenib is beneficial with a hazard ratio for death of 0.72 [95% CI 0.55 to 0.95].

The UK cost of the drug is not available. In the USA one month's supply is very approximately $4300.

In the UK context, long-term commissioning policies on this new anti-cancer drug should ideally await formal licensing and full assessment of cost-effectiveness, such as that considered by NICE .

ACKNOWLEDGMENT
Thanks to National Horizon Scanning Centre for their assistance with this request.

Request Carried Out: May 2006 (NB: New information on this topic highly likely to emerge)

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Archived ARIF Request

Ozone Solution
Methicillin-resisitant Staphlococcus Aurenus (MRSA)

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The Problem Submitted for ARIF to Advise Upon:

Are there any reviews of evidence on the effects/effectiveness of ozone solution for treatment of methicillin-resistant staphyloccus aureus (MRSA)?

Reviews Identified

None.

Other Literature Identified

- Yamayoshi T, Tatsumi N. Microbicidal effects of ozone solution on methicillin-resistant staphylococcus aureus. Drugs Under Experimental Clinical Research 1993;19(2):59-64

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Comments

This study examines the effects in vitro. It suggests that ozone solution has potential in dealing with a problem which represents a considerable challenge in terms of morbidity, mortality and cost. However, on the basis of our search it appears highly likely that many important questions about this therapy remain unanswered particularly, the effects of ozone solution in vivo on MRSA clearance and patient outcome, likelihood of resistance, any associated side-effects and cost. Given that MRSA has effects on organisation of hospital care and its delivery, the potential effects of this intervention should be considered in this area too.

Request Carried Out: September 1997

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Archived ARIF Request

Miglustat
Niemann-Pick Disease

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence on the effectiveness of miglustat for the treatment of Niemann-Pick disease?

Reviews Identified

None identified.

Trials Identified

No published trials.

Case Report

- Lachmann RH. te Vruchte D. Lloyd-Evans E. Reinkensmeier G. Sillence DJ. Fernandez-Guillen L. Dwek RA. Butters TD. Cox TM. Platt FM. Treatment with miglustat reverses the lipid-trafficking defect in Niemann-Pick disease type C. Neurobiology of Disease. 2004;16(3):654-8

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Comments

There are no systematic reviews or published trial results on this topic.

Miglustat is not currently licensed for use in Niemann-Pick disease. It is licensed in the EU only for the treatment of mild to moderate type 1 Gaucher's disease in patients for whom enzyme replacement therapy is unsuitable. Actelion, the manufacturing company, are currently conducting a phase III trial of miglustat for Niemann-Pick disease (and trials for late onset Tay-Sachs and type 3 Gaucher's disease). The trial is due to report mid-late 2005 and subsequent to this Actelion are likely to file for marketing approval on the basis of this study.

Our searches for other research on miglustat for Niemann-Pick disease identified only the single-patient case report by Lachmann et al. and this cannot provide us with robust evidence of effectiveness.

In summary, miglustat is currently an experimental unlicensed treatment for Niemann-Pick disease.

Request Carried Out: October 2004

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Archived ARIF Request

Occipital Nerve Stimulation
Migraine, Chronic

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of occipital nerve stimulation (ONS) for someone with chronic migraine?

Chronic migraine is defined as headaches on a daily or near daily basis, some of which are accompanied by migrainous features (visual and gastrointestinal disturbance). Occipital nerve stimulation is via small wires inserted under the skin (subcutaneously) rather than stimulation through the skin (transcutaneously). The occipital nerve is roughly located at the junction between the back of the neck and the skull.

Reviews Identified

None identified.

Other EvidenceTrials

- Matharu MS, Bartsch T, Ward N, Frachkowiak RSJ, Weiner R, Goadsby PJ. Central neuromodulation in chronic migraine patients with suboccipital stimulators. Brain 2004;127:220-230
- Popeney CA, Alo KM. Peripheral neurostimulation for the treatment of chronic, disabling transformed migraine. Headache 2003;43:369-375

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Comments

The best available evidence came from two small case-series, involving 8 and 25 patients respectively. These provide very encouraging initial results concerning relief of headaches in most (but not all) patients, unresponsive to other treatments. The studies are open to bias, particularly because they have no parallel control groups. Further it is possible that other case-series remain unpublished.

For these reasons ONS should not enter routine use until an ongoing trial (ONSTIM) is complete and has reported its results. Details of this study were supplied to ARIF in confidence, so any further enquiries about progress of the ONSTIM study should be directed to the manufacturer, Medtronic.

Request Carried Out: May 2005

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Archived ARIF Request

Rituximab, Monoclonal Antibody Therapy Relapsed Non-Hodgkin's Lymphoma

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The Problem Submitted for ARIF to Advise Upon:

What is known about the effectiveness of monoclonal antibody therapy for the treatment of patients with relapsed lymphoma? What is the evidence for the effectiveness of this treatment compared to standard chemotherapy?

Question Reformulated

Discussions with the West Midlands Regional Drug Information Service established that rituximab is the only monoclonal antibody which is currently licensed for use in the treatment of relapsed non-Hodgkin's lymphoma and that it is only licensed for use in people in whom all other treatments have failed. We therefore focused our attention on this.

Reviews Identified

- Maloney DG, Press OW. Newer treatments for non-Hodgkin's lymphoma: monoclonal antibodies. Oncology (Huntingt) 1998 Oct;12(Suppl 8):63-76

Trials Identified

- McLaughlin P, Grillo-Lopez A, Link BK et al. Rituximab chimeric anti-CD20 monoclonal antibodyn therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. Journal of Clinical Oncology 1998; 16: 2825-2833

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Comments

We identified no systematic reviews and very little primary research on this question. The general review by Maloney and Press is a good, up-to-date source of background reading on the subject.

The most rigorous and up-to-date of the primary studies is misclassified as a trial [McLaughlin et al]. Although generally regarded as the pivotal trial on the effectiveness of rituximab in this condition, it has a number of methodological limitations. Most importantly, although described as a Phase III trial, it does not meet the generally accepted criteria for this classification as it does not include a comparison group.

As a good-sized prospective case series, it is a well-conducted study, the results of which are important and probably reliable. Its findings suggest significant benefits in terms of disease regression and delayed progression, with minimal serious adverse effects. However, even at this level there are a few areas of concern, particularly around the possibility of selection and detection bias. It is not clear whether the study participants are representative of the target population for treatment. In addition, we have no reliable data on the effectiveness of rituximab relative to other treatments, making it difficult to make an overall judgement on effectiveness.

In summary, it seems highly likely that rituximab is effective, as it is highly unlikely that the observed results could be accounted for by the introduction of bias, but the absence of a parallel control group makes it difficult to quantify the size of this effect. We also have insufficient information to make a judgement on the cost-effectiveness of the treatment. Further research is required to answer these questions and to establish exactly what the place of rituximab might be particularly relative to, and in combination with, other treatments.

This is an area prone to need for regular updating as new information is continually becoming available.

The topic is one of several currently being reviewed by the West Midlands DES Programme.

Request Carried Out: April 1999

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Archived ARIF Request

MRI

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Is there any good evidence about the effectiveness and cost effectiveness of MRI diagnostic scanning? Is there any evidence about when it is of value and when it is not?

Reviews Identified

General:

- National Technology Advisory Panel. MRI Assessment Programme: Final Report. Canberra: Australian Institute of Health, 1990. pp121

Topic Specific:

- Kent DL et al. The clinical efficiency of magnetic resonance imaging in neuroimaging. Annals of Internal Medicine 1994;120:856-871
- Wessex Institute of Public Health Medicine. Low back pain and diagnostic imaging. Winchester: Wessex Institute of Public Health Medicine, 1994. pp22
- Wessex Institute of Public Health Medicine. Magnetic resonance imaging for knee disorders. Winchester: Wessex Institute of Public Health Medicine, 1993. pp14

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Comments

The main aim of this request was to target general reviews accepting that it was unlikely that any of these would provide a good estimate of effect. None of the general reviews identified were systematic. The 1990 Australian report on their MRI assessment programme provides a comprehensive source of background reading. Because of the limitations of the general reviews it was decided to look at more topic specific reviews on MRI.

The review by Kent et al, while not truly systematic, is a good review with a clearly stated method, which summarises a considerable quantity of the literature on the topic in relation to disorders of the nervous system. Appropriately, given the wide variability of the study characteristics and research designs, and the difficulties inherent in the synthesis of sensitivity and specificity estimates, the review does not attempt to meta-analyses the data.

The two DEC reports, on MRI in knees and low back pain, again are not systematic reviews but they are well structured summaries of some of the key literature. When used in combination with the Kent et al review they help provide a more comprehensive coverage of the use of MRI.

Request Carried Out: July 1997

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MRI for the Diagnosis of Knee Disorders

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The Problem Submitted for ARIF to Advise Upon:

Is GP open access to MRI for the diagnosis of knee disorders cost-effective for the selection of patients to be referred for specialist opinion and care?

Reviews Identified

- Magnetic resonance imaging for knee disorders. Report to the Regional Development and Evaluation Committee. Winchester: Wessex Institute of Public Health Medicine, 1993. pp14

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Comments

The review identified gives a good summary of the relevant issues, although focused on provision in secondary care. It is not completely systematic, particular concerns being the completeness of the literature search and little attention being paid to the quality of the studies included as an explanation of the variation in results: Account should also be taken that further relevant literature has probably been published in the last 4 years.

Despite these potential sources of bias, useful information is provided:

- Clear indication of the general range of diagnostic test performance measures for the use of MRI in comparison with diagnostic arthroscopy.
- MRI can avoid unnecessary diagnostic arthroscopy.
- BUT use of MRI as a pre-surgery screening tool in knee disorders is likely at best to lead to a slight cost saving, at worst to increased costs, the actual impact in any specific situation depending partcularly on:
  - the number of "unnecessary" diagnostic occurring initially
  - the relative cost of MRI to arthroscopy

The report expresses doubt about the place of this diagnostic tool in secondary care; there should be as much of not more doubt about its place in primary care based on the research presented in this review.

Request Carried Out: July 1997

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MRI for the Diagnosis of Cause of Low Back Pain

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The Problem Submitted for ARIF to Advise Upon:

Should GPs have open access to MRI, and should they use it in unselected patients with low back pain that remains unresolved after 6 weeks of conservative management with physiotherapy / exercise etc?

Used in this way, does MRI offer a cost effective way of selecting patients for referral to surgeons and reassuring others that there is no serious disease?

Reviews Identified

- Bigos S et al. Acute low back problems in adults. Rockville, MD: Agency for Health Care Policy and Research, 1994. (Clinical Practice Guideline No. 14)
- Clinical Standards Advisory Group. Back pain: report of a CSAG committee on back pain. London: HMSO, 1994. Pp89

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Comments

Both the above contain conclusions based on systematic reviews of the available evidence in relation to use of MRI for low back pain. Neither finds any evidence suggesting that the approach mentioned in the request is actually effective.

Outside the confines of empirical evidence one can make cogent arguments for and against such an approach. In this situation any purchasing decison should await the availability of such evidence or ensure that the scheme is purchased on a pilot basis as part of a rigorous evaluation of its effect.

This is an area prone to the need for regular updating as new information is continually becoming available. In particular primary research on this topic is being conducted as part of the national HTA programme.

Request Carried Out: February 1996

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Archived ARIF Request

Service Delivery
Multiple Sclerosis (MS)

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The Problem Submitted for ARIF to Advise Upon:

Is there any evidence to support the effectiveness of a central multidisciplinary team designated to directly meet the needs of people with multiple sclerosis throughout the country?

Question Reformulated

Preliminary investigations suggested that it was unlikely that any reviews or even good primary research on the specific question as it was posed would be available. Thus the approach taken was to focus initially on interventions which have been shown to be effective in multiple sclerosis as a means of identifying exactly what a team delivering effective services for people would do.

Reviews Identified

- Swain SE. Multiple Sclerosis. Primary health care implications. Nurse Practitioner 1996;21(7):47-50
- Williams R, Rigby AS, Airey M, Robinson M, Ford H. Multiple Sclerosis: its epidemiological, genetic and health care impact. Journal of Epidemiology and Community Health 1995;49(6):563-569

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Comments

A number of good systematic reviews of different treatments for multiple sclerosis were identified and several were shown to be of potential benefit including beta-interferon, copolymer 1, azathioprine and plasma exchange. The majority of these are medical interventions which are administered in the secondary care setting and the role of a specialist team in this instance would probably involve the identification and referral of suitable patients, the co-ordination of treatments, and general support.

No reviews were identified on other aspects of the care of people with MS which might be delivered by different members of the "team" although a large body of primary literature exists in this respect which covers interventions such as rehabilitation, exercise and physical therapy, counselling and other psychological interventions, occupational therapy and different forms of complementary medicine.

The reviews by Swain and Williams et al are not systematic reviews, but together they provide a good

source of background reading and a useful framework for considering the different aspects of the management of people with MS.

A common thread running through most of the literature is the difficulty associated with recognising and meeting the complex needs of people with MS in an efficient and co-ordinated way. There is currently no robust evidence to support a particular model of service delivery which will achieve this coherence.

Request Carried Out: September 1998

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Archived ARIF Request

Nurse Practitioners

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The Problem Submitted for ARIF to Advise Upon:

What is known about the effects of nurse practitioners and what are the implications for commissioned research on this topic?

ARIF was asked by the Regional Department of R&D to identify rigorous research which had been conducted on this topic and draw conclusions on this basis. The work was done in parallel with a scoping review by Prof Ellie Scrivens of Keele University. A formal report of the combined findings has been prepared and should be available from the NHS Executive West Midlands, Department of R&D.

Question Reformulated

The specific questions ARIF set out to answer in this request were:

- What research questions appear to have been asked?
- Are these research questions important?
- Have these important research questions been fully answered and if so what is the answer?
- How confident are we that an extended search for research would reveal that the important questions above had actually been answered?
- Does consideration of the research identified lead to further insights on questions which do not appear to have been asked?
- How confident are we that an extended search for research would reveal that the new questions identified had actually been answered?
- Does the available research adventitiously provide any information to answer questions posed of the scoping review, which were not specifically targeted by our approach, namely:
  - How widespread is the practice in the UK?
  - What training do practitioners get?
  - What is the demand from practices (especially GPs) for this form of care?

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Details and Findings of ARIF Request

Parameters and definitions used in search:

Type of evidence sought - Efficacy/effectiveness (research assessing the effects of nurse practitioners).

Type of research - Primarily any systematic review of research, then any controlled trials.
Intervention - Nurse practitioners or nurses with extended roles ie nurses taking on duties previously undertaken by doctors.
Setting - Although the main focus of the request was the effects of nurse practitioners in primary care in the UK, no restriction was applied on the basis that it was:

- Possible that findings in other settings may be generalisable
- That research in other settings, although not generalisable, may indicate important questions which should be answered in the specific setting of interest
- Explicit that research findings from abroad were to be considered

Population - No restriction was placed on the nature of the patients who were the target of the any nurse practitioner activities.
Outcomes - No restriction was placed on the outcomes examined in the research. Outcomes expected to be important were:

- Reduced time of doctor input
- Equivalence of clinical/patient outcomes
- Cost

Search Strategy:

A search for reviews was undertaken on the following databases:

Cochrane Library; DARE; ARIF database; GEARS; Medline; CINAHL; and a nursing resources web site.

A search of the Controlled Clinical Trials Register of the Cochrane Library was also undertaken for appropriate primary studies.

Search terms used were: Nurse practitioners; advanced nursing practice; extended role of nurses; practice nurses

Research identified & retrieved:

Systematic Reviews on the Effectiveness of Nurse Practitioners

Source - Cochrane Library (CDSR)

- Silagy C, Lancaster T, Fowler G et al. Effectiveness of Training Health Professionals to Provide Smoking Cessation Interventions: Systematic Review of Randomised Controlled Trials. In: Lancaster T, Silagy C (eds.) Tobacco Addiction Module of The Cochrane Database of Systematic Reviews , [updated 02 December 1996]. Available in The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration; Issue 1. Oxford: Update Software; 1997.
- Gibson PG, Hensley MJ, Wilson AJ et al. The effects of patient education and regular practitioner review in asthma. Protocol. In: Ducharme F, Gibson P, Jones P, Rowe B, Wolf F (eds.) Airways Module of The Cochrane Database of Systematic Reviews , [updated 03 December 1996]. Available in: The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration; Issue 1. Oxford: Update Software; 1997.
- Zwarenstein M, Bryant W, Baillie R. The effects on patient care of interventions to change collaboration between nurses and doctors. Protocol. In: Bero L, Grilli R, Grimshaw J, Oxman A (eds.) Collaboration on Effective Professional Practice Module of The Cochrane Database of Systematic Reviews , [updated 02 December 1996]. Available in The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration; Issue 1. Oxford: Update Software; 1997. Updated quarterly.

Source - ARIF database

- Bryant J. Neonatal nurse practitioners. Winchester: Wessex Institute of Public Health, 1995.pp10

Source - Medline 1992-97

Hopkins A et al. Shifting boundaries in professional care. Journal of the Royal Society of Medicine 1996;89(7):364-371

- Anon. Physician assistants and nurse practitioners. American College of Physicians. Annals of Internal Medicine 1994;121(9):714-716
- Brown SA et al. A meta-analysis of nurse practitioners and nurse midwives in primary care. Nursing Research 1995; 44 (6): 332-339

Primary Studies

Source - Cochrane Library (RCCT)

- Whitehouse C. A new source of support. The nurse practitioner role in Parkinson's disease and dystonia. Professional Nurse 1994;9:448:450-1
- Hill J et al. An evaluation of the effectiveness, safety and acceptability of a nurse practitioner in a rheumatology outpatient clinic [see comments]. British Journal of Rheumatology 1994;33:283-8
- Garrard J. Impact of geriatric nurse practitioners on Nursing Home residents' functional status, satisfaction and discharge outcomes. Medical Care 1990;28:271-83
- Drummond DC, Thom B, Brown C. Specialist versus general practitioner treatment of problem drinkers [see comments]. Lancet 1990;336:915-8
- Lewis CE, Cheyovich TK. Who is a nurse practitioner? Processes of care and patients' and physicians' perceptions. Medical Care 1976;14:365-71
- Merenstein JH , Rogers KD. Streptococcal pharyngitis. Early treatment and management by nurse practitioners. Journal of the American Medical Association 1974;227:1278-82
- Spitzer WO, Sackett DL, Sibley JC et al. The Burlington randomized trial of the nurse practitioner. New England Journal of Medicine 1974 ;290:251-6
- Sackett DL, Spitzer WO, Gent M et al. The Burlington randomized trial of the nurse practitioner: health outcomes of patients. Annals of Internal Medicine 1974;80:137-42
- Stein GH. The use of a nurse practitioner in the management of patients with diabetes mellitus. Medical Care 1974;12:885-90
- Micheels TA, Wheeler LM , Hays BJ. Linking quality and cost effectiveness: case management by an advanced practice nurse. Clinical Nurse Specialist 1995;9:107-11
- Kearnes DR. Impact of a nurse practitioner and physician collaborative practice on older adults admitted to a large urban hospital: differences in treatment and outcome [letter]. Nurse Practitioner 1994;19:32, 33-6
- Lees REM. The practice nurse: a comparison of Canadian and British patient acceptance. Canadian Family Physician 1973 :71-77
- Charney E , Kitzman H. The child-health nurse (pediatric nurse practitioner) in private practice. A controlled trial. New England Journal of Medicine 1971;285:1353-8

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Comments

What research questions appear to have been asked?

The meta-analysis by Brown SA et al reveals that there is a significant body of rigorous research (12 randomised controlled trials) on the effects of nurse practitioners in primary care in a North American setting. By definition the review does not cover research undertaken:

- In a UK setting
- Since 1991/2 (the period during which the search for literature was conducted)

We could not identify a systematic review covering these areas, although the reviews by: Bryant J provides a useful consideration of the effects of nurse practitioners in neonatal care.

- Hopkins A et al provide a useful framework to consider issues relating to extending the role of the nurse and references to original studies assessing the effects of nurse practitioners in both primary and secondary care settings. No original studies relating to the effects of nurse practitioners in

primary care in a UK setting were cited.

Of the original studies retrieved, there were only two rigorous evaluations of the effects of nurse practitioners in a UK setting:

- Whitehouse C. A new source of support. The nurse practitioner role in Parkinson's disease and dystonia.
- Hill J et al. An evaluation of the effectiveness, safety and acceptability of a nurse practitioner in a rheumatology outpatient clinic.

Unfortunately neither of these addresses the effects of nurse practitioners in primary care.

Three original articles, referring to two studies, are worthy of particular mention because of the quality and/or direct relevance of the research to the original problem stated by the commissioning group (albeit in both cases in a North American setting):

- Spitzer WO et al and Sackett DL et al.
- Lewis CE, Cheyovich TK.

Are these research questions important?

Potentially the results of the research identified do answer the question what are the effects of nurse practitioners. In order to apply these effects to the UK one must be prepared to generalise results from a US/Canadian setting.

However, a persistent criticism of much of the research is the use of inadequate outcome measures. Thus the balance between positive and negative effects, required to make a judgement on whether nurse practitioners are effective, may be difficult to judge because of uncertainty about whether positive (and negative) effects have been overlooked through the insensitivity of the outcome measures used.

Have these important research questions been fully answered, and if so, what is the answer?

The meta-analysis by Brown SA et al is generally well conducted when judged by standard criteria for appraising systematic reviews. There may be some criticism about lack of detail about the search methods employed and the method used to combine the results. Nonetheless given that it has a reasonable degree of internal validity, it does provide evidence that there are demonstrable positive effects eg improved patient compliance and no clearly demonstrable negative effects. There is also a suggestion that the positive effects are not achieved at the expense of negative effects such as reduced quality of care.

This suggestion is supported by the selection of original studies identified, although one should be aware of the possibility of retrieval and publication bias ie that favourable studies are more likely to be published and retrieved than unfavourable ones. In particular, the two studies in secondary care in the UK are compatible with the balance of positive and negative effects being in favour of nurse practitioners.

How confident are we that an extended search for research would reveal that the important questions above had actually been answered?

It is likely that some relevant research studies have been missed. The large additional number and sophisticated nature of the studies required to answer the question whether nurse practitioners are effective in a UK setting in primary care, suggests that an extended search would not reveal that this question had been answered. This contention is also probably true of the effectiveness of nurse practitioners in N America, as there appears to be a large shortfall in the volume of rigorous evidence to allow quantification of the various effects with sufficient accuracy to allow the nett effect of nurse practitioners to be predicted with a high degree of confidence.

Does consideration of the research identified lead to further insights on questions which do not appear to have been asked?

As implied above, although various effects of nurse practitioners have been demonstrated, the balance between positive and negative effects has not. Similarly, reassurance that the effects demonstrated in

rigorous research in the N American setting are applicable to the UK is required.

The original study by Lewis CE, Cheyovich TK. also suggests that an important aspect of the likely effectiveness of nurse practitioners is the nature of their interaction with doctors and other medical staff . This reflects the complexity of the intervention. In this respect the Cochrane Review in progress by Zwarenstein M et al. "The effects on patient care of interventions to change collaboration between nurses and doctors" could be very illuminating. The importance of being explicit about the detail of the nurse practitioner input was a general shortcoming identified in the meta-analysis by Brown SA et al.

A further important subdivision of the research questions posed, is the likelihood of a clear difference between the effects of nurse practitioners where they substitute for tasks previously undertaken by other health care staff, usually doctors, eg managing common ailments or undertaking routine procedures such as blood taking and the effects of nurse practitioners where they undertake new activities which would not otherwise be provided by any other member of the primary care team eg regular home visiting in specific chronic conditions. The importance of this distinction, lies not just in the likelihood that there is a difference qualitatively in the nurse practitioner acting in these roles, but also:

- That the research design required to assess the effects adequately will need to be different, particularly the nature of the comparator/control
- That existing research assessing the role of nurse practitioners providing new services, may not actually be easily identifiable using search strategies focused on "nurse practitioners". They are equally likely to be labelled according to the new service provided. Thus in the Cochrane Reviews by Silagy C et al and Gibson PG et al, the interventions being tested, training in smoking cessation and regular practitioner review in asthma, are often mediated in a primary care setting by nurse practitioners alone, yet although the research does test the effect of an extended role of nurses in primary care, this fact is not immediately apparent.

A further important question raised in the context of nurse practitioners substituting roles normally fulfilled by doctors, is the research question whether nurses are the most appropriate substitutes. The possibility of carer substitution in certain conditions is raised in the review by Hopkins A et al.

How confident are we that an extended search for research would reveal that the new questions identified had actually been answered?

Of the new questions raised above, the one area where extended searching would be likely to yield further research is nurse practitioners providing new services as opposed to replacing others in providing existing services. This observation in turn suggests that the comments on the results of existing research on the effects and effectiveness of nurse practitioners should be restricted to nurse practitioners substituting existing roles. In the meta-analysis by Brown SA et al, this is implicit by an inclusion criterion being "control group patient data derived from physician managed care".

Does the available research adventitiously provide any information to answer questions posed of the scoping review, which were not specifically targeted by our approach, namely:

How widespread is the practice in the UK?
No information provided.

What training do practitioners get?
A number of the original research articles eg Spitzer WO et al give general details of the training received by nurse practitioners in their study. These might provide useful starting points for investigating the training and experience associated with the demonstrated effects.

What is the demand from practices (especially GPs) for this form of care?
Again the research identified makes little contribution to this answer to this question, other than the obvious point, mentioned by Spitzer WO et al that demand form primary care is heavily influenced by the availability of reimbursement.

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Archived ARIF Request

Obstetric Units

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the evidence to support a decision about whether funding for maternity services should be directed at general practitioner or consultant led obstetric units?

Question Reformulated

Our analysis of the main elements of this question was:

POPULATION
Consideration needs to be given on whether the initial risk status of the mother (however imperfect the assessment of risk may be) has a bearing on the purchasing decision.

OUTCOMES
Can be sub-divided into:

1. Safety (mortality measures - for mother and baby)
2. Morbidity (interventions and complication rates - for mother and baby)
3. Satisfaction (material, paternal, professional)

INTERVENTION
Intrapartum (+/- antenatal) care can vary by:

1. Place
   A particular issue is the degree of spatial separation of the proposed place of birth from an appropriate source of support in cases of emergency. It is worth considering not just the degree of geographical separation but also the degree of functional separation, which may be reduced if there are well developed systems to expedite transfer in cases of emergency.
2. Equipment
   Availability of specialist equipment and facilities. i.e. low tech -vs- high tech.
3. Staff type
   Consider particularly the "leader" of the process. e.g. midwife or GP or consultant, rather than the person who actually delivers, which will in most cases be a midwife.

Reviews Identified

- Campbell R and Macfarlane A. Where to be born? The debate and the evidence. Oxford: National Perinatal Epidemiology Unit, 2nd ed 1994. Pp176

- Changing childbirth Part I and II. London: Department of Health, 1993

The following primary studies were also considered:

- Hundley VA et al. Midwife managed delivery unit: a randomised controlled comparison with consultant led care. British Medical Journal 1994;309:1400-1403
- Turnbull D et al. Does midwife-led care work? The results of a randomised controlled trial of 1299 women. 27th-British-Congress-of-Obstetrics- & -Gynaecology 1995 ;527
- Klein M, Lloyd I et al. A comparison of low risk pregnant women booked for delivery in two systems of care : shared care (consultant) and integrated general practice unit. I. Obstetrical procedures and neonatal outcome. British Journal of Obstetrics & Gynaecology 1983;90:118-122
- Klein M, Lloyd I et al. A comparison of low risk pregnant women booked for delivery in two systems of care: shared crae (consultant) and integrated general practice unit. II. Labour and delivery management and neonatal outcome. British Journal of Obstetrics & Gynaecology 1983;90:123-128
- Lowe SW et al. A comparison of outcome of low risk labour in an isolated general practitioner maternity unit and a specialist maternity hospital. Journal of the Royal College of General Practitioners 1987;37:484-487.
- Turnbull D et al. Randomised, controlled trial of efficacy of midwife managed care. Lancet 1996; 348:213-218

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Comments

Much of the evidence of higher validity relates to the effect of staff active in the unit rather than place. Without a proper systematic review it is difficult to be precise about what the overall effect of a service being midwife led is, but there seems to be a trend towards lower rates of intervention and greater satisfaction with care.

None of the individual studies identified really contributes to the debate about safety as measured by mortality. Campbell R et al is as good as review of quantitative evidence of place, equipment and staffing on mortality measures as there is ever likely to be. Their analysis does successfully challenge the assumption that hospital based, high tech care has been responsible for falls in mortality. However, the equivocal nature of this evidence cuts both ways - an influence of hsopital based, high tech care is not excluded either.

In summary the empirical/research evidence we have identified suggests that for low-risk pregnancies:

- We do not know whether place, equipment or staff have an influence on mortality of mother or baby.
- We have little indication about the effect of place/functional availablility of high technology equipment on rates of intervention and complications.
- We have some indications that midwife led care reduces rates of intervention and increases maternal satisfaction.

The following comment in changing childbirth seems to sum up the situation well: "Whether a mother with an uncomplicated pregnancy is putting herself and her child at any greater risk by choosing to have her baby away from a general maternity unit is a topic which has been argued with a vehemence and emotion for decades. The inability to reach agreement after this length of time suggests that there is no clear answer".

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Oncology
Positron EmissionTomography
PET Scanning

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The Problem Submitted for ARIF to Advise Upon:

What are the current and future prospects of the use of Positron Emission Tomography (PET) in oncology?

Reviews Identified

- Robert G, Milne R. Positron emission tomography: establishing priorities for health technology assessment. Health Tech Assess 1999;3(16)
- Medicare Services Advisory Committee. Positron emission tomography: MSAC assessment report. Canberra: Medicare Services Advisory Committee; 2001 http://www.msac.gov.au

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Comments

The main objective of the Robert and Milne systematic review (1999) was to review the state of knowledge regarding the clinical applications of PET and to determine the key HTA questions relating to PET use in the UK. Important issues appear to be the relative cost-effectiveness of both PET compared to existing diagnostic techniques, and in detecting and quantifying metabolic abnormalities of disease processes. Defining the precise role of PET in staging and monitoring of treatment response in breast cancer is also a priority.

The MSAC report was systematic, comprehensive and well conducted. The reviewers stated there was insufficient evidence from which to draw definitive conclusions about the clinical and cost effectiveness of PET, and that in most indications, PET is used alongside other diagnostic modalities. The evidence suggests the use of PET is safe and is potentially clinically and cost effective as a diagnostic tool In particular, PET appears to be a more powerful diagnostic tool than comparators such as CT scanning and MRI.

For all the oncological conditions reviewed by MSAC, there was little information relating to changes in clinical management of patients resulting from information derived from the use of PET. Nevertheless, this appears to be a promising area, in that PET may have an impact on the timing of existing therapy, and may enable assessments of the efficacy of a therapeutic regimen therapy during treatment courses

for various types of malignancy.

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Archived ARIF Request

Oseltamivir (Tamiflu) Pandemic Influenza

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The Problem Submitted for ARIF to Advise Upon:

Does Oseltamivir reduce mortality in an influenza pendemic situation?

Influenza pandemics occur every few decades and are due to antigenic shift in the virus, which creates a completely new influenza virus to which the general population has no immunity. Historically influenza pandemics have resulted in high mortality rates particularly in young healthy adults. Vaccination is not an option particularly at the onset of outbreak as time is needed to isolate the virus and make the vaccine, which could take up to 6 months. Neuraminidase inhibitors (NIs) are antiviral drugs that inhibit the virus from multiplying, they can be used for prevention and treatment of influenza. UK Health Departments are at the moment building stockpiles of the oral neuraminidase Oseltamivir (Tamiflu) which will comprise 14.6 million treatment courses including powder for children when completed.

Reviews Identified

- Husereau DR, Brady B, McGreer A. Oseltamivir for the treatment of suspected influenza: a clinical and economic assessment. Canadian Coordinating Office for Health Technology Assessment 2002;89
- Matheson NJ, Symmonds-Abrahams M, Sheikh A, Shepperd S, Harnden A. Neuraminidase inhibitors for preventing and treating influenza in children. Cochrane Database Syst.Rev. 2003;CD002744
- Mørland B,.Nilsen E. Oseltamivir (Tamiflu (R)) for the prevention and treatment of influenza during an influenza pandemic. The Norwegian Knowledge Centre for the Health Services (NOKC) 2005;86
- Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35):1-182. Health Technol.Assess. 2005;7:1-182
- Jefferson T, Demicheli V, Deeks J, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst.Rev. 2000;CD00126

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Comments

Five systematic reviews in total were identified that have investigated the effectiveness of the treatment of Oseltamivir. The most of up-to-date of these was by Mørland B 2005 but was written in Norwegian. Whilst it has an English summary of results, no reference was made to mortality in the summary. This is unfortunate as the review targets effectiveness and costs in a pandemic situation. The review by Turner 2003 was a NICE Health Technology Assessment (HTA), but does not refer to mortality outcomes within the effectiveness review. The economic section does extrapolate hospital episodes as a proxy for mortality within the economic model. The NICE guidance relating to this HTA explicitly states that the information relates to epidemic, not pandemic situations. The Cochrane review by Jefferson 1999 states that one of its main aims was to assess the effectiveness of NI's in preventing deaths in healthy adults. However, there were no further references to death or mortality throughout the rest of the review. Thus only 2 reviews make some reference to death or mortality outcomes (Husereau 2002, Matheson 2003).

Husereau's review was well conducted. The primary outcome was to evaluate Oseltamivir in relation to its effectiveness on reducing influenza mortality. The searches were up to 2001, making it 4 years out of date. The authors found that only 1 trial reported an actual death, but that the cause of death was not given. The trial was conducted in an elderly population with the death occurring in the placebo arm. The review authors discuss their results in the context that serious influenza related events are rare and consequently the sample size even with meta-analysis is underpowered to detect an effect. They calculated that a sample size of more than 200,000 would be needed, and suggest that the results should be viewed as an absence of evidence rather than evidence of no effect.

The systematic review by Matheson 2003, was a Cochrane review on the role of NI's in treatment and prophylaxis in children less than 12 years. Again it was well conducted, and simply reports that there were no deaths reported in any of the trials included in the review (n= 2 trials).

In summary, there are few references to mortality within the recent systematic reviews undertaken to assess the effectiveness of Oseltamivir. The reviews however, only used data from RCTs, which have relatively small sample sizes and are most likely underpowered to detect an effect on mortality outcomes. The reviews do not contain data on pandemic influenza, which have higher mortality rates and which in the past have affected different populations. To extrapolate the information from these reviews into a pandemic situation would need careful consideration and expert input. Higher incidence of death, without confounding treatments such as vaccines may alter Oseltamivir's effectiveness on mortality. An additional consideration is the role of Oseltamivir as prophylaxis rather than treatment for influenza. If Oseltamivir is an effective prophylaxis there may be scope to model the results regarding how many deaths could be prevented. Again the trial data that has investigated this would be from epidemic situations and an extrapolation to pandemic situations would be needed and require considerable amounts of educated guesswork.

Request Carried Out: December 2005

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Out of Hours Service (Type and Location) Primary Care

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The Problem Submitted for ARIF to Advise Upon:

During 2004 and 2005 ARIF has been approached twice on the effectiveness of different ways of delivering out-of-hours primary care. The most recent request considered the particular merits of co-location with a hospital accident and emergency department.

Reviews Identified

- Leibowitz R, Day S, Dunt D. A systematic review of the effect of different models of after-hours primary medical care services on clinical outcome, medical workload and patient and GP satisfaction. Family Practice 2003;20(3):311-317
  http://fampra.oxfordjournals.org/cgi/content/full/20/3/311

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Comments

The best summary of the available effectiveness is still the review by Leibowitz et al. It provides a useful starting point for making commissioning decisions in this area.

However, even with this review definitive statements on the effectiveness of different methods to achieve out-of-hours services in primary care are challenging. The complexity of the issue, the limited amount of research and its openness to bias mitigate against clear conclusions for or against alternative approaches to providing out-of-hours care at the current time.

Request Carried Out: February 2006

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Screening in those with Family History Ovarian Cancer

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence base of the proposals made for the West Midlands Familial Cancer Initiative, particularly those concerning screening of individuals with a positive family history of ovarian cancer?

Question Reformulated

What are the effects of annual CA125 or gynaecological examination or trans-vaginal ultrasound scanning in those with a positive family history of ovarian cancer on that cancer's incidence, severity, mortality and morbidity?

An appropriately strong family history is two or more first degree relatives with ovarian cancer.

Reviews Identified

- Bell R et al. Screening for ovarian cancer: a systematic review. Health Technology Assessment 1998;2(2):1-84
- Carlson KJ et al. Screening for ovarian cancer. Ann Intern Med 1994;121:124-132

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Comments

Both reviews are systematic in approach. Although they indicate that rigorous research on the specific question of interest is not available, the summaries of research on related aspects of screening for ovarian cancer are useful. Important findings include:

- In the population at general risk, there is at present no clear evidence that screening by CA125 estimation and/or trans-vaginal ultrasound screening and/or gynaecological examination at any interval produces overall benefit, particularly in terms of reduced ovarian cancer deaths. RCTs are in progress which will improve our knowledge of the effectiveness of screening for ovarian cancer.
- The main factor limiting the effectiveness of screening appears to be rarity of the condition in any population likely to be screened. This means that even small imperfections in the specificity of the screening test generate large numbers of false positive diagnoses for every true positive result obtained.

- However, this suggests that effectiveness of screening is likely to be greater where it is restricted to a smaller group at higher risk, such as those with a positive family history. Unfortunately there is still insufficient evidence to show whether the likely reduction in numbers of false positive diagnoses where screening is restricted to those with a positive family history is such that overall the risks of the screening process are worth the benefits.

Thus, annual screening for ovarian cancer in women with a positive family history should only be undertaken in the context of rigorous evaluation. In ARIF's view it has not been proved that annual screening by CA125 testing, gynaecological examination or trans-vaginal ultrasound scanning in those with a positive family history will definitely guarantee an individual is less likely to suffer death from ovarian cancer than if they had not been screened.

This is an area prone to need for regular updating as new information is continually becoming available.

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Archived ARIF Request

Pain Management
Post-Polio Syndrome

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The Problem Submitted for ARIF to Advise Upon:

What interventions are effective for the treatment of pain associated with Post-Polio Syndrome?

Post-Polio syndrome (PPS) affects people who have been infected by the poliomyelitis virus in earlier life. Symptoms can developed anywhere between 10-40 years after recovery from initial polio. Symptoms include fatigue, muscle weakness and joint pain. PPS ranges in severity from mild symptoms to causing considerable disability. The question is focussing specifically on the problem of pain associated with PPS. The pain experienced in PPS varies greatly in type and location (e.g. muscles, bones and joints) and can be associated with cramps and spasms.

Reviews Identified

None relevant.

Randomised Controlled Trials

- Strumse YA, Stanghelle JK, Utne L, Utne P, Svendsby EK Treatment of patients with postpolio syndrome in a warm climate. Disability and Rehabilitation 2003;25(2):77-84
- Vallbona C, Hazlewood CF, Jurida G Response of pain to static magnetic fields in postpolio patients: a double-blind pilot study. Archives of Physical Medicine and Rehabilitation 1997;78(11):1200-3

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Comments

There appears to be only a limited amount of research on interventions for PPS and that much of this has not targeted pain associated with the syndrome.

Conventional pain management strategies do not appear to have been specifically studied in PPS but these may give benefits as they do in other conditions. Fatigue associated with some conventional pain management regimens may be compounded in PPS.

Two primary studies were identified that have looked at interventions for persistent pain relief in PPS.

One of the studies assessed the effectiveness of static magnetic fields (Strumse et al 2003). Whilst the findings are interesting, their generalisability and applicability are limited by amongst other factors the very short follow up and that the magnets were only applied to one small area on each patient.

The second study looked at the effectiveness of a rehabilitation programme in a warm climate (Vallbona et al 1997). Although undertaking a rehabilitation programme in a warmer climate showed greater improvement in the short term compared to those undergoing rehabilitation in Norway, the findings need to be treated with a great deal of caution due to amongst other things, the inability to blind patients and investigators to the treatment being given.

Further good quality evidence is needed in this area as the studies that have been undertaken with regard to pain management have not identified an appropriate intervention with long-term success.

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Palivizumab
Respiratory Syncytial Virus

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence of effectiveness of palivizumab in preventing respiratory syncytial virus (RSV) infection in infants?

Reviews Identified

- Simpson S, Burls A. A systematic review of the effectiveness and cost-effectiveness of palivizumab (Synagis) in the prevention of respiratory syncytial virus (RSV) infection in infants at high risk of infection. Report number 25, December 2001, BTAG, Department of Public Health & Epidemiology, University of Birmingham. This review can be downloaded from the WMHTAC website.

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Comments

We identified a recent systematic review on this topic. The review appears to be well conducted and focused on palivizumab for high risk infants as defined by the licensed indications for palivizumab (ie (a) children born at 35 weeks of gestation or less, and who were less than 6 months old at the onset of the RSV season or (b) children less than 2 years of age who have received treatment for bronchopulmonary dysplasia (BPD) within the preceding 6 months). Only one randomised controlled phase three trial on this topic was identified and this met the inclusion criteria for the review.

The findings of the review, based on this single RCT, suggest that palivizumab appears to be an effective prophylaxis for the prevention of serious lower respiratory tract infection caused by RSV and requiring hospitalisation in high-risk infants (as defined above). The results indicate a statistically significant reduction in risk of hospitalisation compared to placebo.

The duration of the RCT was only one RSV season, and as such the study does not address long-term benefits or harms, nor effects of more than one season of prophylaxis with palivizumab. The review reports that the safety and immunogenicity of palivizumab given to a relatively small cohort of infants for a second season has been undertaken and published. The review does not report the details or the findings of this study. The review indicates that a number of questions regarding the safety and efficacy

of palivizumab for other RSV high risk groups need to be addressed, in particular infants with congenital heart disease and infants with cystic fibrosis. Studies on these patient groups are underway and are due to be completed in 2002.

Request Carried Out: September 2001

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Vagal Nerve Stimulation
Persistent Severe Depression

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Aim - to identify the efficacy of vagal nerve stimulation for treatment of severe depression and enduring depression.

The VNS device has had the CE mark approval for use in Europe and Canada since 2001 and was approved by the FDA in July 2005 (http://www.fda.gov/cdrh/mda/docs/p970003s050.html) for the treatment of patients with severe treatment resistant depression.

Reviews Identified

None identified.

Randomised Controlled Trials

One RCT referred to in 3 publications:

- (Study 1)
  Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK , Davis SM et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biological Psychiatry 2005;58:347-54
- (Study 2)
  Rush AJ, Sackeim HA, Marangell LB, George MS, Brannan SK , Davis SM et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. Biological Psychiatry 2005;58:355-63
- (Study 3)
  George MS, Rush AJ, Marangell LB, Sackeim HA, Brannan SK , Davis SM et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. Biological Psychiatry 2005;58:364-73

Other Evidence

- Groves DA, Brown VJ. Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. Neuroscience and Biobehavioral Reviews 2005;29:493-500

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Comments

The trial included adults aged between 18 and 70 years. Patients had to have a diagnosis of DSM-IV major depressive disorder or biopolar I or II. They had to be in a major depressive episode (MDE) of at least 2 years duration or had to have had at least 4 MDEs in their lifetime. Patients were allowed to continue antidepressants at the same level as those established during the pre-op baseline period. Patients were not allowed to increase the dose of these nor take any other investigational drug or treatment with ECT.

The primary outcome was measured on the Hamilton Depression Rating Score (HDRS). Other psychological scores were also used to measure manic symptoms and overall psychological status. Quality of life was also measured using SF-36. Adverse events were also sought.

There were 3 phases to the trial. The first phase was the acute phase (study 1), where 235 patients were randomized into intervention and control. The control group received the implant but it was not activated. Quality-wise this is a well conducted RCT. At 10 weeks the response rate (defined as above as a 50% or more reduction in the baseline HDRS) was 15.2% for the intervention group (n = 112) and 10% for the control group (n=110). This result was not statistically significant. Side effects appeared in both groups and included voice alteration, increased cough, dyspnoea, dysphagia, neck pain, paresthesia, vomiting, laryngismus, dyspepsia, wound infection and palpatations.

After 10 weeks all the patients received VNS stimulation for 12 months (study 2). The total number of patients followed in this second phase was 205. The response rate was 27.2% (55/202) with a remission rate (HRSD <9) of 15.8% (32/202). Whilst these results are encouraging it is difficult to attribute the results to VNS without a control group, in addition, the patients were in naturalistic conditions and were able to alter antidepressant regimes, which may have been a source of confounding. Intention to treat analysis was not conducted, this meant that of the initial sample of 235, 28 were excluded from the analysis because they did not reach the criteria for VNS device activation i.e. they had a HRSD score of less than 20. This included 21 patients from the control group. In addition 2 patients were excluded from analysis because 1 committed suicide during the acute phase and 1 had a secondary infection and had to have the device removed. The group to which these latter 2 patients were randomised was not described.

To try and overcome the lack of control group in study 2, study 3 compared a group of patients with treatment resistant depression who had not undergone device implantation (n=124) with the group described above (n=205). The assessment was over 12 months. Response rates at 12 months were 27% for VNS group and 13% for the group without device implantation. ($p<0.011$). Whilst this is again encouraging, it is not definitive due to the trial design.

In summary, the trial described above suggests that VNS is a hopeful but not a completely proven form of therapy for treatment resistant depression. The narrative review by Groves and Brown suggests that there may be additional studies, which could provide further evidence of the effectiveness of this treatment. They describe the results of a web of science search for VNS trials and report that 15 original articles were identified that investigated the antidepressant properties of VNS. The review stated that with one exception all of these original articles reported an improvement in mood in patients receiving VNS. The exception was a study by Chavel 2003 but in this trial patients had epilepsy not depression. Unfortunately, Groves does not reference these 15 original articles, nor give details of individual trial results therefore it is not possible to judge the validity of the statements.

To conclude, this is an experimental and as yet unproven method of treatment for severe depression. If this treatment is utilized, patients should be advised of the experimental nature of the treatment and should be assessed by an expert in the field, who is familiar with the treatment. The treatment should ideally be given as part of a robust evaluation of clinical effectiveness and safety in order to add to the current evidence base.

Request Carried Out: October 2005

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Archived ARIF Request

Therapeutic Communities Personality Disorder

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in November 1998.

The Problem Submitted for ARIF to Advise Upon:

What is known about the effectiveness of treating people with severe personality disorders in therapeutic communities?

Reviews Identified

- Cornah D et al. The therapeutic community method of treatment for borderline personality disorder. Southampton: Wessex Institute for Health Research and Development, 1997 (DEC Report 67)

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Comments

Because the DEC report provides minimal detail on the methods it employed it is impossible to make a detailed assessment of the methodological quality of the review. No RCTs were identified and the majority of included studies were case series of quasi-experiments with a high inherent risk of bias. The population of interest is people with borderline personality disorder, however, the authors note that intensive inpatient treatments of this nature are usually reserved for the most severely affected patients.

The review does not address the issue of potential adverse effects and the acceptability of the treatment, despite generally high drop-out rates, nor does it give any indication as to which components of the intervention work best for which patients or sets of symptoms. As the effectiveness of the therapeutic community appears to rest on the unique "community analysis" aspect of the treatment, this specific aspect of the intervention needs to be isolated in the context of a formal evaluation.

In summary, the research base on therapeutic communities does not appear to have reached a stage of development which would allow a judgment to be made as to the effectiveness of the treatment. More research is required which is both rigorous in design and clearly focused in terms of the question, before this is likely to be possible.

Request Carried Out: November 1998

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Back to the ARIF Homepage

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Critical appraisal of Waisbren SE et al. Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. Molecular Genetics and Metabolism 2007;92(1-2):63-70

Synopsis

Question:	To critically appraise the above review to determine whether the level of phenylalanine (PHe) in the blood is a reliable measure of neurotoxicity in patients with phenylketonuria (PKU).
Comments:	There are areas of concern in this review which reduce confidence in the strength of the results and conclusions. There are particular concerns regarding the literature searches, data analysis, heterogeneity and date interpretation. Without undertaking a de novo review it is not possible to estimate the effect on the findings of the restricted research strategy nor the heterogeneity.
Date Completed:	April 2010

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About ARIF

ARIF is a specialist unit (based at the University of Birmingham) whose role is to improve the incorporation of research findings into population level health care decisions in the NHS in the West Midlands region.

ARIF provides an “on demand” information service for health care decision makers. This is achieved by providing timely access to, interpretation of and advice on the application of research evidence, principally from existing systematic reviews of the effects and effectiveness of health care interventions.

Critical appraisal of: Waisbren SE, Noek K, Fahbrach K, Cella C, Frame D, Dorenbaum A et al. Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. Molecular Genetics and Metabolism 2007;92(1-2):63-70

Request completed: April 2010

The review aimed to assess whether the level of Phe in the blood could be used as a biomarker to predict clinical outcomes in patients with PKU. Blood measurements were assessed at three time points: critical time period, encompassing the period when the brain was at maximum development[**]; lifetime, defined as the "mean of 6 or 12 month median assessments for each patient from birth to last measurement in each study"; and concurrent, defined as Phe levels obtained at the time of testing. Neurotoxicity was measured in the meta-analysis using Intelligence Quotient (IQ) as a proxy.

Whilst there are merits to the paper (e.g. double data checking and clear inclusion criteria), there are several areas of concern which may impact the reliability of the findings. The main areas of concern are highlighted here, however, Appendix C gives more detail about the review as a whole.

Four areas of concern were identified which can be divided into literature searches, data analysis, heterogeneity and data interpretation.

Literature Searches

Overall, the search strategy was rather limited, out of date and inconsistent. Electronic searches of MEDLINE (via PubMed) were conducted between1980 and 2004 (the review was published in 2007). Limiting the electronic searches to just MEDLINE may have missed studies which could have introduced publication bias* into the data set. It is also unclear when the searches were updated; the authors say that PubMed was searched for the "past six months" but do not state the dates this took place. The authors also state that "recent reviews (last two years)" were also citation searched but again no dates were given. Search restrictions varied depending upon when the searches were undertaken, e.g. electronic searches between 1980 and 2004 were restricted to English language, whereas the updated searches had no language restrictions.

[**] which in the review fell into two categories 0 to 10 years and 0 to 6 years.
[*] Publication bias = a tendency for positive trials (in this case highly correlated studies) to be published in easily accessible journals that has the effect of skewing results in reviews.

In addition to the critical appraisal, a standard ARIF search was undertaken to identify more recent reviews which aimed to find a reliable biomarker for neurotoxicity in patients with PKU (see Appendix A, full search results can be found in Appendix B).

Data analysis

There is a major problem with the data analysis in that the effect size of the correlation coefficient (r) and its variances should have been converted to Fisher's z metric (see Borenstein and colleagues[2]). A statistician from the Birmingham Technology Assessment Group has advised that without this conversion, the degree of correlation is likely to be overestimated.

It is also unclear how the imputed slopes were calculated and therefore how they predicted IQ loss with rising Phe blood levels.

In addition, there are several discrepancies with the data presented in the review. For instance, in Table 2 of the review (page 65), the number of treatment groups does not add up and in the abstract, the r given for mean lifetime Phe level for early treated patients should be minus 0.34.

Heterogeneity

There are several sources of heterogeneity in the review. The first is that there is no quality assessment of the included studies, therefore, there is no way of telling if the included studies differed in terms of their internal validity.

Secondly, there seem to be a lot of differences and unknowns regarding the patient populations. In particular it was difficult to define "early treated", as the review authors did not state what this category represented. From reading up about the topic it has been ascertained that early treated patients have had diet restrictions from the time of diagnosis (which is shortly after birth in babies who are screened for this condition). However, there seem to be a variety of guidelines[1] regarding how long patients should stay on the diet and what are the optimum levels of Phe, therefore, the patient populations within the review may differ substantially between studies.

Inconsistency also appears in the definitions about what are the critical time periods, with two given in the review from 0 to 10 years and 0 to 6 years. It is also not stated in any of the time periods how old the tested patients are. Wide age ranges could introduce clinical heterogeneity given that control of levels of Phe by diet can vary by age.4 It may also be that the susceptibility of the brain to be damaged by Phe may vary at different stages of development.

There is also considerable heterogeneity regarding how IQ was measured. Across the included studies, 12 different scales were employed. To deal with this statistically the review authors correctly standardised the data by using only within study correlations within the meta-analysis, however, this does not address reliability and validity issues related to the individual scales. The review authors do discuss how heterogeneity had impacted on the results of the review and this gives insight into the difficulties heterogeneity poses to research in this patient population.

Interpretation of the data

Most of the statistically significant correlations are described as 'moderate' negative correlations, with most of these point estimates lying between -0.3 and -0.4. However, it needs to be borne in mind that there is no agreement about what terms such as "weak", "moderate" or "strong" correlations signify.[3] As a perfect negative correlation (where a rise in one variable is accompanied by a drop in the other variable) would be -1 and a correlation of 0 denotes that there is no correlation between the two variables measured, the review authors description of correlations of -0.3 to -0.4 as moderate, is questionable.

Taking the review results at face value, one has also to question how clinically meaningful are the reductions in IQ.

Results from inputted slopes and intercept

CRITICAL PERIOD	100µmol/l increase in Phe predicts an average of 1.3 to 3.1 point reduction over a range of Phe from 423-750 µmol/l
Early treated classic	
All early treated	
LIFETIME	100µmol/l increase in Phe predicts an average of 1.9 to 4.1 point reduction over a range of Phe from 394 to 666 µmol/l
Early treated classic	
All early treated	
CONCURRENT	100µmol/l increase in Phe predicts an average of 0.5 to 1.4 point reduction over a range of Phe from 429 to 1644 µmol/l
Early treated classic	
All early treated	

where range = Phe levels studied in the trials/meta-analyses

Conclusions

In summary, there are areas of concern in this review which reduce confidence in the strength of the results and conclusions.

References

1. Waisbren SE, Noel K, Fahrbach K, Cella C, Frame D, Dorenbaum A et al. Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. Mol Genet Metab 2007; 92(1-2):63-70.

2. Borenstien M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to Meta-Analysis. Chichester: John Wiley & Sons; 2009.

3. De Veaux RD, Velleman PF, Bock DE. Stats Data and Models. 2nd ed. Boston: Pearson Addison Wesley; 2008.

4. Anastasoaie V, Kurzius L, Forbes P, Waisbren S. Stability of blood phenylalanine levels and IQ in children with phenylketonuria. Mol Genet Metab 2008; 95(1-2):17-20.

5. Albrecht J, Garbade SF, Burgard P. Neuropsychological speed tests and blood phenylalanine levels in patients with phenylketonuria: a meta-analysis. Neurosci Biobehav Rev 2009; 33(3):414-421.

Appendix A – Literature search

The following search strategy was used in MEDLINE and was adapted for use in the other information sources:

1 phenylalanine.mp.
2 exp Phenylalanine/
3 PHE.mp.
4 or/1-3
5 phenylketonuria$.mp.
6 exp Phenylketonurias/
7 pku.mp.
8 phenylketonuric.mp.
9 hyperphenylalaninemia.mp.
10 hyperphenylalaninaemia.mp.
11 or/5-10
12 4 AND 11

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Appendix B – Literature search results

Systematic reviews and meta-analyses

Source – Internet searches

De Roche K, Welsh M. Twenty-five years of research on neurocognitive outcomes in early-treated phenylketonuria: Intelligence and Executive Function *Developmental Neuropsychology* 2008; **33(4)**: 474-504 http://www.informaworld.com/smpp/877352039-1480582/content~db=all~content=a794313342

Source – MEDLINE (Ovid) 1950 to March Week 2 2010

Albrecht J, Garbade SF, Burgard P. Neuropsychological speed tests and blood phenylalanine levels in patients with phenylketonuria: a meta-analysis. Neuroscience & Biobehavioral Reviews 2009; 33(3): 414-21

Moyle JJ, Fox AM, Arthur M, Bynevelt M, Burnett JR. Meta-analysis of neuropsychological symptoms of adolescents and adults with PKU. Neuropsychology Review. 2007 ; 17(2):91-101

Waisbren SE, Noel K, Fahrbach K, Cella C, Frame D, Dorenbaum A. Levy H. Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. Mollecular Genetics & Metabolism. 2007; 92(1-2) :63-70

Primary studies

Source – HTAi Vortal

Anastasoiae V, Kurzius L, Forbes P, Waisbren S Stability of blood phenylalanine levels and IQ in children with phenylketonuria. Mol Genet Metab 2008; 95(1-2): 17-20 http://www.ncbi.nlm.nih.gov/pubmed/18703366

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Appendix C

Aim	"To assess the use of blood Phe as a predictive biomarker for clinical outcomes in patients with PKU, based on an assessment of the global relationship between blood Phe and intelligence quotient (IQ)"
Population	Any patient with the clinical phenotype of PKU (classic, mild PKU or hyperphenylalaninemia)
Intervention	Use of blood Phe to determine the effect on neurological outcomes.
Control	N/A
Outcome	Correlation between blood Phe and neurological outcomes where these are measured by IQ, MRI or by neurophysiologial testing. Specifically the aim of the meta-analysis was to "develop a quantitative proportional relationship between blood Phe and IQ".
Quality of Review	× Potential for publication bias to creep in via the search strategy (see below). ✓ Methods used to conduct the systematic review are good, i.e. double checking , clear description of inclusion exclusion criteria, particularly that of the studies included in the meta-analysis etc × Quality assessment of included studies not done. ↔ Analysis, correct that only studies with within –study correlations were included in the meta-analysis due to the variation of measures between studies. However, this does not address validity issues regarding the individual IQ scales measured – of which there were a total of 12 different scales. × Problems with data analysis in that the effect size of the correlation coefficient (r) and its variances should have been converted to Fisher's z metric (see Borenstein pages 99 and 147, and BTAG statistician). Without this conversion, the degree of correlation is likely to be overestimated. × There are a number of discrepancies with the data presented, for example: ▪ Within tables 2, 3 and 4 the numbers or 'early treated' do not add up in both column 't' and column 'n'. ▪ Table 2 within 'classic' the numbers do not add up in both 't' and 'n'. ▪ Table 4 within 'classic' the numbers do not add up in both 't' and 'n'. ▪ In the abstract the r given for mean lifetime Phe level for early treated patients should be minus 0.34.
Study design	Systematic review.
Search date/ search strategy	January 1980 to 2004. Electronic searches, just MEDLINE (via PubMed). Unclear if the searches were updated, the authors say that PubMed was searched for the "past 6 months" but do not state the dates this took place, they also state that "recent reviews (last 2 years)" were also citation searched but again no dates are given. Thus whilst the search appeared wide ranging, the search was not as systematic as it could have been. Search restrictions varied depending upon when the searches were undertaken, e.g. electronic searches between 1980 and 2004 were restricted to English language, whereas updated searches did not restrict language.
Data analysis	Descriptive analysis. Meta-analysis restricted to papers reporting within-study correlations due to the heterogeneity of outcomes reported across the studies, particularly in papers reporting neuropsychological outcomes. Excluded from the meta-analysis were studies reporting multiple regression analyses, the results of these studies were described. Studies were also stratified according to different time points when the tests were

<table>
<tr><td></td><td>done i.e. CRITICAL TIME period (which encompassed the time when the brain was at maximum development = time of birth to 6 -12 years of age),
LIFETIME (defined as “the mean of 6 or 12 month median assessments for each patient from birth to last measurement in each study”).
CONCURRENT which included Phe levels obtained at time of testing for other clinical outcomes.

Early treated – not defined in the review.

Within the meta-analysis studies were stratified according to the type of disease i.e. classical PKU, mild PKU, non-PKU hyperphenylalaninemia, or mixed/unspecified.

Meta-analysis = “a meta-analysis of slopes was performed by determining the slope of Phe level predicting IQ, based on the meta-analytic correlation (r) between Phe level and IQ and the standard deviation (SD) for mean Phe and mean IQ. No formal statistical analyses were performed. Statistical significance was assumed where 95% CI did not cross zero”.

Problem with meta-analysis in that r should have been converted into Fisher’s z metric.

Results categorised as:

Phe measure (critical, lifetime, concurrent) x Type of disease (classic, mild, mixed/unspecified) +/- early treated (early treated not defined).</td></tr>
<tr><td>Number of studies included</td><td>64 studies included in the review, 40 included within study correlations between blood Phe and IQ therefore included in the meta-analysis. No quorum diagram.</td></tr>
<tr><td>Trial characteristics</td><td>“The majority of studies used a retrospective, observational design (56%), took place in Europe (64%), and were published during the 1990’s (59%). A total of 3,361 patient were included and most had a diagnosis of classic (34%) or unspecified PKU (46%).</td></tr>
<tr><td>Effectiveness – results</td><td>Critical period from Table 2, page 65
<table>
<tr><td></td><td>0-10yrs</td><td>0-6 yrs</td></tr>
<tr><td>ALL EARLY TREATED</td><td>-0.35 (-0.44, -0.027)</td><td>-0.33 (-0.50, -0.15)*</td></tr>
<tr><td>CLASSIC
Early treated
Mixed treatment history
Total</td><td>
-0.38 (-0.48, -0.29)
-0.45 (-0.65, -0.18)
-0.39 (-.48, -0.29)</td><td>
-0.34 (-0.49, -0.21)
-0.45 (-0.66, -0.17)
-0.36 (-0.49, -0.21)</td></tr>
<tr><td>MIXED/UNSPECIFIED
Early treated
Mixed treatment history
Total</td><td>
-0.26 (-0.40, -0.09)
-0.66 (-0.92, 0.01)
-0.28 (-0.42, 0.12)</td><td>
-0.07 (-0.56, 0.45)
No result
-0.07 (-0.56, 0.45)</td></tr>
</table>
*Significant between study heterogeneity.

Life time
<table>
<tr><td></td><td>PKU population</td></tr>
<tr><td>ALL EARLY TREATED</td><td>-0.34 (-0.42, -0.25)</td></tr>
<tr><td>CLASSIC
Early treated
Mixed treatment history
Total</td><td>
-0.37 (-0.48, -0.26)
-0.46 (-0.64, -0.23)
-0.39 (-.49, -0.29)</td></tr>
<tr><td>MIXED/UNSPECIFIED</td><td></td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>Early treated
Mixed treatment history
Total</td><td>-0.27 (-0.40, -0.013)
No result
-0.27 (-0.40, 0.13)</td></tr>
</table>
Concurrent
<table>
<tr><td></td><td>PKU population</td></tr>
<tr><td>ALL EARLY TREATED</td><td>-0.31 (-0.41, -0.20)</td></tr>
<tr><td>CLASSIC
Early treated
Mixed treatment history
Total</td><td>
-0.25 (-0.34, -0.15)
-0.04 (-0.35, -0.15)
-0.23 (-0.32, -0.14)</td></tr>
<tr><td>MIXED/UNSPECIFIED
Early treated
Mixed treatment history
Total</td><td>
-0.42 (-0.60, -0.19)*
0.02 (-0.82, 0.53)
-0.29 (-0.48, 0.07)*</td></tr>
<tr><td>MILD</td><td>-0.28 (-0.82, 0.53)</td></tr>
<tr><td>HYPERPHENYLALANINEMIA</td><td>-0.08 (-0.55, 0.43)</td></tr>
</table>
*Significant between study heterogeneity.
</td></tr>
<tr><td>Adverse events</td><td>Not reported</td></tr>
<tr><td>Cost effectiveness results</td><td>Not reported</td></tr>
<tr><td>Conclusions</td><td>“In conclusion, this meta-analysis has demonstrated a quantitative proportional relationship between blood Phe level and IQ for early treated patients with PKU, assessed during critical, early childhood years (age 0 to 12 years) or by a lifetime IDC. A 100µmol/l increase in Phe resulted in a 1.3 to 4.1 point reduction in IQ. A statistically significant, moderate correlation was also found between concurrent Phe level and IQ for early treated individuals. These statistically significant correlations suggest that blood phe level can be used reliably as a predictive biomarker for IQ in future clinical trials”.</td></tr>
<tr><td>ARIF comments</td><td>Without undertaking a de novo review, it is not possible to estimate the effect on the findings of the restricted search strategy nor the heterogeneity in this review.</td></tr>
</table>

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Archived ARIF Request

Pulse Dye Laser Treatment
Port Wine Stains

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in February 1997.

The Problem Submitted for ARIF to Advise Upon:

What is the evidence on the use of pulsed dye lasers to relieve the psychological effects of port wine stains in children and adults?

[ARIF was particularly asked to appraise the report by the Wessex Institute of Public Health listed below. The comments section provides our opinion.]

Reviews Identified

- Best L. Pulsed Dye Laser Treatment of Port Wine Stains (DEC Report 43) Winchester: Wessex Institute of Public Health Medicine, 1995 (DEC Report No. 43)
- Stewart M, Hailey D. Laser treatment of superficial cutaneous vascular lesions. Canberra: Australian Institute of Health and Welfare, 1994

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Comments

Stewart M et al is not a systematic review and reports two incomplete case series in Australia.

The Wessex report relies principally on case series. In order to accept the results of this as valid we must feel that the natural history of port wine stains (PWS) is sufficiently clear that there is no necessity for a control group. This does not seem unreasonable in the case of infants and children with port-wine stains, but for adults may not be as certain.

Having accepted that a case-series will give a reasonable measure of the effects of a procedure in infants and children, our appraisal of the case series as presented in this review is as follows:

- The case series were NOT concerned with measuring psychological benefits and risks, and do not help us answer the question.
- It is important, as in studying any cohort, that all those entering the case-series do so with a similar extent and pattern of disease. In this report we have little information beyond the effect size and we are left to assume that the patients at entry had comparable cutaneous lesions.

- It is important that all those entering a case-series are included in the final analysis. In this report we again have no information by which to make a judgement on whether this is the case. There is always a natural tendency to ignore those who were lost to follow-up when considering a case-series retrospectively.
- It is always important to ensure that the outcome is assessed as objectively as possible, ideally independently of those undertaking the procedure. Again we have little detail about the method of assessing skin lightening and scarring. It is difficult to envisage a completely objective method of assessing extent and lightening of skin after treatment. However, one could reasonably assume that any change in outcome observed is not entirely due to a placebo effect.

Thus this review's conclusions are open to some bias, and potentially the reported outcomes may overestimate the effect size.

Bearing the above in mind, we consider the key points are :

There are two separate questions : (i) the psychological effects of pulsed dye laser (PDL) treatment in infants and children with PWS, and (ii) the psychological effect of PDL treatment in adults with PWS. The potential benefits of laser treatment include skin lightening, psychological improvement and consequent change in social situation. The potential risks include non lightening of skin and skin scarring, exposure to multiple anaesthetics in children and psychological morbidity.

The psychological problems associated with facial or extensive port-wine stains are likely to be long term and severe in at least some, if not most, of those affected, and that the psychological effects and social consequences of PDL treatment have not been considered in the DEC report. There is no recommended treatment other than cosmetic camouflage and counselling for port-wine stains in infants and children. Even with the problems associated with the case series reported in the DEC report, the average lightening in children is probably clinically significant in the majority receiving treatment. There is a lack of long term evaluation of the balance of risk and benefits of PDL treatment. Expert advice may help to clarify if a laser treated port-wine stain is likely to regress or progress over time.

In conclusion, our appraisal of this review is compatible with the use of PDL in infants and children, although it should be acknowledged that the research evidence is not as complete as it might at first appear, especially in relation to the psychological effects. In adults there is more uncertainty, the natural changes in the nodularity and colour of port-wine stains over the years may make them less responsive to PDL, the psychological benefits may be different if adults have adjusted to their condition, and there are other laser treatments available that are not routinely used in children.

Request Carried Out: February 1997

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Archived ARIF Request

Prevention
Postnatal Depression

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in August 2005.

The Problem Submitted for ARIF to Advise Upon:

Can postnatal depression be prevented?

See related requests: Can mental illness be prevented?, Can depression be prevented in children and adolescents?, Can depression be prevented in adults?, Can eating disorders be prevented?

Reviews Identified

- Dennis C-L, Creedy D. Psychosocial and psychological interventions for preventing postpartum depression. The Cochrane Database of Systematic Reviews: Reviews 2004 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD001134.pub2 YR: 2004 No: 4
- Dennis C-L, Psychosocial and psychological interventions for prevention of postnatal depression: systematic review. BMJ 2005;331(7507):15
- Dennis CL, Ross LE, Herxheimer A. Oestrogens and progestins for preventing and treating postpartum depression. The Cochrane Database of Systematic Reviews: Reviews 1999 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD001690 YR: 1999 No: 2 US

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Comments

This excellent review by Dennis 2004 originally written as a Cochrane review but also published in the BMJ, has managed to deal with the complex data in a very comprehensive and informative manner.

The review assessed the effects of psychosocial and psychological interventions compared with usual antepartum, intrapartum or postpartum care on the risk of postnatal depression.

Fifteen RCTs involving 7,697 women met the inclusion criteria. Women were either pregnant or new mothers less than 6 weeks postpartum. Psychosocial or psychological interventions were included which could be instigated antenatally or within the first month of birth by a professional or layperson.

The primary outcome of the occurrence of postnatal depression (however measured) found a Relative Risk of 0.81 with a 95% Confidence Interval (CI) of 0.65 to 1.02. This means that in comparison to the

control group, the intervention group were 19% less likely to suffer from postnatal depression. However, because the 95% CI ranged from 0.65 to 1.02 there could be a larger benefit of up to 35% or no benefit at all, because the 95% CI range passes 1. A Relative Risk measure of 1 means that there is no difference between the intervention and control groups. Subgroup analysis found that there was a benefit if the intervention was given by a health care professional, if the women were at risk from postnatal depression and if it was during the postpartum period. Individual based therapies also had a tendency toward benefit.

Overall the author concludes that diverse psychosocial and psychological interventions do not significantly reduce the number of women who develop postnatal depression but the most promising intervention is the provision of intensive, professionally based postpartum support in women who are at higher risk from postnatal depression.

Request Carried Out: August 2005

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Archived ARIF Request

Smoking Cessation (pre-operative)
Pre-Operative Smoking Cessation
Smoking

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of pre-operative smoking cessation interventions?

Reviews Identified

- Møller A, Villebro N Interventions for pre-operative smoking cessation. The Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD002294.pub2. DOI: 10.1002/14651858.CD002294.pub2.

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Comments

The review by Møller and Villebro (2005) was the most relevant as it assessed the evidence base of smoking cessation in pre-operative patients. It was generally well conducted and also up-to-date with the last search occurring in February 2005.

The findings of the review suggest that pre-operative cessation programmes maybe effective in the short term in reducing post-operative complications and improving smoking cessation/reduction rates. However, there may be no effect on hospital length of stay. Evidence on the long-term effects is lacking.

The findings must be viewed with some caution as they were based on a maximum of four generally small and heterogenous trials.

Smoking cessation interventions are complex and multifactorial in nature and several issues remain unanswered and require further investigation through robust primary studies. For example: whether the effects of smoking session programmes differ with respect to disease and/or type of surgery, settings in which the interventions were administered, specific patient characteristics, specific intervention components, complete pre-operative smoking cessation vs. reduction, how long the interventions start prior to surgery and the length of time patients are smoke-free prior to surgery.

We would suggest that if a pre-operative smoking cessation intervention is to be introduced, it is done so as part of a robust evaluation of effectiveness of the programme with the aim of addressing some of the limitations of the current evidence as outlined above.

Request Carried Out: January 2006

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Archived ARIF Request

Prescribing Budgets Resource Allocation

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of manoeuvres to manage prescribing budgets in PCTs?

Reviews Identified

- Gill PS, Makela M, Vermeulen KM, Freemantle N, Ryan G Bond C et al. Changing doctor prescribing behaviour. Pharmacy World and Science 1999;21(4):158-67

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Comments

This is a well conducted review which provides a framework within which individual articles directly relevant to primary care in the UK could be considered in detail. However, it only incorporates literature up to 1996. Given the volume of literature that the review attempts to consider it does an excellent job summarising it, although inevitably detail about individual studies is sacrificed. Caution must also be exercised in interpreting the results as it relies on a vote-counting technique which the authors themselves highlight as a potential weakness. Despite this it is clear that behavioural change interventions do have capacity to change prescribing behaviour.

Request Carried Out: August 2003

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Archived ARIF Request

Prostate specific antigen (PSA) to detect prostate cancer
Prostatism (symptoms referable to the prostate)

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WARNING
This is a brief summary of the evidence available at the time. Readers should not use the comments made in isolation and may wish to consult the references provided. Please be aware that new evidence may have become available since the request's completion in September 1997 and update in February 2000.

The Problem Submitted for ARIF to Advise Upon:

What are the effects/effectiveness of PSA testing to detect prostate cancer in those with "prostatic symptoms"?

Question Reformulated

Given that the case against population screening seems reasonably robust on the basis of the current evidence, the question can be usefully rephrased as:

Is PSA use in all patients with prostatic symptoms (frequency, nocturia, hesitancy and post micturitional dribbling) more or less likely to be effective and efficient in terms of improving survival from prostate cancer than general population screening?

Reviews Identified

- Coley CM et al. Early detection of prostate cancer. Part I: Prior probability and effectiveness of tests. Annals of Internal Medicine 1997;126:394-406
- Coley CM et al. Early detection of prostate cancer. Part II: Estimating the risks, benefits and costs. Annals of Internal Medicine 1997;126:468-479

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Comments

There are a number of relevant systematic reviews addressing the effects/effectiveness of PSA screening in the general population. The review by Coley CM not only falls into this category, but also provides information relevant to the reformulated question above.

Two pieces of research evidence, as presented in the review appear particularly relevant:

- The incidence of prostate cancer (and its severity) in those with symptoms referable to the prostate appears to be no greater than the general male population.
- The specificity of the PSA test in those with symptoms referable to the prostate is worse than in the general population. Thus we would expect the number of false positives generated by PSA

testing to be proportionately greater if all men with prostatic symptoms were tested, than if all the population were tested.

On this basis, it is difficult to see how PSA testing of all men with prostatic symptoms could give a better ratio of benefits to costs than general population screening, and so one would have to conclude that there can be little justification for systematic PSA testing in the group.

As with general population screening with PSA, assessment of programme effectiveness is at present greatly hampered by uncertainty about the effects/effectiveness of available treatments. Trials are in progress which will provide useful information, thus in the same way that decisions on population screening should be kept under review, so too should any decision on PSA use in men with prostatic symptoms.

This is an area prone to need for regular updating as new information is continually becoming available.

Request Carried Out: September 1997

Update: February 2000 - In response to an error observed by Joe Cuniff MD (New Hampshire, USA) a detail in this webpage has been changed. In the second sentence of the second bulleted point in the Comments section "false negatives" has been changed to "false positives". The conclusions are not altered by this amendment.

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Stents with percutaneous transluminal renal artery angioplasty (PTRA)
Renal Artery Stenosis

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The Problem Submitted for ARIF to Advise Upon:

Is stenting for renal artery stenosis an effective procedure especially in terms of life years gained & how many patients are likely to be suitable?

Question Reformulated

Consideration of the important elements of this question is instructive. Our assessment of the key components was as follows:

Population/condition:
Any person with atherosclerotic stenoses of their renal arteries (stenoses due to fibromuscular dysplasia were not considered).

Intervention:
All interventions to relieve such stenoses and/or their proposed sequelae, including medical treatments for renal failure eg antihypertensive agents, dialysis and transplantation as well as open surgery, and angioplasty (percutaneous transluminal renal artery angioplasty - PTRA) with or without stent insertion (Strecker, Palmaz, Wallsent types).

Outcomes:

- Patency of renal artery
- Reduced blood pressure
- Improved/stabilised/reduced rate of decline of renal function
- Need for/time to dialysis or other renal replacement therapy (RRT)
- Survival

Reviews Identified

- Kidney DD, Deutsch LS. The indications and results of percutaneous transluminal angioplasty and stenting in renal artery stenosis. Seminars in Vascular Surgery 1996;9:188-197
- Novick AC. Evaluation and management of atherosclerotic renal vascular disease to prevent end stage renal failure. Seminars in Urology 1994;12:67-73
- Rimmer JM, Gennari FJ. Athersoclerotic renovascular disease and progressive renal failure.

Annals of Internal Medicine 1993;118:712-719

Trials Identified

None examining the effects of PTRA with stenting.

Other Studies

- Harden DN et al. Effect of renal artery stenting on progression of renovascular renal failure. Lancet 1997;349:1133-1136

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Comments

The first two reviews are useful, but are most severely limited in the validity of their conclusions by the nature of the included studies. Thus far, only uncontrolled studies, mostly examining short term outcomes appear to have been conducted. The study by Harden DN et al is the first such study to look in detail at renal function. The importance of the lack of controlled studies is highlighted in the third review by Rimmer JM which indicates that although we know in general terms that the outcome in untreated/medically treated renal artery stenosis is poor, it is not possible to quantify this, and there is uncertainty. As a result it is extremely difficult to interpret the effectiveness of PTRA with stenting in studies which do not have a comparison group.

In conclusion, PTRA with stenting is clearly a technology with potential, but it has wide implications. In this situation our inability from the available research to accurately guage its effectiveness and cost-effectiveness is critical. Thus, if this procedure is purchased it should only be employed in the context of a rigorous research evaluation which builds on rather than duplicates the limitations of existing research.

Request Carried Out: August 1997

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Rituximab
Systemic Lupus Erythematosus (SLE)

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of rituximab for SLE?

SLE is a condition which predominantly causes arthritis and skin lesions. It can also have life-threatening effects on lungs, heart, kidneys and the brain. Rituximab is a genetically engineered antibody to the CD20 marker which is found on the surface of B lymphocytes. It's use has been mainly explored in cancers of lymphocytes and it is licenced for use in treatment of lymphomas. However, although there are theories to explain why rituximab might be useful in rheumatic diseases, such as rheumatoid arthritis and SLE, it is not currently licenced for use in these conditions.

Reviews Identified

None identified.

Primary Studies

The best available evidence appears to be a number of Phase I/II studies:

- Leandro MJ, Edwards JC, Cambridge G, Ehrenstein MR, Isenberg DA. An open study of B lymphocyte depletion in systemic lupus erythematosus. Arthritis & Rheumatism 2002;46(10):2673-7
- Looney RJ, Anolik JH, Campbell D, Felgar RE, Young F, Arend LJ et al. B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. Arthritis & Rheumatism 2004;50(8):2580-9

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Comments

The best evidence identified supports the effectiveness of rituximab in SLE. However, it must be emphasised that such studies are case-series, without parallel control groups, and as such are highly suceptible to bias and confounding. Given this it is unsurprising that there is clear consensus among the research literature that the next stage in the development of use of rituximab in SLE should be properly conducted randomised controlled trials.

In our view it appears that rituximab is still experimental with respect to its use in SLE and that patients receiving it should ideally be part of an RCT. There appear to be limited grounds at this point in time for routinely NHS-funded use.

Request Carried Out: November 2004

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Archived ARIF Request

Traffic Calming
Road Accidents

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of traffic calming schemes in reducing road accidents?

Traffic calming was taken as any intervention to alter roads and their immediate surrounds with the intention of reducing traffic speed or diverting traffic away from an area to a more appropriate road.

The key outcomes of interest were accidents (fatal, non-fatal, and property damage only) in the area subject to traffic calming, and surrounding areas. There are many other outcomes of potential interest particularly impact on pollution and noise (there are arguments both suggesting improvement and deterioriation in these respects) but it was judged that accident reduction if demonstrated, was likely to be weighted more highly than say increased motorist dissatisfaction and other concerns.

Reviews Identified

- Elvik R. Area-wide urban traffic calming schemes: a meta-analysis of safety effects. Accident Analysis and Prevention 2002;33(3):327-336

Primary Studies

- Janssen ST. Road safety in urban districts. Final results of accident studies in the Dutch demonstration projects of the 1970's. Traffic Engineering and Control 1991;292-6
(Controlled before-after design)

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Comments

Assessing the effectiveness and cost-effectiveness of a wide variety of traffic calming schemes is inevitably complex. However, the review by Elvik is systematic and provides a reliable overview of research in this area indicating an important impact on accidents. The primary study by Janssen indicates both the type of schemes which have been successful and that rigorous assessment of impact is possible and supportive of traffic calming being effective.

Request Carried Out: October 2002

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Schizophrenia

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

Request from GRIP Committee to assist in the development of a GRIPKIT advising on evidence based purchasing of services for care of patients suffering schizophrenia.

Question Reformulated

The available evidence, particularly systematic reviews of research, examining the effects of interventions targeting schizophrenia were mapped. The reviews were scrutinised by the GRIP committee and on this basis a decision was made to focus on the following two areas:

- Family therapy
- Selected aspects of acute drug treatment

Reviews Identified

- Mari JJ, Adams CE , Streiner D. Family intervention for schizophrenia. In: Adams CE, de Jesus Mari J, White P Schizophrenia Module of The Cochrane Database of Systematic Reviews , [updated 04 March 1997]. Available in The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration; Issue 2. Oxford: Update Software; 1997. Updated quarterly.
- Davis JM. Overview: maintenance therapy in pyschiatry: 1. Schizophrenia. American Journal of Psychiatry 1975;132:1237-1245
- Essali MA, Rezk E, Wahlbeck K et al. Clozapine vs 'typical' neuroleptic medication for schizophrenia. In: Adams CE, de Jesus Mari J, White P Schizophrenia Module of The Cochrane Database of Systematic Reviews , [updated 04 March 1997]. Available in The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration; Issue 2. Oxford: Update Software; 1997. Updated quarterly.
- Robert G. Risperidone for the treatment of refractory schizophrenia. Southampton: Wessex Institute of Public Health, Dec 1995. Pp 9. (DEC report 48)

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Comments

Two purchasing objectives were developed, consistent with the four systematic reviews of evidence above. General background, formal critical appraisal of the reviews and audit tools are included in the

GRIPKIT:

- Getting to GRIPs with schizophrenia.
  Birmingham: West Midlands Regional GRIP Group, 1997.

This is available from NHS Executive West Midlands, Bartholomew House, 142 Hagley Road, Birmingham. B16 9PA. (Contact Dr R Jecock: Phone - 0121 224 4600.)

This is an area prone to the need for regular updating as new information is continually becoming available. In particular the Cochrane Reviews quoted are regularly updated.

Request Carried Out: July 1997

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Archived ARIF Request

School Health Services
School Age Children

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

School health services generally focus on physical health. Is there any evidence to support a different model encompassing social and mental health and development?

Question Reformulated

The question we addressed was re-defined as follows:
Population - school age children.
Intervention - a “new” model of school health services, which focuses on mental and social needs and development, with less emphasis on physical needs, routine surveillance and disease prevention. This might typically encompass: health needs assessment; family support; health promotion/prevention/education; and monitoring of health status.
Outcomes - increased detection of physical and mental health problems; improved physical and mental health status and general well-being; reduced risk-taking behaviour; increased uptake and/or access to health services.

Reviews Identified

None identified.

Trials Identified

None identified.

Other Evidence Identified

- Kisker EE, Brown RS. Do school based health centres improve adolescents' access to health care, health status and risk taking behaviour? Journal of Adolescent Health 1996; 18: 335-434

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Comments

We identified no relevant systematic reviews on school health services and the health needs of school age children as a totality. The paper by Kisker and Brown cannot truly be described as a trial, although it does compare outcomes in the general urban adolescent population, with those of the children in the

participating schools. Although it is set in urban USA, the aim of the intervention is broadly similar in principle to the proposed new model of school health services as it aims to meet both the physical and psychological health needs of adolescent children. It is however, limited to adolescents and the intervention itself probably extends well beyond what could realistically be achieved by the average school health service in the UK. Nevertheless, the results are of interest as they suggest that while this type of service [which would have significant cost implications in the UK setting] did result in improved access to health services and health knowledge, these were not sufficient to bring about reductions in risk-taking behaviour in this age group.

Readers should note that there are a large number of systematic reviews available which consider the effectiveness of different elements of school health services, which are central to the proposed new model. These are generally around health promotion in schools, or school age children, and most consider a specific “undesirable” outcome such as obesity, suicide and unwanted pregnancy, or health related behaviours such as sunbathing, smoking, alcohol and substance abuse, and high risk sexual behaviour.

Request Carried Out: June 1999

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Archived ARIF Request

Sexual Behaviour
Sexually Transmitted Infections

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of interventions designed to change sexual behaviour in preventing new or recurrent sexually transmitted infections?

Reviews Identified

- Wilkinson D, and Rutherford G. Population-based interventions for reducing sexually transmitted infections, including HIV infection (Cochrane Review). In: The Cochrane Library, Issue 4 2001.

Trials Identified

- Shrier LA, Ancheta R, Goodman E, Chiou VM, Lyden MR, Emans SJ Randomized controlled trial of a safer sex intervention for high-risk adolescent girls. Archives of Pediatrics & Adolescent Medicine 2001;155(1):73-9
- The NIMH Multisite HIV Prevention Trial: reducing HIV sexual risk behavior. The National Institute of Mental Health (NIMH) Multisite HIV Prevention Trial Group. Science 1998;280(5371):1889-94
- Branson BM, Peterman TA, Cannon RO, Ransom R, Zaidi AA Group counseling to prevent sexually transmitted disease and HIV: a randomized controlled trial. Sexually Transmitted Diseases 1998;25(10):553-60
- O'Donnell CR, O'Donnell L, San Doval A, Duran R, Labes K Reductions in STD infections subsequent to an STD clinic visit. Using video-based patient education to supplement provider interactions.Sexually Transmitted Diseases 1998 ;25(3) :161-8
- Wong ML, Chan KW, Koh D A sustainable behavioural intervention to increase condom use and reduce gonorrhoea among sex workers in Singapore: 2-year follow-up. Preventive Medicine 1998; 27(6):891-900

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Comments

The review by Wilkinson and Rutherford examined behavioural changes and recurrence of STI after

interventions to increase safe sex behaviour. Although there were reported increases in safe behaviour and decreases in STI recurrence after such interventions, the populations studied were in developing countries and therefore there is some difficulty in applying the results to the UK.

There appears to be some evidence for decreased incidence of recurrent STI in the trials listed above. However the findings from these trials need to be treated with some caution because of variation in the length of time over which the intervention was given, the length of follow up, high losses to follow-up, and uncertainty surrounding the combination of intervention/s required to elicit the best response.

Request Carried Out: February 2002

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Skin Cancers - Squamous Cell Carcinoma, Basal Cell Carcinoma, Malignant Melanoma
Sunbeds - Sunlamps, Solaria, Sun Tanning Equipment

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What are the health effects of sunbeds, sunlamps, sun tanning equipment & solaria?

Question Reformulated

Two issues need to be taken into account in considering this question:

1. That the main hazard associated with tanning equipment is the "radiation" it emits. Further, that the main type of "radiation" emitted by most modern tanning equipment is ultraviolet radiation of a wavelength of 340-400 nm - the longer wavelengths of the UVA spectrum. This is important because these wavelengths are thought to be least damaging relative to other parts of the UV light spectrum, particularly shorter wavelength UVA (315-340 nm) and UVB. However, depending on the type of machine used tanning equipment may emit significant amounts of shorter wavelength UVA (up to 40% of total emissions) and small amounts of UVB (generally <5% of total emissions).
2. There are many potentially important health outcomes. This request concentrates particularly on cutaneous cancers, squamous cell carcinoma (SCC), basal cell carcinoma (BCC) [together these are often referred to as non-melanoma skin cancers (NMSC)] and malignant melanoma (MM).

Reviews Identified

- National Radiological Protection Board. Board statement on the effects of ultraviolet radiation on human health and health effects from ultraviolet radiation. Didcot: National Radiological Protection Board, 1995

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Comments

No truly systematic reviews were identified.

The review given was the starting point of further interrogation of the available research literature on the

basis that it was the most apparently up-to-date, comprehensive and authoritative review identified in our initial literature search. The results of this lengthy report, which addressed more than the effects of sunbeds etc, and considered a range of different types of evidence (cellular and molecular effects; effects in experimental animal studies; effects in experimental human studies; clinical effects; and epidemiology) were summarised in a series of tables, which together with the full report on which this summary is based, are available from ARIF on request.

The conclusions drawn were as follows:

1. On the basis of the available evidence presented in the NRPB report, it is clear that UVR is strongly associated with cutaneous malignancies, and is probably causal. However, the details of the causal pathway are not clear, particularly which aspects of UVR exposure are most implicated, particularly with regard to malignant melanoma. Given this, there must be greater uncertainty about the effects of modern tanning equipment, which predominantly emit what are thought to be the least harmful elements of the UV spectrum, UVA 340-400nm. This uncertainty seems to be supported by lack of direct evidence of any effects of tanning equipment (as opposed to UVR generally) on malignant melanoma in particular.
2. Given this, it seems that the available research evidence is more compatible with warning individuals about the likely risks of tanning equipment use, rather than active discouragement of that use eg by banning use of sunbeds in Local Authority premises.
3. The only proviso to this is that there is a possibility that the NRPB report may have understated the impact of epidemiological evidence (and other types of evidence) by failing to systematically review the available research. Literature searches by ARIF, focused on identifying case-control studies of the effects of sun-beds, suggests that there is significant under-ascertainment of the available literature in this area by the NRPB report.
4. Given the last two points, active discouragement of tanning equipment use might be supportable, BUT ONLY on the basis of the results of systematic review of the available literature.

Request Carried Out: December 1996

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Archived ARIF Request

Surgery
Sleep Apnoea

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What are the effects/effectiveness of surgery for the treatment of obstructive sleep apnoea/hypoapnoea (OSA)?

This question arose as an extension of requests on the effects/effectiveness of CPAP for OSA - see related entry.

Reviews Identified

Initial searches revealed no systematic review of the effects of surgery on OSA. Thus ARIF commissioned such a review:

- Bridgman SA, Dunn KM. The use of surgery for the treatment of obstructive sleep apnoea. Keele University, 1997.

This review appears on the Cochrane Library.

Other Literature Identified

The review above identifies a range of studies which apparently addressed the question, which were excluded from the review because the evaluations of were not sufficiently rigorous and unbiased.

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Comments

The following is a brief abstract of the review (prepared by ARIF staff). The full text of the review appears on the Cochrane Library.

Objective:
To review current efficacy of surgery in the treatment of obstructive sleep apnoea

Inclusion criteria:
Participants - Diagnosis of OSA using the criteria of more then 5 apnoeas or hypoapnoeas per hour of sleep. No gender or age restrictions.

Types of intervention - Any specific surgical interventions for OSA (including tracheostomy, uvulopalatopharyngoplasty (UPP), tonsillectomy, inferior sagittal mandibular osteotomy and genioglossal advancement with hyoid myotomy and suspension (GAHM), laser midline glossectomy and lingualplasty, maxillomandibular osteotomy and advancement, epiglottoplasty and surgical removal of obstructing pathological lesions) compared with other surgical interventions or non-surgical interventions or no intervention.
Types of study - All randomised or quasi-randomised comparisons.
Types of outcome measures - 12 sets of outcomes identified including daytime sleepiness, oxygen desaturation, quality of life, surgical complications, postoperative morbidity and mortality.

Search strategy:

- Searches of bibliographic databases - Medline, Embase and Cinahl
- Examination of reference lists of potentially relevant studies
- Contacts with national organisations eg the National Health Technology Assessment Programme
- Contacts with experts in the fields of sleep/respiratory medicine and ENT surgery
- Hand searches of specialised journals

Findings:

Although 594 potentially relevant articles were identified, none met the inclusion criteria. There were no trials of the effects/effectiveness of surgery for obstructive sleep apnoea.

Implications for practice:

"Clinicians: In the light of current lack of good trial-based evidence, clinicians should consider restricting surgery for obstructive apnoea to that carried out as part of clinical trials. Where practice is continued, patients should be informed of the experimental nature of the operations."

Additional information relevant to this request is available in the request entitled: Continuous Positive Airways Pressure/Sleep Apnoea.

Request Carried Out: January 1997

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Speech Therapy
Special Educational Needs

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What evidence is there that speech therapy for children of school age who have special education needs is effective?

Reviews Identified

- Nye C, Foster SH, Seaman D. Effectiveness of language intervention with the language learning disabled. Journal of Speech and Hearing Disorders; 1987:52:348-357
- Pearson VA. Speech and language therapy: is it effective? Public Health 1995;109:143-153
- Enderby P, Emerson J. Does Speech and Language Therapy Work? A Review of the Literature. London: Whurr Publishers Limited, 1995. pp180

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Comments

These two reviews seem to indicate that there is evidence of a beneficial effect of speech therapy. However, the size of this effect is not clear. Both reviews rightly point to the need for better research on the effects of speech therapy, a point which should be reflected in any purchasing decision.

Request Carried Out: April 1996

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Sterilisation Reversal - Female

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WARNING
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The Problem Submitted for ARIF to Advise Upon:

What is the evidence for the effectiveness of female sterilisation reversal?

Studies Identified

- Dubuisson JB et al. Sterilization reversal: fertility results. Human Reproduction 1995;10(5): 1145-1151
- Rouzi AA et al. Predictors of success of reversal of sterilization. Fertility and Sterility 1995;64(1): 29-36

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Comments

No reviews were identifed. The two papers cited refer to primary studies which were suggested to help the requester begin to consider the research evidence on this question. Any purchasing decisions should take into account the fact that the two studies:

1. may be unrepresentative of all studies undertaken on this subject
2. are uncontrolled case-series, with high susceptibility to bias.

Not withstanding this, the two studies do show that there is research evidence demonstrating that reversal of female sterilisation is effective in achieving subsequent intrauterine pregnancies which were very unlikely to occur if the operation had not taken place.

Request Carried Out: February 1997

Updated: May 1997 - A cochrane review on "Tubal Surgery Techniques" provides a useful comparison between the effects of microsurgical versus macrosurgical reversal of sterilisation.

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Sterilisation Reversal - Male
Vasectomy Reversal

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The Problem Submitted for ARIF to Advise Upon:

Is vasectomy reversal of proven effectiveness with regard to patency and fertility?

Reviews Identified

- Hendry WF. Vasectomy & Vasectomy Reversal. British Journal of Urology 1994;73:337-344

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Comments

The review identified is not systematic and comprises mainly case series. It does begin to answer both parts of the question posed. There is clearly a variation between the case series presented in respect to pregnancy/fertility which may be due to the different mixes of cases in the studies. The method of reversal and length of sterilisation prior to reversal need to be taken into account.

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Stroke

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The Problem Submitted for ARIF to Advise Upon:

Request from GRIP Committee to assist in the development of a GRIPKIT advising on evidence based purchasing of services for care of patients suffering stroke.

Reviews Identified

- Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy--I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. British Medical Journal. 1994;308(6921):81-106
- Atrial fibrillation investigators: Atrial fibrillation, aspirin, anticoagulation study; Boston area anticoagulation trial for atrial fibrillation study; Canadian atrial fibrillation anticoagulation study; Stroke prevention in atrial fibrillation study; Veterans affairs stroke prevention in nonrheumatic atrial fibrillation study. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Archives of Internal Medicine 1994;154:1449-1457
- Koudstaal P. Secondary prevention following stroke or transient ischemic attack in patients with nonrheumatic atrial fibrillation: anticoagulant therapy versus control. [revised 14 February 1995] In: Warlow C, Van Gijn J, Sandercock P (eds.) Stroke Module. In: The Cochrane Database of Systematic Reviews [database on disk and CDROM]. The Cochrane Collaboration; Issue 2, Oxford: Update Software; 1995. Available from BMJ Publishing Group, London.
- Stroke Unit Trialists' Collaboration. A systematic review of specialist multidisciplinary team (stroke unit) care for stroke inpatients. [revised 27 February 1995] In: Warlow C, Van Gijn J, Sandercock P (eds.) Stroke Module. In: The Cochrane Database of Systematic Reviews [database on disk and CDROM]. The Cochrane Collaboration; Issue 2, Oxford: Update Software; 1995. Available from BMJ Publishing Group, London.

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Comments

Five purchasing objectives were developed, consistent with the four systematic reviews of evidence above. Formal critical appraisal of the reviews is included in the GRIPKIT. *

This is an area prone to the need for regular updating as new information is continually becoming

available. In particular the Cochrane Reviews quoted are regularly updated.

* Getting to GRIPs with stroke. GRIPKIT 1996/97. Birmingham: West Midlands Regional GRIP Group, 1996. pp51. Contact NHS Executive, West Midlands Regional Office.

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Sudden Infant Death Syndrome

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence underpinning guidance on the prevention of sudden infant death syndrome?

Reviews Identified

- Creery D and Mikrogianakis A. Sudden Infant death syndrome. Clinical Evidence 2004: 10: 457-46

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Comments

This article appears to be the most comprehensive, up-to-date, single review of the topic and deals with the evidence base on key interventions that are recommended to parents, such as avoidance of prone sleeping, tobacco smoke, bed sharing and overheating etc.

The methodology with which Clinical Evidence articles are compiled appears to be robust and therefore the findings in this article can be relied upon as an accurate reflection of the current evidence base.

The article is self-explanatory and should as far as possible inform any guidance on this topic.

Request Carried Out: September 2004

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Surgery
Varicose Veins

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of surgery for CEAP Class 2 varicose veins with significant symptoms?

C - Clinical Signs (Grade 0-6), a= asymptomatic, s = symptomatic
E - Etiology (congenital, primary, secondary)
A - Anatomical distribution (superficial, deep, perforator veins)
P - Pathophysiological dysfunction (reflux + obstruction)

NICE Guidance

NICE Referral Guidance http://www.nice.org.uk/nicemedia/pdf/Referraladvice.pdf

Reviews Identified

- Abidia A, Hardy Sc. Surgery for deep venous incompetence (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software
- Rigby KA, Palfreyman SJ, Beverley C, Michaels JA. Surgery for varicose veins: use of tourniquet (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software
- Tisi PV, Beverley CA. Injection sclerotherapy for varicose veins (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software
- Pittler MH, Ernst E. Horse chestnut seed extract for chronic venous insufficiency (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software.
- Bazian Ltd. Varicose Veins. Clinical Evidence 2003;9:262-267
- Simpson S, Roderick P. Varicose veins. In: Health Care Needs Assessment. 3rd Series. Eds Stevens A, Raftery J, Mant J. Oxford: Radcliffe 2004

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Comments

Detailed feedback was provided on the specific question posed (further information is available on request).

The main purpose of this web-page is to highlight resources which would be of value in generally addressing the effectiveness of surgery for varicose veins (see above). A Regional Evaluation Report (REP) report on radio-frequency ablation for varicose veins has also recently been completed.

Request Carried Out: October 2003

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Teaching Hospitals

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The Problem Submitted for ARIF to Advise Upon:

What are the effects of teaching hospital status on patient outcomes?

In particular, is there any research looking at the effect of any given hospital changing from a non-teaching hospital to a teaching hospital?

Reviews Identified

None identified.

Trials Identified

None identified.

Other Literature Identified

No pre-post comparisons identified.

Several cross-sectional comparisons were identified, for example:

- Rosenthal GE, Harper DL, Quinn LM et al. Severity-adjusted mortality and length of stay in teaching and nonteaching hospitals. JAMA 1997;278:485-490
- Wolfe CD, Tilling K, Raju KS. Management and survival of ovarian cancer patients in south east England. Eur J Cancer 1997;33:1835-1840
- Richards MA, Wolfe CD, Tilling K et al. Variations in the management and survival of women under 50 years with breast cancer in the South East Thames region. British Journal of Cancer 1996;73: 751-757
- Lee-Feldstein A, Anton-Culver H, Feldstein PJ. Treatment differences and other prognostic factors related to breast cancer survival. Delivery systems and medical outcomes. JAMA 1994;271: 1163-1168
- Zimmerman JE, Shortell SM, Knaus WA et al. Value and cost of teaching hospitals: a prospective, multicenter, inception cohort study. Crit Care Med 1993;21:1432-1442

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Comments

The list of studies identified above is a selection of all those likely to be available, and we cannot guarantee that it is representative. With this proviso, the most notable feature is that there is variation in results between studies, to an extent that it is not completely clear that teaching hospital status confers any benefit at all. It is certainly extremely difficult to estimate what the general size of any effects might be. This suggests that a formal systematic review of the available cross-sectional studies would be useful to determine whether the observed variation in outcomes was mainly attributable to differences in study quality, chance or actual differences in the effect of teaching hospital status depending on the nature of the condition/s being examined.

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Telemedicine (Video Links)

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The Problem Submitted for ARIF to Advise Upon:

What is the evidence that telemedicine is useful in improving quality of care and in what circumstances is it most useful?

Question Reformulated

Recognising that telemedicine is not a single entity, but rather a collection of interventions where communication technology has been applied to solve a wide range of health service problems, this request focused on the use of video-links between general practitioners and hospital specialists, particularly in dermatology.

Reviews Identified

- Wootton R. Telemedicine: a cautious welcome. BMJ 1996;313:1375-77
- Balas EA, Jaffrey F, Kuperman GJ et al. Electronic communication with patients: evaluation of distance medicine technology. JAMA 1997;278(2):152-159
- Currell R, Urquhart C, Wainwright P, Lewis R. The impact of telemedicine as an alternative to face to face patient care, on professional practice and patient care (Cochrane Review). In: The Cochrane Library, Issue 3, 1998. Oxford: Update Software

Trials Identified

None specific to dermatology.

Other Literature Identified

List of potentially relevant studies to dermatology, supplied by R Currell, available on request to ARIF.

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Comments

The first review is not systematic in approach, but is well structured and provides useful background.

The second is systematic, but does not directly address the use of video-links in doctor to doctor contact. It does, however, remind us of the documented value of more traditional communication

innovations i.e. telephone, and that telemedicine may be just as valuable in improving patient-health care worker interactions, as doctor-doctor contact.

The third review is highlighted to indicate that a systematic review is in progress which will be invaluable in understanding the evidence-base of telemedicine projects.

Ahead of this few statements can be made with confidence. In general, it appears that there are reasonable grounds for believing that telecommunications technology can help solve health service problems, particularly where this technology is not blindly applied, but carefully tailored to a particular problem. Rigorous research evidence on the specific effects and effectiveness of newer technology, particularly using video-links in dermatology, appears to be lacking. These observations suggest that it would be reasonable for commissioners to support telemedicine projects involving new communication technology, but only as part of a rigorous evaluation.

This proviso might not apply to telemedicine projects using more established communication technology, where there may already be evidence of effectiveness for specific applications.

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Telepathology

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The Problem Submitted for ARIF to Advise Upon:

What evidence is there on the effectiveness of telepathology?

Reviews Identified

No systematic reviews were identified.

Primary Studies

No primary studies on the effectiveness of telepathology were available.

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Comments

We identified no systematic reviews on the evidence of effectiveness of telepathology.

We did identify a few primary studies, however some of these were not assessed due to being inaccessible, foreign language publications or conference abstracts. None of the primary studies we were able to obtain were on the effectiveness of telepathology but addressed comparisons of telepathology systems and the introduction of a telepathology service. Please contact ARIF for further details.

It is evident that there have been no robust assessments of the literature (i.e. systematic reviews) specifically relating to telepathology. Furthermore, there appears to have been few if any robust studies assessing of the effectiveness of telepathology.

Finally, readers should note that considerable literature exists on telemedicine, including systematic reviews.

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Tempero-mandibular Joint Replacements

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The Problem Submitted for ARIF to Advise Upon:

What is the effectiveness of Tempero-mandibular Joint (TMJ) replacements (e.g. Christiensen joint replacement system) in conditions causing severe degeneration and scarring (fibrosis)?

The TMJ is the joint which allows the jaw to open and close. Problems with the TMJ, such as clicking and discomfort are increasingly recognised – TMJ replacements are not appropriate for these conditions. In contrast, occasionally diseases such a rheumatoid arthritis can cause severe destruction of the TMJ resulting in extreme pain and/or inability to move the jaw if serious scarring has occurred.

Reviews Identified

There were no systematic reviews.

The most useful information which ARIF identified in lieu of this were the documents used to support the US Food & Drug Administration's (FDA) decision about conditional approval of newer versions of TMJ replacements in 2001. These documents are located at the following web addresses:

- http://www.fda.gov/cdrh/consumer/tmjupdate.html
- http://www.fda.gov/cdrh/mda/docs/p000023.html
- http://www.fda.gov/cdrh/pdf/p000023.html

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Comments

There are several different types of TMJ replacements. Some of the older versions caused severe adverse events and have been withdrawn. For the newer generation evidence of clinical effectiveness is limited to case-series. These provide some reassurance that benefits in terms of pain and improved jaw opening outweigh risks in those with the most severe forms of TMJ degeneration, but case-series are highly susceptible to bias.

This is presumably why the FDA approval in 2001 was provisional on further research and monitoring being undertaken by the manufacturers, and ARIF suggests that an approach where commissioning is contingent on TMJ replacement being part of a rigorous long-term evaluation would also be appropriate by commissioners in the NHS in 2003.

Assessment at a national level in the UK may clearly be of assistance. We have already alerted NICE's Interventional Procedures group to the possible need for action concerning TMJ replacements. Commissioners experiencing problems with this technology should contact NICE to reinforce the need for such an assessment www.nice.org.uk

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Very Low Brithweight

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The Problem Submitted for ARIF to Advise Upon:

What are the outcomes of VLBW infants?

Question Reformulated

Specifically ARIF was asked to comment on the strengths and weaknesses of a review (Escobar 1991) addressing this issue, and to identify whether there was a more up-to-date review.

Reviews Identified

- Escobar GJ, Littenberg B, Petitti DB. Outcome among surviving very low birthweight infants: a meta-analysis. Archives of Diseases in Childhood 1991;66:204-11
- Nashida H. Outcome of infants born preterm with special emphasis on extremely low birthweight infants. Ballieres Clinical Obstetrics & Gynecology 1993;7(3):611-631

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Comments

A detailed critical appraisal of the two articles is available on request from the ARIF office.

In brief, both reviews provide a useful starting point for examining research on the outcomes of VLBW infants. However, the conclusions should be interpreted cautiously because the review methods used in each case are likely to introduce bias. A particular concern is whether all relevant literature has been ascertained, leaving the reviews open to publication bias, the likelihood of which seems great - that is it seems highly plausible that centres experiencing, what they perceive to be poorer outcomes for their VLBW infants, will publish the results.

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Waiting Lists

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The Problem Submitted for ARIF to Advise Upon:

What is the availability of comparative research on the effects/effectiveness of alternative methods of dealing with patients waiting for operations and other procedures ("waiting lists")?

Reviews Identified

No reviews of comparative research identified.

Trials Identified

None identified.

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Comments

The conclusions on the availability of robust comparative research on this topic were based on the following search strategy:

1. Contact with established sources of local expertise - the HSMC, University of Birmingham
2. Bibliographic database searches of:
   MEDLINE 1992-97
   Healthstar 1993-97
   Cochrane Library (1997, Issue 2)
3. Interrogation of an in-house database of comparative studies identified from a hand-search of Medical Care on behalf of the Cochrane Collaboration on Effective Professional Practice (CCEPP).

Thus, although there are copious articles describing specific initiatives eg the New Zealand priority criteria project, it seems unlikely that comparative studies already exist addressing the effects/effectiveness of alternative methods of dealing with patients waiting for operations and other procedures ("waiting lists").

However, it should be noted that the topic does not lend itself to identification of literature through bibliographic databases alone because of:

- Inconsistent use of terminology
-

Failure to apply "standard" terms when actually addressing a relevant topic
- Research being undertaken by many different disciplines
- Research being published in many different outlets, including grey literature

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Search Strategy

STRATEGIES FOR IDENTIFYING REVIEWS OF RESEARCH EVIDENCE

Systematic Reviews

Cochrane Library

Consists of a regularly updated collection of evidence based medicine resources. Available at: http://www.library.nhs.uk/default.aspx

The Cochrane Library contains the following databases:

- Cochrane Database of Systematic Reviews (CDSR)
  Regularly updated systematic reviews prepared by the Cochrane Collaboration
- Database of Reviews of Effects (DARE)
  A collection of structured abstracts and bibliographic references of systematic reviews assembled by the Centre for Reviews and Dissemination (CRD). A more up to date version is available at: http://www.crd.york.ac.uk/crdweb/
- Health Technology Assessment Database (HTA)
  Bibliographic references and author abstracts by the International Network of Agencies for Technology Assessment (INAHTA) and other healthcare technology agencies. A more up to date version is available at: http://www.crd.york.ac.uk/crdweb/
- Cochrane Central Register of Controlled Trials (CENTRAL)
  Includes RCTs and other controlled studies identified by contributors to the Cochrane Collaboration. It includes many sources not included in bibliographic databases.

ARIF reviews Database

Database of reviews compiled by scanning current journals and internet sites. Available at the ARIF website: http://www.arif.bham.ac.uk/databases.shtml

CRD Research

A list of systematic reviews and other projects including CRD Reports.
http://www.york.ac.uk/inst/crd/projects_title_ascending.htm

HTAi Vortal

Compiled by Health Technology Assessment International, it provides links to resources relevant to HTA. The IRG Vortal allows searching across all public access web sites currently listed in the HTAi Vortal, inlcuding publications of HTA agencies and organisations.
http://www.htai.org/index.php?id=226

Many national and international organisations produce health technology assessments. Some sources are as follows:

- NIHR Health Technology Assessment Programme
  A national programme of research which is co-ordinated by the NHS Co-ordinating Centre for Health Technology Assessment. http://www.ncchta.org/
- National Institute for Health and Clinical Excellence (NICE)
  Issues evidence-based guidance to the NHS and patients on health technologies and clinical management of specific conditions. Guidance, technology appraisals, guidelines and recommendations on the use of interventional procedures used for diagnosis or treatment can be

obtained from: http://www.nice.org.uk

- West Midlands Health Technology Assessment Collaboration
  Peer reviewed rapid systematic reviews and cost-effectiveness analyses of health care interventions. http://www.wmhtac.bham.ac.uk/publications.shtml
- National Horizon Scanning Centre
  Provides advance notice to the DoH and national policy makers in England of selected new and emerging health technologies. Publications can be found at:
  http://www.pcpoh.bham.ac.uk/publichealth/horizon/index.htm
- NHS Quality Improvement Scotland
  The health technology assessment and health care quality improvement agency for Scotland.
  http://www.nhshealthquality.org/nhsqis/CCC_FirstPage.jsp
- Canadian Agency for Drugs and Technologies in Health (CADTH)
  Publications can be found at: http://www.cadth.ca/
- Swedish Council on Technology Assessment in Health Care (SBU)
  Publications can be found at: http://www.sbu.se/en
- Agency for Healthcare Research and Quality (AHRQ)
  Includes technology assessments, evidence based guidelines and Evidence Reports.
  http://www.ahcpr.gov
- Centre for Clinical Effectiveness, Monash Institute of Health Services Research
  Publications can be found at: http://www.mihsr.monash.org/cce

MEDLINE and EMBASE
Search strategies for identifying reviews in MEDLINE and EMBASE (and other databases) can be found at the InterTASC Information Specialists' Sub-Group (ISSG) Search Filter Resource:
http://www.york.ac.uk/inst/crd/intertasc/

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Evidence Summaries

Clinical Evidence
A compendium of evidence on the effects of clinical interventions which is regularly updated. It summarises the best available evidence. (A subscription is required for this service).
http://www.clinicalevidence.com/ceweb//index.jsp

Bandolier
A rich source of evidence based healthcare information.
http://www.medicine.ox.ac.uk/bandolier

ARIF
Provides an effectiveness information service to healthcare purchasing organisations in the UK West Midlands region. Summaries of the research evidence uncovered in response to requests received are available at: http://www.arif.bham.ac.uk

TRIP Database
A database which allows 'health professionals to easily find the highest quality material on the web'. Resources Include references to resources such as systematic reviews, guidelines and e-textbooks. http://www.tripdatabase.com/index.html

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Ongoing Research

UK Clinical Research Network Portfolio Database
This replaces the National Research Register as the source of Department of Health ongoing and completed research. http://www.ukcrn.org.uk/index.html

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Critical appraisal of:

Bertholet N, Daeppen J-B, Wietlisbach V, Fleming M, Burnand B. Reduction of Alcohol Consumption by Brief Alcohol Intervention in Primary Care. *Arch Intern Med.* 2005; **165:** 986-995

By Wendy Greenheld

Purpose of this appraisal

Critical appraisals attempt to identify the strengths and weaknesses of pieces of information, often research literature, to enable readers to apply that information within identified limits. There are two important sets of limits:

1) The INTERNAL validity of the information i.e. the focus/clarity of the question posed by the researcher/reviewer and the extent to which this facilitates a systematic, unbiased retrieval and summary of the available evidence.
a) The EXTERNAL validity of the information i.e. the relevance of the information provided by the researcher/ reviewer to the specific question posed by the reader.

This appraisal checklist is specifically designed for reviews of research information. It is based on: Oxman AD. Checklists for review articles. *BMJ* 1994; **309**: 648-51, updated version in Chalmers I, Altman DG (eds). Systematic reviews. London: BMJ Publishing; 1995. This has in turn been modified on the basis of ARIF's experience reviewing many different types of reviews of research retrieved in its responses to requests for research information on the effects/effectiveness of health care interventions.

Implicit in the checklist is our belief that the following elements of a review are particularly important:

- Clear, explicit statement of method (in sufficient detail that another person undertaking the same review might be able to repeat the processes and arrive at the same conclusion AND make an assessment of any bias that the reviewers may have introduced in their identification and summary of the research).
- Comprehensive ascertainment of all the available research literature relevant to the question the reviewer sets out to answer.
- Processing the ascertained literature in a way that reduces bias or makes explicit any bias that has been introduced, so that the reviewer or reader can make allowance for this in their conclusions.
- An appropriate numerical summary of the size of any effect (or equivalent), including its confidence intervals.

If a review met the first three general criteria it would be a 'systematic review'. If a review met all four criteria it would be a 'systematic review with meta-analysis'.

A further belief this checklist seeks to incorporate is that reviews generally provide the most important means of accessing and interpreting research information. As such they are a valuable resource that should only be discarded lightly. Accordingly, the checklist attempts to define a range of uses for any particular review in addition to those that would require a 'systematic review with meta-analysis'. These uses depend on whether the review has met some, rather than all of the above stated general criteria.

ARIF CRITICAL APPRAISAL CHECKLIST

1. Assessor's screening questions

1.On first reading is there sufficient information to make a detailed appraisal?
Yes

2.Is this a highly contentious review on a topic of clear importance to the health service?
Yes

3.Is there no obvious alternative review of better quality available?
No

2. In relation to what question is this review being appraised (target question)?

The target question seeks to ascertain the effectiveness of brief interventions delivered by healthcare professionals at all levels, that promote a healthy lifestyle or lifestyle change, for all types of patients, in any primary care setting.

3. Has a clear question been defined (review question)?

The authors sought to evaluate the efficacy of brief alcohol interventions aimed at reducing long-term alcohol use and related harm in individuals attending primary care facilities but not seeking help for alcohol-related problems.

The review appeared to be conducted within the following parameters:

Question type: Effects/effectiveness.

Population: Outpatients actively attending a primary health care centre or provider but not seeking help for alcohol related problems.

Intervention: 1) Interventions delivered individually that focused on alcohol consumption with a face-to-face component during the initial session.
2) Interventions defined as 'brief interventions' or 'motivational interventions' or reporting the use of feedback or advice to reduce alcohol consumption. No restrictions were applied to repeated interventions or reinforcement sessions.

Comparators: No intervention, usual care or up to 5 minutes of advice.

Outcomes: Change in alcohol intake, drinking status, health related quality of life or functional status, laboratory markers related to alcohol use, utilization of health care resources, or cost data.

The review question was sufficiently well defined to allow the review to be carried out in a systematic way i.e. it had internal validity. The review question also had external validity in that it focused on brief interventions to promote a healthier lifestyle (in this case relating to reduced alcohol use) for patients in primary care settings, thereby reflecting the main requirements of the target question.

4. What are the implications for the validity of the review given the type and range of study designs included?

The review aimed to provide a medium/high level of validity. It focused on randomised controlled trials thereby reducing the possibility of selection bias.

5. Were inclusion/exclusion criteria clearly stated?

The following inclusion/exclusion criteria were consistent with the review question:

Study design:

Included:

- Randomised controlled trials

Population/setting:

Included:

- Out-patients who were actively attending a primary health care centre or provider

Excluded:

- Patients seeking alcohol treatment
- Studies conducted in a hospital ward or in an emergency department
- Studies that selected patients by means of registers or patient lists or that specifically convened individuals for alcohol screening

Intervention:

Included:

- Interventions delivered individually that focused on alcohol consumption with a face-to-face component during the initial session.
- Interventions defined as 'brief interventions' or 'motivational interventions' or reporting the use of feedback or advice to reduce alcohol consumption. No restrictions were applied to repeated interventions or reinforcement sessions.

Outcomes:

Included:

- Change in alcohol intake, drinking status, health related quality of life or functional status, laboratory markers related to alcohol use, utilization of health care resources, or cost data.

6. Was the search strategy adopted likely to have missed many potentially relevant studies?

Sources searched:

- The Cochrane Central Register of Controlled Trials (from inception to January 2003)
- MEDLINE (from inception to January 2003)
- PsycINFO (from inception to January 2003)
- ISI Web of Science
- ETOH databases
- Bibliographies of retrieved references and previous reviews
- Authors bibliographic resources

The authors searched a comprehensive range of databases with no language restriction thereby reducing the possibility of publication bias. However the absence of details of the search terms used prevented the replication of this process.

7. How were inclusion/exclusion criteria applied?

Two reviewers independently assessed the titles and abstracts. Abstracts were selected for full text reading whenever selected by one or two authors. The same two authors then read the selected articles independently and applied the inclusion and exclusion criteria.

A flow diagram provided details of the number of studies retrieved and assessed at the various stages of the review process. Information on the number of studies excluded, along with reasons for their exclusion, was also provided.

In their search strategy the authors seemed to aim for a high level of sensitivity (i.e. they aimed to be as comprehensive as possible in the identification of all the 'included studies') and a medium level of precision with regard to the relevance of some of the studies initially located.

8. Was the validity of included studies assessed?

Two reviewers independently assessed trial quality, and awarded (by consensus if necessary) a quality score ranging from 0 (low) to 18 (high). The instrument used to assess trial quality was adapted from a validated scoring system. It evaluated randomisation, concealment of allocation, blinding in assessment of outcomes, attrition during follow-up, presence of an intention to treat analysis, clear definition of intervention, selection and performance bias, and presence of a measure of intervention exposure.

9. Was the process of data abstraction adequate?

For each selected article two reviewers independently performed data abstraction. Disagreements were discussed and submitted to a third author when necessary thereby reducing the possibility of selection bias. However details of the criteria applied were not reported.

10. Were the important steps in the review reproducible and bias free?

The potential reproducibility and validity of the review was influenced by the following factors:

- A comprehensive range of databases and additional sources were searched with no language restriction, increasing the validity of the review. However the absence of information on the search terms used reduced the reviews potential reproducibility.
- The inclusion/exclusion criteria were clearly stated and details of the number of studies retrieved and assessed at the various stages of the process were clearly outlined in the form of a flow diagram.
- Study quality was rigorously assessed for potential sources of bias.
- Two reviewers independently extracted the data, thereby reducing the possibility of selection bias. However the lack of information on the items extracted reduced the reproducibility of the review.

11. What was (were) the relevant and justifiable review bottom line(s) - as stated in the review?

Trial characteristics

- 19 trials conducted between 1987 and 2002 were identified.
- Trial size ranged from 80 to 774, with 5,639 subjects in total.
- All 19 trials included some advice being given to the brief alcohol intervention (BAI) group.
- 18 of the 19 trials reported the use of feedback regarding alcohol consumption levels and/or adverse effects of alcohol consumption.
- Intervention length ranged from 5 to 45 minutes.
- In 10 trials the brief alcohol intervention was repeated or included a booster session, in 4 trials a follow-up visit was offered.
- 13 trials had no intervention or usual care as the control group, in 6 trials the control intervention consisted of up to 5 minutes of advice.
- Length of follow-up ranged from 6-48 months.
- Trial quality scores ranged from 5 to 14 with a mean of 9.6 (a 10-point score was arbitrarily determined to be the cut off between 'high quality' and 'low quality'). A low quality rating resulted principally from inadequate randomisation or insufficient reporting of concealment of allocation.
- High quality trials were more likely than low quality trials to report statistically significant positive effects of intervention (χ^2 =3.9, p=0.048).

Results

- 17 trials reported a measure of alcohol consumption of which 8 trials reported a significant effect of intervention.
- 10 trials reporting data for change in alcohol consumption with either 6 or 12 months follow-up were included in a meta-analysis.
- The adjusted intention to treat analysis showed a mean difference of –38g ethanol/week (95%CI: -51 to –24g/week) in favour of the intervention group (1 unit of alcohol = 8g).
- A significantly greater effect size was found in trials published after 1996 than those published earlier (effect: -54.8 vs 6.6, p= 0.02).
- 8 trials assessed a reduction in alcohol intake using laboratory values: 7 assessed γ-glutamyltransferase levels, 5 assessed mean corpuscular volume, 3 assessed aspartate aminotransferase and alanine aminotransferase, and 1 assessed carbohydrate deficient transferring.
- 2 trials reported a statistically significant difference in favour of the treatment group. One trial reported an improvement of aspartate aminotransferase and one

an improvement of alanine amino transferase. The remaining trials found the intervention had no significant effect on laboratory values in comparison with the control.

- 3 trials reported health care utilisation measures to test the impact of BAI on health care costs. One trial found a lower number of medical visits by the treatment group than by the control group. One found no significant differences in emergency department visits between the groups during 6 and 12 months after BAI but significantly fewer emergency department visits in the BAI group at 48 months and significantly fewer hospital days in the BAI group at 6, 12 and 48 months. One trial found no significant differences in health care utilization during the 2 years after BAI.
- One trial performed a cost-benefit analysis comparing the reduced costs associated with reduced hospitalisations, emergency department visits, motor vehicle accidents or criminal events with the overall cost of screening, assessments and interventions. The cost-benefit ratio for brief alcohol intervention was 4.3:1 from a medical perspective and 39:1 from a societal perspective.
- 9 trials reported data related to mental and physical health perception status, well being and other problems. There were significant improvements in 9 of the 21 measures reported for the treatment group in comparison with the control group but no significant differences in the remaining 12 measures.
- One trial examined mortality and found a significant reduction in the number of deaths amongst the treatment group compared with the control group at 36 months. However this effect disappeared by 48 months.

12. Was the review up-to-date?

The review was published in 2005 and searches were conducted up to January 2003.

13. General comments

This well documented recently published systematic review and meta-analysis provides an up to date evaluation of the efficacy of brief alcohol interventions, for patients attending primary care facilities but not actively seeking help for alcohol related problems, in reducing long-term alcohol use and related harm.

The meta-analysis indicates that brief alcohol interventions are effective for both men and women in reducing alcohol consumption at 6 and 12 months. This is supported by the homogeneity of the selected studies and the clear effect shown in high quality studies.

6 of the 7 trials that reported a significant improvement in BAI groups compared with control groups assessed an intervention lasting between 5 and 15 minutes. Also 6 of the 7 trials reported the use of written materials and proposed a repeated intervention either routinely or after a decision by the patient. However whilst the authors advised that all intervention included a feedback and advice component, precise details were not reported.

14. Recommendation for implementation of this review by purchasers

The results would appear to lend broad support for the provision of brief advice on alcohol consumption levels in primary care settings. It appears that brief alcohol interventions lasting from 5 to 15 minutes accompanied by written material and the opportunity for the patient to schedule a follow-up visit have the potential to significantly reduce alcohol consumption compared with either no intervention, usual care or less than 5 minutes intervention. To tease out the most beneficial elements of the intervention itself however further research is needed.

Critical appraisal of:

Carlberg B, Samuelsson O, Lindholm LH. Atenonol in hypertension: is it a wise choice? *Lancet* 2004; **364:** 1684-89

By Wendy Greenheld and Chris Hyde

Purpose of this appraisal

Critical appraisals attempt to identify the strengths and weaknesses of pieces of information, often research literature, to enable readers to apply that information within identified limits. There are two important sets of limits:

1) The INTERNAL validity of the information i.e. the focus/clarity of the question posed by the researcher/reviewer and the extent to which it facilitates a systematic, unbiased retrieval and summary of the available evidence.
2) The EXTERNAL validity of the information i.e. the relevance of the information provided by the researcher/ reviewer to the specific question posed by the reader.

This appraisal checklist is specifically designed for reviews of research information. It is based on: Oxman AD. Checklists for review articles. *BMJ* 1994; **309**: 648-51, updated version in Chalmers I, Altman DG (eds). Systematic reviews. London: BMJ Publishing; 1995. This has in turn been modified on the basis of ARIF's experience reviewing many different types of reviews of research retrieved in its responses to requests for research information on the effects/effectiveness of health care interventions.

Implicit in the checklist is our belief that the following elements of a review are particularly important:

- Clear, explicit statement of method (in sufficient detail that another person undertaking the same review might be able to repeat the processes and arrive at the same conclusion AND make an assessment of any bias that the reviewers may have introduced in their identification and summary of the research).
- Comprehensive ascertainment of all the available research literature relevant to the question the reviewer sets out to answer.
- Processing the ascertained literature in a way that reduces bias or makes explicit any bias that has been introduced, so that the reviewer or reader can make allowance for this in their conclusions.
- An appropriate numerical summary of the size of any effect (or equivalent), including its confidence intervals.

If a review met the first three general criteria it would be a 'systematic review'. If a review met all four criteria it would be a 'systematic review with meta-analysis'.

A further belief this checklist seeks to incorporate is that reviews generally provide the most important means of accessing and interpreting research information. As such they are a valuable resource that should only be discarded lightly. Accordingly, the checklist attempts to define a range of uses for any particular review in addition to those that would require a 'systematic review with meta-analysis'. These uses depend on whether the review has met some, rather than all of the above stated general criteria.

ARIF CRITICAL APPRAISAL CHECKLIST

1. Assessor's screening question

On first reading is there sufficient information to make a detailed appraisal?
Yes

2. In relation to what question is this review being appraised (target question)?

The paper is being appraised within the context of the question posed by the authors i.e. the effect of atenolol on cardiovascular morbidity and mortality in hypertensive patients.

3. Has a clear question been defined (review question)?

The authors aim to systematically review the effect of atenolol on cardiovascular morbidity and mortality in hypertensive individuals. The review question thus appears to focus on what are traditionally regarded as the consequences of hypertension.

The review question is sufficiently well defined to allow the review to be carried out in a systematic way in terms of an assessment of the effect of atenolol on cardiovascular morbidity and mortality in hypertensive individuals i.e. it has internal validity.

The extent to which reductions in hypertension per se form part of the review rationale it is not made clear. Changes in blood pressure are reported on and discussed by the authors however the effect of atenolol in reducing hypertension does not appear to be one of the reviews formally stated aims.

The review and meta-analysis appear to be executed within the following parameters:

Question type:	effects/effectiveness
Population:	patients with primary hypertension
Intervention:	atenolol, alone or as the first-line drug
Comparators:	(i) placebo
	(ii) other anti-hypertensive drugs
Outcomes:	all-cause mortality, cardiovascular mortality, myocardial infarction, stroke

The review focuses specifically on atenolol therefore its findings are only relevant (externally valid) for this specific preparation of β-blocker and cannot be extended to β-blockers in general.

4. What are the implications for the validity of the review, given the type and range of study designs included?

Ostensibly the review seems to provide a high level of validity as it focuses exclusively on randomised controlled trials. However the randomisation methods of the included trials, for example the extent to which randomisation was concealed, are not reported therefore selection bias cannot be ruled out.

5. Were inclusion/exclusion criteria clearly stated?

The inclusion criteria reflect the review question encompassing the following points:

Study design: randomised controlled trials
Population: patients with primary hypertension
Intervention: atenolol
Outcome: cardiovascular morbidity and mortality

More specific inclusion criteria for the meta-analyses are:

1. primary hypertension
2. randomised controlled trial
3. predefined criteria of myocardial infarction, stroke and cardiovascular death
4. atenolol alone as the first-line drug in one of the treatment arms

No exclusion criteria are reported.

6. Was the search strategy adopted likely to have missed many potentially relevant studies?

Sources searched:

- The Cochrane Library
- Medline
- Textbooks
- Personal communication with established researchers in hypertension

Database search terms used:

- atenolol (MESH) OR atenolol 'text' AND cerebrovascular disorders (MESH) OR myocardial infarction (MESH)
- atenolol AND systematic
- beta-blocker AND hypertension AND systematic

The scope of the search was extremely narrow and many details were not discussed:

- only two databases searched: major databases such as Embase were not accessed
- sections searched in the Cochrane Library were not reported
- dates used for the Cochrane Library & Medline searches were not reported
- database search terms whilst covering the main facets of the question were not comprehensive
- use of a language restriction was not reported
- names of the textbooks accessed were not reported
- no follow-up from reference lists was undertaken
- no search for unpublished studies was made

The search strategy was consistent with the review question. However the brevity of the search strategy employed raises serious doubts that all potentially relevant studies have been accessed. This in turn raises concerns regarding the validity and generalisability of the reviews findings.

7. How were inclusion/exclusion criteria applied?

Of the 17 randomised controlled trials identified by the search 9 were excluded for the following reasons:

- atenolol was one of two or more drug alternatives in the same treatment arm (5 studies)
- multi-drug strategies were compared rather than individual agents (1 study)
- atenolol was the add-on drug (3 studies)

The authors did not provide any information on the number of potentially relevant RCT's identified to yield the final 8 included studies and 9 excluded studies. This omission undermines the reproducibility of the review and raised questions of possible selection bias.

8. Was the validity of included studies assessed?

No assessment of the validity of the included studies was reported. A quality assessment does not appear to have been undertaken. Consequently the sensitivity of the conclusions to internal validity has not been assessed.

9. Was the process of data abstraction adequate?

No information was provided on the data abstraction process.

10. Were the important steps in the review reproducible and bias free?

The main steps of the review contained noticeable flaws:

- The search for all potentially relevant studies was poorly reported and too narrow in its focus thus raising doubts about the validity and generalisability of the reviews conclusions.
- No exclusion criteria were reported and the application of the inclusion criteria and steps taken to identify potentially relevant studies were unclear. These factors undermined the reproducibility of the review and raised concerns about possible selection bias.
- An assessment of the validity of the included studies was not reported.
- The data abstraction process was not reported, again negating the reproducibility of the review.

11. What was (were) the relevant and justifiable review bottom line(s) - as stated in the review?

Of the 8 included studies, 4 compared atenolol with placebo or no treatment and 5 compared atenolol with other anti-hypertensive drugs (1 study using placebo & other anti-hypertensive drugs as comparators). Meta-analyses were performed on these two subsets. Both meta-analyses assessed all-cause mortality, cardiovascular mortality, myocardial infarction and stroke. The mean blood pressure change (systolic/diastolic mmHg) with atenolol versus its comparator was also reported for the individual studies. However this data did not form part of the meta-analysis.

The main outcomes for atenolol vs placebo/ no treatment were as follows:

- All-cause mortality (n = 4)
  Relative risk (RR) 1.01 (95% CI 0.89, 1.15)
  Test for heterogeneity χ^2 = 2.63, p = 0.45

- Cardiovascular mortality (n = 4)
  RR 0.99 (95% CI 0.83, 1.18)
  Test for heterogeneity χ^2 = 3.51, p = 0.32

- Myocardial infarction (n = 4)
  RR 0.99 (95% CI 0.83, 1.19)
  Test for heterogeneity χ^2 = 1.80, p = 0.62

- Stroke (n = 4)
  RR 0.85 (95% CI 0.72, 1.01)
  Test for heterogeneity χ^2 = 3.74, p = 0.29

- There were major differences in blood pressure lowering ranging from –4.0/-3.0 to -18.0/-11.0 (mm Hg)

The results of the analysis therefore suggest that the ostensibly beneficial impact of reduced hypertension does not lead to improved cardiovascular outcomes.

The main outcomes for atenolol vs other antihypertensive drugs were as follows:

- All-cause mortality (n = 5)
  RR 1.13 (95% CI 1.02, 1.25)
  Test for heterogeneity χ^2 = 3.45, p = 0.49

- Cardiovascular mortality (n = 4)
  RR 1.16 (95% CI 1.00, 1.34)
  Test for heterogeneity χ^2 = 6.66, p = 0.08

- Myocardial infarction (n = 4)
  RR 1.04 (95% CI 0.89, 1.20)
  Test for heterogeneity χ^2 = 8.66, p = 0.03

- Stroke (n = 4)
  RR 1.30 (95% CI 1.12, 1.50)
  Test for heterogeneity χ^2 = 1.21, p = 0.63

- There were no major differences in blood pressure lowering

The results of the analysis suggest that whilst atenolol has a similar impact on hypertension to other anti-hypertensive drugs it is less effective in improving clinical outcomes such as cardiovascular mortality and stroke.

12. Was the review up-to-date?

Studies published up to 2002 are included in the review. However it is unclear whether or not the review is up-to-date as the authors did not report the periods over which the Cochrane Library and Medline searches were undertaken.

13. General comments

The general quality of the review is poor:

- It does not contain a clear explicit statement of method. Insufficient information is reported to allow another person to repeat the same review processes and reach the same conclusions.
- The search strategy employed appears to be too narrow to access all potentially relevant studies thus raising serious doubts about the validity of the review.
- The methods used to process the available literature are inadequately explained making it difficult to rule out the possibility of bias.
- The meta-analyses provide appropriate numerical summaries of the size of any effect. The meta-analysis of the 4 studies comparing atenolol with placebo or no treatment appears appropriate. However the rationale for the meta-analysis comparing atenolol with other anti-hypertensive drugs is less clear given the different preparations used and the heterogeneity displayed in some of the results.

Given the discrepancies outlined the review's conclusions that atenolol may not be a suitable drug for hypertensive patients are not convincing.

14. Recommendation for implementation of this review by purchasers

This is a thought provoking review. However methodological flaws in important areas suggest a repeat of the meta-analysis would be reasonable if further action were to be anticipated. We feel the effect of atenolol should be viewed alongside other β blockers however we could not find an existing review which did this. Freemantle et al[1] have published a systematic review assessing the effectiveness of β blockers in short term treatment after acute myocardial infarction and in longer term secondary prevention, and we should like to see a similar review for β blockers in hypertension. There appears to be a protocol for a Cochrane review[2] which will quantify the effects of β blockers on morbidity and mortality in adults with hypertension and compare these effects with other classes of anti-hypertensive drugs.

In conclusion this is an interesting observation which should be regarded as a hypothesis requiring further testing.

References

1. Freemantle N, Cleland J, Young P, Mason J, Harrison J. β Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999; **318:** 1730-37
2. Volmink J, Bradley H, Maroney R, Mbewu A, Opie L. Betablockers for hypertension (Protocol). *The Cochane Database of Systematic Reviews* 1998; Issue 4. Art No: CD002003. DOI: 10.1002/14651858.CD002003. This version first published online: 26 October 1998 in Issue 4, 1998

Critical appraisal of:

Ammerman A, Pignone M, Fernandez L, Lohr K, Jacobs AD, Nester C et al. 18. Counseling to promote a healthy diet. In: Guide to clinical preventive services, 3rd ed. Evidence syntheses, formerly systematic evidence reviews. HSAT, Health Services/Technology Assessment Text; 2000 [cited 29th June 2006]
Available from (http://www.ncbi.nih.gov/books/bv.fcgi?rid=hstat3.chapter.3509)

By Wendy Greenheld

Purpose of this appraisal

Critical appraisals attempt to identify the strengths and weaknesses of pieces of information, often research literature, to enable readers to apply that information within identified limits. There are two important sets of limits:

1) The INTERNAL validity of the information i.e. the focus/clarity of the question posed by the researcher/reviewer and the extent to which this facilitates a systematic, unbiased retrieval and summary of the available evidence.
a) The EXTERNAL validity of the information i.e. the relevance of the information provided by the researcher/ reviewer to the specific question posed by the reader.

This appraisal checklist is specifically designed for reviews of research information. It is based on: Oxman AD. Checklists for review articles. *BMJ* 1994; **309**: 648-51, updated version in Chalmers I, Altman DG (eds). Systematic reviews. London: BMJ Publishing; 1995. This has in turn been modified on the basis of ARIF's experience reviewing many different types of reviews of research retrieved in its responses to requests for research information on the effects/effectiveness of health care interventions.

Implicit in the checklist is our belief that the following elements of a review are particularly important:

- Clear, explicit statement of method (in sufficient detail that another person undertaking the same review might be able to repeat the processes and arrive at the same conclusion AND make an assessment of any bias that the reviewers may have introduced in their identification and summary of the research).
- Comprehensive ascertainment of all the available research literature relevant to the question the reviewer sets out to answer.
- Processing the ascertained literature in a way that reduces bias or makes explicit any bias that has been introduced, so that the reviewer or reader can make allowance for this in their conclusions.
- An appropriate numerical summary of the size of any effect (or equivalent), including its confidence intervals.

If a review met the first three general criteria it would be a 'systematic review'. If a review met all four criteria it would be a 'systematic review with meta-analysis'.

A further belief this checklist seeks to incorporate is that reviews generally provide the most important means of accessing and interpreting research information. As such they are a valuable resource that should only be discarded lightly. Accordingly, the checklist attempts to define a range of uses for any particular review in addition to those that would require a 'systematic review with meta-analysis'. These uses depend on whether the review has met some, rather than all of the above stated general criteria.

ARIF CRITICAL APPRAISAL CHECKLIST

1. Assessor's screening questions

1.On first reading is there sufficient information to make a detailed appraisal?
Yes

2.Is this a highly contentious review on a topic of clear importance to the health service?
Yes

3.Is there no obvious alternative review of better quality?
No

2. In relation to what question is this review being appraised (target question)?

The target question seeks to ascertain the effectiveness of brief interventions delivered by healthcare professionals at all levels, that promote a healthy lifestyle or lifestyle change, for all types of patients, in any primary care setting.

3. Has a clear question been defined (review question)?

The authors aimed to examine the effectiveness of primary care counselling to promote a healthy diet and assist the US Preventive Services Task Force in making recommendations on this topic. Their comprehensive review was developed around an analytic framework that contained the following key questions:

1. What is the relationship between dietary patterns and health outcomes?
2. What are valid, feasible tools for assessment of dietary risk?
3. What are the adverse effects of dietary assessment?
4. **What is the efficacy of primary care counselling and dietary behaviour change interventions?**
5. What are the adverse effects and associated costs of dietary behaviour intervention?
6. Which of the following system influences facilitate or impede dietary intervention:
   - Features of the health care team
   - Features of the practice setting
   - Features of the health care system
7. Can dietary supplements improve nutrition in patients identified as undernourished?

The review questions were sufficiently well defined to allow the review to be carried out in a systematic way i.e. they had internal validity. Whilst some elements considered in this review are beyond our remit key question no. 4, which seeks to ascertain the efficacy of primary care counselling and dietary behaviour change interventions, is broadly relevant to our target question (i.e. externally valid). Our appraisal has therefore focused on this section of the report.

4. What are the implications for the validity of the review given the type and range of study designs included?

The review aimed to provide a medium/high level of validity by focusing on randomised controlled trials (RCT's) of dietary counselling interventions.

5. Were inclusion/exclusion criteria clearly stated?

The following inclusion/exclusion criteria appeared consistent with the review question:

Inclusion criteria:

- English language studies.
- RCT's with baseline and follow-up measures of relevant dietary outcomes.
- Studies evaluating nutrition interventions delivered to primary care patients (either within a primary care setting or after referral).
- Studies that assessed the impact of dietary change for patients with chronic disease (e.g. raised cholesterol).
- Studies evaluating physician training programmes to improve physician counselling practices were included if a control or comparison group was part of the evaluation and if the counselling approach tested was relevant to the primary care setting.
- Studies with a retention rate of at least 50%.
- Studies with least 3 months follow-up.

Exclusion criteria:

- Studies of patients with a diagnosed illness that:
  1. might directly effect their dietary intake (e.g. cancer)
  2. required a specialised diet (e.g. renal disease)
  3. required entry into the studies immediately following a life-threatening, disease related event (e.g. hospitalisation for acute myocardial infarction).

- Studies that reported physiologic measures or biomarkers associated with dietary change (e.g. serum vitamin levels) but no direct measure of diet behaviour.

6. Was the search strategy adopted likely to have missed many potentially relevant studies?

The following strategy was adopted to find articles relevant to the questions about dietary assessment and the effectiveness of diet counselling in the primary care setting:

Sources searched:

- Medline (from 1966 to 2001)
- Reference lists of the relevant articles reviewed
- Experts in the field contacted

Search strategy:

Medical Subject Heading (MeSH) terms were used for the following categories:

- Diet: 'diet', 'nutrition', food frequency', 'food habits', dietary assessment', 'diet records', 'diet surveys', 'nutrition assessment'
- Primary care: 'family practice', 'primary health care', 'primary care setting'
- Counselling: 'counseling', 'dietary counseling'(textword), 'diet counseling' (textword), 'nutrition counseling' (textword)

The search strategy employed was consistent with the research question. However although a good range of different sources were accessed a search of some of the other major databases

i.e. Embase would have provided added value, as potentially relevant trials not indexed in Medline may have been missed. A further drawback was the restriction of the search to papers published in English raising concerns about publication bias.

7. How were inclusion/exclusion criteria applied?

In their search strategy the authors seemed to aim for a high level of sensitivity (i.e. they aimed to be as comprehensive as possible in the identification of all of the 'included studies') and a medium level of precision with regard to the relevance of some of the studies initially located.

Senior investigators reviewed titles and abstracts to identify which full manuscripts to review and made final decisions about inclusion or exclusion. A flow diagram gave details of the number of articles retrieved and assessed at the various stages of the process. Details of studies excluded and the reasons for their exclusion were also noted.

8. Was the validity of included studies assessed?

The internal quality of the included trials was graded as good or fair based on allocation concealment, blinding of outcomes assessment, and completeness of follow-up.

The external validity of the included trials was also assessed. Studies were classified as having low, medium, or high external validity based on representativeness of the providers and patient population as well as the feasibility of replicating the intervention in a primary care setting without additional research infrastructure.

9. Was the process of data abstraction adequate?

Senior investigators, assisted by nutrition doctoral students, reviewed the articles chosen for inclusion and abstracted selected information onto evidence tables. It was unclear whether any independent checks were performed, raising the possibility of selection bias.

10. Were the important steps in the review reproducible and bias free?

The potential reproducibility and validity of the review was influenced by the following factors:

- The search strategy employed was generally good but a search of some of the other major databases would increase its validity. Also the restriction to English language reports raises some concerns about the possibility of publication bias.
- Details of the inclusion/exclusion criteria adopted and the methods used to apply them were well documented. The overall transparency of the review also benefited from the inclusion of a flow diagram that gave details of the number of studies retrieved and assessed at the various stages of the process.
- Study quality was assessed for potential sources of selection and assessment bias.
- It was unclear whether or not the data extraction process included any independent checks, raising some concerns about selection bias.

11. What was (were) the relevant and justifiable review bottom line(s) - as stated in the review?

Our appraisal of the results focused on the authors' report of the evidence on the efficacy of primary care counselling and dietary behaviour change interventions (key question no. 4).

The review provided a general overview of all types of dietary counselling offered within the following settings:

1. Primary care providers (counselling done by a physician, physician assistant, nurse practitioner, or registered nurse within the primary care setting).
2. Primary care clinic referral (referral within a primary care practice, such as a registered dietitian or nurse employed by the clinic).
3. Research clinic.
4. Mailings or computer-generated messages and intervention materials.

29 studies were identified of which 12 examined more than 1 nutrient or food group. 25 trials examined dietary fat, 11 trials examined fruit and vegetable intake intakes, and 7 trials examined dietary fibre. Based on randomised design, high retention rates, and the use of appropriate outcome measures the included studies were judged to be of good or fair quality.

Two senior reviewers independently rated the intensity of the dietary intervention as low, medium or high based on the number and length of counselling contacts, the magnitude and complexity of educational materials provided and the use of supplemental interventional elements, such as support group sessions or cooking classes. Low-intensity interventions generally involved 1 contact lasting less than 30 minutes. High-intensity interventions involved greater than 6 contacts, each lasting at least 30 minutes. Medium intensity was in between low and high.

Whilst our remit was to assess the effect of brief dietary interventions within a primary care setting we felt the report made some interesting comparisons on the relative effectiveness of interventions of different intensity and have therefore included these results.

Results:

Effect of counselling on intake of total and saturated fat

- 25 studies examined the effect of counselling on total fat and saturated fat intakes.

- For outcomes stated as the percentage of calories from total or saturated fat the following effect sizes were defined:
  Large: >10% change in total fat or >3% change in saturated fat
  Medium: >5% to 10% change in total fat or >1.3% to 3% change in saturated fat
  Small: 0% to 5% change in total fat or 0% to 1.3% change in saturated fat

- 17/25 studies examined the effect of counselling on the percentage of calories derived from total fat:

  6 studies reported large effects on change (in at least 1 element of the study); 7 studies reported medium effects (in at least 1 arm or outcome measure); 1 study achieved a medium effect on the DINE fat score; 13 studies (one with 2 published articles) achieved small effects on dietary fat (in at least one part of the study).

- 11/25 studies examined the effect of counselling on the percentage of calories derived from saturated fat and reported net differences in percentage reductions ranging from 0.9% to 5.3%. Three other studies showed small or medium changes in other measures of saturated fat

- Five of the 25 studies examined low-intensity interventions.

  2 studies assessed interventions delivered by primary care providers:
  - One trial assessed a 5-minute intervention in which a registered nurse provided an introduction to self-help materials with follow-up 10days later. There was a no intervention control group.
  - One trial assessed an intervention in which a GP provided a 3-minute introduction to a self-help booklet and then sent a reminder letter. The control group was not described.
  - Both trials reported a small effect size.

  1 study assessed interventions following referral within the primary care practice:
  - The study population were low income, pregnant women of Mexican descent in a prenatal clinic. The intervention comprised of nutrition education classes delivered by a Spanish-speaking registered nurse, however the intervention duration was not reported. The control group received usual care. A small effect size was reported.

  2 studies assessed interventions comprised of mailings and computer generated messages:
  - One study assessed tailored and non-tailored messages mailed to the patients home following completion of a self administered survey, the control group also completed self-administered surveys but did not receive any messages. A medium effect size was reported for the group receiving tailored messages and a small effect size was reported for the group receiving the non-tailored messages.
  - One study assessed the effect of mailed advice from a doctor suggesting the patients visit their GP. The control was no intervention. A small effect size was reported.

Effect of counselling on fruit and vegetable intake

- 11 studies examined the effect of counselling on fruit and vegetable intake.

- The recommended intake of fruit and vegetables is 5 servings/day.

- Effect sizes for studies reporting results in terms of increases in daily servings were defined as follows:
  Large: >1 serving
  Medium: 0.2 to 0.9 servings
  Small: <0.2 servings

- Of the 8 studies that reported results in terms of increases in daily servings, 1 reported a small effect, 5 reported a medium effect and 2 reported a large effect.

- 2 studies used the percentage of subjects increasing their consumption of fruits or vegetable above a defined threshold as the main outcome variable. Both found little or no change in intake with net increases of 0 to 8 percentage points in the proportion of subjects meeting the defined goals. The reviewers therefore classified this as a small effect size.

- 1 study presented grams of fruit and vegetables per day as their outcome measure in a 2-arm study. Group education alone achieved a 20g/day increase in fruit and vegetable intake (small effect). By contrast, group education plus tailored messages resulted in a 99g/day increase (medium effect).

- Four of the 11 studies examined low-intensity interventions delivered by primary care providers:

  The 4 studies all assessed interventions comprised of mailings and computer generated messages:
  - One study assessed tailored and non-tailored messages mailed to the patients home following completion of a self administered survey, the control group also completed self-administered surveys but did not receive any messages. A small effect size was reported for the groups receiving both tailored messages and non-tailored messages.
  - Two studies appraised a self-administered assessment mailed to the patients home followed up with a mailing of tailored messages. The control group did not receive a newsletter. Medium effect sizes were reported for the intervention groups in both studies.
  - One study appraised a self-administered assessment mailed to the patients home followed up with a mailing of non-tailored messages. The control group did not receive a newsletter. A medium effect size was reported.

Effect of counselling on fibre intake

- 7 studies examined the effect of counselling on fibre intake.

- In the USA the currently recommended daily fibre intake is 20 to 30g/day and the average intake is 15g/day.

- UK recommendations for fibre are 18g/day (individual range 12 to 24g/day) for adults.

- Effect sizes were defined as follows:
  Large: >6g/day increase
  Medium: 1 to 6g/day increase
  Small: <1g/day change in consumption

- 4 studies reported increases in the amount of fibre consumed ranging from 0.6 to 3g/day (classified as a medium effect size by the reviewers). 2 studies reported small effect sizes. 1 study which reported grams of fibre consumed per 1,000 kcals had only a small effect size.

- Two of the 7 studies examined low-intensity interventions delivered by primary care providers:
  - One trial assessed a 5-minute intervention in which a registered nurse provided an introduction to self-help materials with follow-up 10days later. The control group received a baseline interview only.
  - One trial assessed an intervention in which a GP provided a 3-minute introduction to a self-help booklet and then sent a reminder letter. The control group was not described.
  - Both trials reported a small effect size.

Factors affecting response to dietary counselling

Risk status of patients:

- Across all nutrient groups, studies of patients at average or low risk generally reported small to medium effects on dietary behaviour.
- Studies of patients at moderate risk generally achieved small to medium levels of dietary change, but the change tended to depend on the intensity of the intervention.
- Studies of high-risk patients were somewhat more likely to achieve large effects than studies of non-high-risk patients, but many studies of high-risk patients still only produced only small or medium changes.

Intensity of the intervention:

- Nearly all studies achieving a large effect size fell into the high-intensity intervention category.
- Studies combining very intensive interventions with high-risk patients tended to show the greatest impact.
- Most medium-intensity studies achieved small to medium effects.
- Low-intensity counselling interventions achieved only small to medium effects on dietary behaviour.

Combined effect of risk and intensity:

- Across all risk groups, more intensive interventions were somewhat more likely to produce larger changes in behaviour than less intensive interventions.
- Studies conducted in high-risk patients were also more likely to be of higher intensity and hence more effective.
- Low-intensity interventions delivered to average-risk patients in primary care settings produced only small changes.

12. Was the review up-to-date?

The review was published in 2002 and searches were conducted up to 2001.

13. General comments

The review begins with an informative overview of the evidence linking dietary patterns with important health outcomes. It focuses on a range of different dietary elements: fat, fruit & vegetables, legumes (beans & peas), wholegrains & fibre, fish or fish oils, sodium, potassium, and calcium. It then examines the feasibility of using dietary assessment instruments in a primary care setting before assessing the efficacy of counselling and dietary behaviour change interventions.

This well conducted systematic review provides a medium/high level of validity by focusing on RCT's of dietary counselling interventions. The complex nature of dietary counselling for patients in primary care is highlighted. Any interpretation of the data is effected by numerous factors such as differences in the risk status of the patients, the intensity of the intervention, the dietary elements targeted, and the outcome measures used.

Our appraisal has concentrated on the authors' report of the evidence on the efficacy of primary care counselling and dietary behaviour change interventions and sought more specifically to highlight evidence relating to low-intensity interventions.

14. Recommendation for implementation of this review by purchasers

The evidence presented in this report indicates low-intensity interventions delivered to average-risk patients in primary care settings produce only small changes in dietary behaviour. The evidence however is based on the results of only two trials that each assessed changes in dietary fat and fibre. To-date evidence on the effectiveness of brief advice on dietary behaviour would therefore seem insufficient to either support of refute its routine use in primary care.

Critical appraisal of:

Lawlor DA, Hanratty B. The effect of physical activity advice given in routine primary care consultations: a systematic review. [Review] [54 refs] *Journal of Public Health Medicine*. 2001; **23(3)**: 219-26

By Jayne Wilson

Purpose of this appraisal

Critical appraisals attempt to identify the strengths and weaknesses of pieces of information, often research literature, to enable readers to apply that information within identified limits. There are two important sets of limits:

1) The INTERNAL validity of the information i.e. the focus/clarity of the question posed by the researcher/reviewer and the extent to which this facilitates a systematic, unbiased retrieval and summary of the available evidence.

a) The EXTERNAL validity of the information i.e. the relevance of the information provided by the researcher/ reviewer to the specific question posed by the reader.

This appraisal checklist is specifically designed for reviews of research information. It is based on: Oxman AD. Checklists for review articles. *BMJ* 1994; **309**: 648-51, updated version in Chalmers I, Altman DG (eds). Systematic reviews. London: BMJ Publishing; 1995. This has in turn been modified on the basis of ARIF's experience reviewing many different types of reviews of research retrieved in its responses to requests for research information on the effects/effectiveness of health care interventions.

Implicit in the checklist is our belief that the following elements of a review are particularly important:

- Clear, explicit statement of method (in sufficient detail that another person undertaking the same review might be able to repeat the processes and arrive at the same conclusion AND make an assessment of any bias that the reviewers may have introduced in their identification and summary of the research).
- Comprehensive ascertainment of all the available research literature relevant to the question the reviewer sets out to answer.
- Processing the ascertained literature in a way that reduces bias or makes explicit any bias that has been introduced, so that the reviewer or reader can make allowance for this in their conclusions.
- An appropriate numerical summary of the size of any effect (or equivalent), including its confidence intervals.

If a review met the first three general criteria it would be a 'systematic review'. If a review met all four criteria it would be a 'systematic review with meta-analysis'.

A further belief this checklist seeks to incorporate is that reviews generally provide the most important means of accessing and interpreting research information. As such they are a valuable resource that should only be discarded lightly. Accordingly, the checklist attempts to define a range of uses for any particular review in addition to those that would require a 'systematic review with meta-analysis'. These uses depend on whether the review has met some, rather than all of the above stated general criteria.

ARIF CRITICAL APPRAISAL CHECKLIST

1. Assessor's screening questions

1.On first reading is there sufficient information to make a detailed appraisal?
Yes

2.Is this a highly contentious review on a topic of clear importance to the health service?
Yes

3.Is there no obvious alternative review of better quality available?
No

2. In relation to what question is this review being appraised (target question)?

The target question seeks to ascertain the effectiveness of brief interventions delivered by healthcare professionals at all levels, that promote a healthy lifestyle or lifestyle change, for all types of patients, in any primary care setting.

3. Has a clear question been defined (review question)?

The authors aimed to determine the effect of advice given in routine primary care consultations on levels of physical activity.

The review appeared to be conducted within the following parameters:

Question type: Effects/effectiveness

Population:	Not explicitly stated, the setting was within the confines of a routine consultation in primary care therefore assume any age.
Intervention:	Advice aimed at increasing physical activity within the setting of a routine primary care consultation.
Comparator:	Assume usual care.
Outcomes:	Assume increase in physical activity.

The review question was sufficiently well defined to allow the review to carried out in a systematic way i.e. it had internal validity. The review question also had external validity in that it focused on lifestyle advice (in this case relating to increasing physical activity) provided in a routine primary care setting, thereby reflecting the main requirements of the target question.

4. What are the implications for the validity of the review given the type and range of study designs included?

The review includes non-randomised control trials and there may be a risk of bias in favour of the intervention within the results of the trials with this design.

5. Were inclusion/exclusion criteria clearly stated?

Inclusion criteria:

- Randomised controlled trials (RCT's) or controlled trials (where the outcome measures for the control and intervention groups were measured in the same way).
- Trials where advice which aimed to increase levels of physical activity was given within the confines of a routine consultation in a primary care setting (including studies where activity advice was part of an overall package of lifestyle advice).
- Any primary healthcare professional could deliver the intervention.

Exclusion criteria:

- Trials where the outcome was motivation to exercise or a self-efficacy outcome.

6. Was the search strategy adopted likely to have missed many potentially relevant studies?

Search strategy
Any language, electronic search of Medline 1966 to 2000, Embase 1980 to 2000, Sport discus 1975 to 2000, Cochrane Database of Systematic Reviews and Controlled Trials Register, author contact, bibliographies of retrieved papers searched, leading researchers in the field also contacted.

Comment: standard search strategy plus a sports specific site, perhaps the nursing database Cinahl may have tapped into the nursing press which may have had trials on these types of intervention however, overall, this strategy is acceptable.

7. How were inclusion/exclusion criteria applied?

Studies were assessed from the electronic search on basis of title and abstract, if exclusion could not be determined from this the complete paper was obtained.

8. Was the validity of included studies assessed?

Quality assessed on the following: study design (RCT vs controlled trial), concealment of allocation, any intention to treat (ITT) analysis undertaken, blinding of outcome assessment, activity levels objectively validated.

9. Was the process of data abstraction adequate?

Yes, double data extracted, discrepancies discussed or a third party assessment undertaken.

10. Were the important steps in the review reproducible and bias free?

Yes.

11. What was (were) the relevant and justifiable review bottom line(s) - as stated in the review?

Trial characteristics

- 8 trials including 4747 patients, conducted between 1999 and 1988.
- 5 trials = physical activity only, 3 trials = mixed lifestyle interventions.
- 6 trials were conducted in the USA, 2 trials were conducted in Australia.
- 2 trials were RCT's (both were cluster randomised (Goldstein 1999, Graham-Clarke 1994) but they were not analysed as cluster RCT's).
- Most trials involved sedentary patients (all adults), all excluded patients with severe diseases.
- All trials = advice given by physicians.
- Interventions:
  5 trials = brief advice to increase physical activity, 3 trials = more general lifestyle advice including increasing exercise. Control groups were not described in the review. In 5 trials the intervention consisted of 1 single office visit, of the remaining 3 trials, 1 sent written advice to the patient 2 days after consultation, 1 offered office follow up and 1 telephoned patients 1 month after the initial consultation. Two trials preceded the intervention with a pre-assessment questionnaire around which the advice was given.
- Trial quality:
  Within the 2 RCT's neither concealed randomisation and in 1 the outcome assessor was not blind to allocation, which could potentially bias the outcome assessment. In both RCT's the clustering was not taken into account during analysis, with the potential for increasing the treatment effect.
  In all the trials there were opportunities for bias in particular bias that could favour the intervention arms.

Results

- Follow-up varied from 1 to 12 months. Two trials measured activity at 1 and 12 months, one of these reporting a statistically significant increase of activity at 1 month. An additional trial reported data at 1 month only and found in favour of the intervention. One trial reported data at 1 month and 8 months at both times no effect was observed. Three additional trials reported data at 6 weeks only 2 of these were statistically significant for the intervention. In one trial follow up was at 12 months, whilst not significant, the odds ratio in favour of the intervention was 1.39 (CI 0.99-1.96). Two trials used PASE administered by telephone interview, in 3 trials outcomes were measured by a self-administered questionnaire, and in the remaining 3 trials patients were questioned by verbal interview regarding levels of activity.
- In summary, 4 trials found a statistically significant result in favour of the intervention. Due to issues of quality and the variety of outcome measures used, it is not possible to quantify this effect further. Even within these simple interventions there are issues such as the effect of a pre-assessment

questionnaire and tailored advice vs. general advice, and the effect of follow up interventions such as mailed literature and follow up contacts.

12. Was the review up-to-date?

The review was published in 2001 and searches were conducted up to 2000.

13. General comments

The results of the review are limited by the validity of the trials, in particular the study conduct and the bias that is inherent within a non randomised controlled trial. In addition the review authors also discuss the problem that none of the trials were conducted within the NHS and that the health care systems in the USA and Australia, due to their reimbursement systems, may have had an effect of the intervention delivery and its effectiveness. The authors suggest that a well-conducted RCT should be undertaken within the UK.

The review authors also present an interesting discussion regarding the problems of promoting interventions aimed at the individual, in particular difficulties of individuals undertaking simple interventions such as walking where the environment, particularly in deprived areas, is not a safe place to exercise.

14. Recommendation for implementation of this review by purchasers

The evidence is not of sufficient quality to recommend the intervention, indeed the intervention is not particularly well defined. There is a need for a well-conducted RCT ideally based within the NHS.

Critical appraisal of:

DiCenso A, Guyatt G, Willan A, Griffith L. Interventions to reduce unintended pregnancies among adolescents: systematic review of randomised controlled trials. *BMJ.* 2002; **324:**
1426-30

By Wendy Greenheld

Purpose of this appraisal

Critical appraisals attempt to identify the strengths and weaknesses of pieces of information, often research literature, to enable readers to apply that information within identified limits. There are two important sets of limits:

1) The INTERNAL validity of the information i.e. the focus/clarity of the question posed by the researcher/reviewer and the extent to which this facilitates a systematic, unbiased retrieval and summary of the available evidence.
a) The EXTERNAL validity of the information i.e. the relevance of the information provided by the researcher/ reviewer to the specific question posed by the reader.

This appraisal checklist is specifically designed for reviews of research information. It is based on: Oxman AD. Checklists for review articles. *BMJ* 1994; **309**: 648-51, updated version in Chalmers I, Altman DG (eds). Systematic reviews. London: BMJ Publishing; 1995. This has in turn been modified on the basis of ARIF's experience reviewing many different types of reviews of research retrieved in its responses to requests for research information on the effects/effectiveness of health care interventions.

Implicit in the checklist is our belief that the following elements of a review are particularly important:

- Clear, explicit statement of method (in sufficient detail that another person undertaking the same review might be able to repeat the processes and arrive at the same conclusion AND make an assessment of any bias that the reviewers may have introduced in their identification and summary of the research).
- Comprehensive ascertainment of all the available research literature relevant to the question the reviewer sets out to answer.
- Processing the ascertained literature in a way that reduces bias or makes explicit any bias that has been introduced, so that the reviewer or reader can make allowance for this in their conclusions.
- An appropriate numerical summary of the size of any effect (or equivalent), including its confidence intervals.

If a review met the first three general criteria it would be a 'systematic review'. If a review met all four criteria it would be a 'systematic review with meta-analysis'.

A further belief this checklist seeks to incorporate is that reviews generally provide the most important means of accessing and interpreting research information. As such they are a valuable resource that should only be discarded lightly. Accordingly, the checklist attempts to define a range of uses for any particular review in addition to those that would require a 'systematic review with meta-analysis'. These uses depend on whether the review has met some, rather than all of the above stated general criteria.

ARIF CRITICAL APPRAISAL CHECKLIST

1. Assessor's screening questions

1.On first reading is there sufficient information to make a detailed appraisal?
Yes

2.Is this a highly contentious review on a topic of clear importance to the health service?
Yes

3.Is there no obvious alternative review of better quality available?
No

2. In relation to what question is this review being appraised (target question)?

The target question seeks to ascertain the effectiveness of brief interventions delivered by healthcare professionals at all levels, that promote a healthy lifestyle or lifestyle change, for all types of patients in any primary care setting.

3. Has a clear question been defined (review question)?

The authors sought to evaluate the effectiveness of primary prevention strategies in delaying sexual intercourse, improving the use of birth control, and reducing the incidence of unintended pregnancy amongst adolescents.

The review appeared to be conducted within the following parameters:

Question type: effects/effectiveness

Population: adolescents (aged 11 to 18 years)

Intervention: pregnancy prevention programmes including sex education classes, school based clinics, family planning clinics, and community based programmes

Comparators: alternative intervention or no intervention

Outcomes: delay in the initiation of sexual intercourse, consistent use of birth control,
and avoidance of unintended pregnancy

The review question was sufficiently well defined to allow the review to be carried out in a systematic way i.e. it had internal validity. The review was also broadly relevant (externally valid) to the target question in terms of the questions it sought to address. However it included a wide range of interventions many of which were delivered in settings other than primary health care, and the majority of which were offered as

part of a long term sex education programme. Therefore whilst the review gave an accurate account of the type of interventions generally offered in this area its results are not strictly applicable to the type of brief general practice intervention focused on by the target question.

4. What are the implications for the validity of the review given the type and range of study designs included?

The review aimed to provide a medium/high level of validity. Its focus on published and unpublished randomised controlled trials (RCTs) reduced the possibility of selection bias.

5. Were inclusion/exclusion criteria clearly stated?

The following inclusion/exclusion criteria were consistent with the review question:

Study design: Included:
Randomised controlled trials (published & unpublished)

Population: Included:
Adolescents (aged 11-18 years)

Intervention: Included:
Pregnancy prevention programmes including sex education classes, school based clinics, family planning clinics, and community based programmes
Excluded:
Pregnancy prevention programmes offered in colleges or universities, programmes that evaluated interventions designed to prevent a second pregnancy, programmes that evaluated only knowledge and attitudes, studies that measured only condom use

6. Was the search strategy adopted likely to have missed many potentially relevant studies?

Computerised databases searched (from 1970 to December 2000):

- CATLINE
- CINAHL
- Conference papers index
- Dissertation abstracts online
- Embase
- ERIC
- Medline
- NTIS
- POPLINE
- PsycINFO
- Sociological abstracts
- Cochrane library controlled clinical trials register

Contents lists from the following journals reviewed (from January 1993 to December 2000):

- American Journal of Public Health
- Canadian Journal of Public Health
- Adolescence
- Health Education and Behaviour
- Family Planning Perspectives
- Journal of School Health
- Youth and Society (1993 only)
- Journal of Adolescence (1993 only)
- Journal of Adolescent Research (1993-4 only)
- Journal of Adolescent Health Care (1993-6 only)

Other sources searched:

- Dissertations, conference proceedings, technical reports, and other unpublished documents that met the inclusion criteria
- Reference lists of all papers retrieved reviewed for relevant citations

The search strategy was extremely comprehensive. Factors such as the absence of a language restriction and extended searches for unpublished work helped to reduce the possibility of publication bias. However, as details of the search terms used in the database searches were not documented, the search process could not be repeated.

7. How were inclusion/exclusion criteria applied?

The methods used to apply the study inclusion/exclusion criteria were not reported. Nor were any details given on the number of studies retrieved and assessed at the different stages of the review process. The omission of this information therefore negated the transparency and reproducibility of the review process.

8. Was the validity of included studies assessed?

The methodological quality of the included studies was assessed using a modified version of the Jadad scoring system. Studies were rated according to the appropriateness of randomisation, extent of bias in data collection, proportion of study participants followed to the last point of follow-up (adequate follow-up included data on ≥80% of participants at the last point of follow-up), and similarity of attrition rates in the comparison group (within 2%). One point was awarded for each of the 4 aspects outlined and studies were considered to be poor quality if they scored ≤2.

9. Was the process of data abstraction adequate?

Two reviewers independently extracted data on setting, participants, unit of randomisation and analysis, theoretical framework guiding the intervention, intervention, outcome variables, length of follow-up, proportion of follow-up, proportion followed to study completion and study findings at the last follow-up by sex (if possible). Any discrepancies were resolved by joint review and consensus. Also

the assessments of methodological quality and data extraction were evaluated with 16 of the study authors who provided extra information when necessary.

10. Were the important steps in the review reproducible and bias free?

The potential reproducibility and validity of the review was influenced by the following factors:

- A very comprehensive range of databases and additional sources was searched, enhancing the validity of the reviews findings. However the transparency and reproducibility of the review process was negated by the omission of information on the search terms used in the database searches.
- The inclusion/exclusion criteria were clearly outlined however the methods used to apply them were not reported, nor was any information on the number of studies retrieved and assessed at the various stages of the review process provided. These omissions negated the transparency and potential reproducibility of the review process.
- Study quality was assessed for potential sources of selection and assessment bias.
- Two reviewers independently undertook data extraction and any disagreements were resolved by joint consensus thereby reducing the possibility of selection bias. Details of the data information categories also helped to ensure the transparency and reproducibility of the process.

11. What was (were) the relevant and justifiable review bottom line(s) - as stated in the review?

Trial characteristics

- 26 RCTs described in 22 reports (dated from 1981 to 2001) were identified.

- Of the 22 reports, 17 were published, 4 were unpublished dissertations, and one was an unpublished report.

- 21 studies were conducted in the USA and one in Canada.

- 3 studies included only African-Americans; 10 studies included >50% African-American or Hispanic subjects; and 9 studies included combinations of different races.

- 10 studies evaluated school or community based sex education; 3 studies evaluated abstinence programmes; 4 studies evaluated multifaceted programmes; and 5 studies evaluated education and counselling in family planning clinics.

- The programmes evaluated were generally conducted over several months and were sometimes offered over the course of the school year. However some shorter 1-hour interventions were evaluated.

- Study quality was generally poor with only 8 of the 22 studies scoring more than 2 points out of a possible 4 (using a modified Jadad scale).

Results

Delaying time of first sexual intercourse:

Young women:

- A meta-analysis of 13 studies involving 9,642 young women showed no delay in the initiation of sexual intercourse amongst those receiving the intervention in comparison with controls: OR 1.12 (95%CI: 0.96 to 1.30). Results were consistent across studies (heterogeneity: p=0.99).

Young men:

- A meta-analysis of 11 studies involving 7,418 young men also showed no delay in initiation of sexual intercourse amongst subjects in the intervention group in comparison with controls: OR 0.99 (95%CI: 0.84 to 1.16). There was no significant heterogeneity amongst the studies: p=0.28.

Use of birth control:

Young women:

- The use of birth control at every intercourse was assessed in a meta-analysis of 8 studies involving 1,967 young women. The results showed the intervention did not improve the use of birth control at every intercourse: OR 1.34 (95%CI: 0.53 to 3.40). However there was significant heterogeneity amongst the studies: p=0.08.
- The use of birth control at last intercourse was assessed in a meta-analysis of 3 studies involving 799 young women. The results showed the intervention did not improve the use of birth control at last intercourse: OR 1.05 (95%CI: 0.50 to 2.19). However there was significant heterogeneity amongst the studies: p=0.07.

Young men:

- The use of birth control at every intercourse was assesses in a meta-analysis of 3 studies involving 1,505 young men. Again the results showed the intervention did not improve the use of birth control at every intercourse: OR 0.90 (95%CI: 0.70 to 1.16). Results were consistent across the studies with no significant heterogeneity: p=0.97.
- The use of birth control at last intercourse was assessed in a meta-analysis of 4 studies involving 1,262 young men. The results showed the intervention did not improve the use of birth control at last intercourse: OR 1.25 (95%CI: 0.99 to 1.59). There was no significant heterogeneity amongst the studies: p=0.99.

Pregnancy:

- A meta-analysis of 12 studies involving 8,019 young women showed that the interventions did not reduce pregnancy rates: OR 1.04 (95%CI: 0.78 to 1.40). There was no significant heterogeneity amongst the studies: p=0.23.

- A meta-analysis of 5 studies involving 3,759 young men showed that the interventions increased pregnancies amongst their partners: OR 1.54 (95%CI: 1.03 to 2.29). There was no significant heterogeneity amongst the studies: p=0.58.

12. Was the review up-to-date?

The review was published in June 2002 and searches extended up to December 2000.

13. General comments

This comprehensive and generally well-documented systematic review provided an up to date account of the effectiveness of primary prevention strategies in delaying sexual intercourse, improving the use of birth control, and reducing the incidence of unintended pregnancies amongst adolescents. None of the programmes described in the review could be described as brief interventions. Most of the reports evaluated long-term sex education programmes conducted over approximately 2 to 12 months. Only 5 studies evaluated single-session shorter-term interventions and all of these were of at least 1 hour in duration. The results of the review are therefore not strictly generalisable to the type of brief primary care intervention that is the focus of our target question. However the review usefully illustrates the main types of primary prevention strategies that have been used to promote sexual abstinence and reduce unintended pregnancies amongst adolescents. Furthermore it draws attention to the gaps in the evidence base regarding the appraisal of brief primary care interventions on these topics.

14. Recommendation for implementation of this review by purchasers

The evidence presented in this report indicates primary prevention strategies aimed at delaying time of first intercourse and/or preventing pregnancy are generally offered as part of a long-term sex education programme often integrated within the school curriculum. Clearly these longer-term interventions are not strictly generalisable to the very brief primary care interventions focused on by our target question. However we feel their broad relevance to the topic is important, given the lack of research/evidence on the effectiveness of brief interventions in primary care aimed at delaying time of first intercourse and/or reducing unintended pregnancies amongst adolescents.

In summary the report indicates that these longer-term primary prevention strategies are not effective in delaying the initiation of sexual intercourse, improving the use of birth control amongst young men and women, or reducing the number of pregnancies in young women. To-date the available evidence on the effectiveness of brief interventions aimed at delaying time of first intercourse and/or preventing pregnancy neither supports or refutes their use in primary care. Further research in the form of a well-conducted RCT in a UK setting is needed to adequately address this question.

Critical appraisal of:

White D, Pitts M. Educating young people about drugs: a systematic review. *Addiction.* 1998; **93(10)**: 1475-87

By Wendy Greenheld

Purpose of this appraisal

Critical appraisals attempt to identify the strengths and weaknesses of pieces of information, often research literature, to enable readers to apply that information within identified limits. There are two important sets of limits:

1) The INTERNAL validity of the information i.e. the focus/clarity of the question posed by the researcher/reviewer and the extent to which this facilitates a systematic, unbiased retrieval and summary of the available evidence.

a) The EXTERNAL validity of the information i.e. the relevance of the information provided by the researcher/ reviewer to the specific question posed by the reader.

This appraisal checklist is specifically designed for reviews of research information. It is based on: Oxman AD. Checklists for review articles. *BMJ* 1994; **309**: 648-51, updated version in Chalmers I, Altman DG (eds). Systematic reviews. London: BMJ Publishing; 1995. This has in turn been modified on the basis of ARIF's experience reviewing many different types of reviews of research retrieved in its responses to requests for research information on the effects/effectiveness of health care interventions.

Implicit in the checklist is our belief that the following elements of a review are particularly important:

- Clear, explicit statement of method (in sufficient detail that another person undertaking the same review might be able to repeat the processes and arrive at the same conclusion AND make an assessment of any bias that the reviewers may have introduced in their identification and summary of the research).
- Comprehensive ascertainment of all the available research literature relevant to the question the reviewer sets out to answer.
- Processing the ascertained literature in a way that reduces bias or makes explicit any bias that has been introduced, so that the reviewer or reader can make allowance for this in their conclusions.
- An appropriate numerical summary of the size of any effect (or equivalent), including its confidence intervals.

If a review met the first three general criteria it would be a 'systematic review'. If a review met all four criteria it would be a 'systematic review with meta-analysis'.

A further belief this checklist seeks to incorporate is that reviews generally provide the most important means of accessing and interpreting research information. As such they are a valuable resource that should only be discarded lightly. Accordingly, the checklist attempts to define a range of uses for any particular review in addition to those that would require a 'systematic review with meta-analysis'. These uses depend on whether the review has met some, rather than all of the above stated general criteria.

ARIF CRITICAL APPRAISAL CHECKLIST

1. Assessor's screening questions

1.On first reading is there sufficient information to make a detailed appraisal?
Yes

2.Is this a highly contentious review on a topic of clear importance to the health service?
Yes

3.Is there no obvious alternative review of better quality available?
No

2. In relation to what question is this review being appraised (target question)?

The target question seeks to ascertain the effectiveness of brief interventions delivered by healthcare professionals at all levels, that promote a healthy lifestyle or lifestyle change, for all types of patients in any primary care setting.

3. Has a clear question been defined (review question)?

The authors sought to evaluate the effectiveness of interventions directed at the prevention, or reduction in use of, illicit substances by young people or those directed at reducing harm caused by continuing use.

The review appeared to be conducted within the following parameters:

Question type: effects/effectiveness

Population: young people (aged 8 to 25 years)

Intervention: psycho-educational prevention measures designed to prevent or delay onset of drug use, lead to the cessation of drug use, or minimise harm associated with drug use (no restrictions stated in terms of delivery setting or intervention length)

Comparators: alternative intervention or no intervention

Outcomes: prevention or delay in the onset of drug use, and cessation of drug use amongst existing drug users

The review question was sufficiently well defined to allow the review to be carried out in a systematic way i.e. it had internal validity. The review set broad parameters in terms of possible delivery settings and intervention lengths but, whilst these definitions encompassed brief interventions in primary care settings, the identified studies assessed group interventions delivered over relatively long time-scales (5 to

30 sessions) and predominantly based in schools. The intervention settings and delivery timescales therefore differ quite markedly from those of our target question. However we feel this work is important as it usefully explores the effectiveness of the main strategies employed to-date to delay/prevent/reduce drug use amongst young people.

4. What are the implications for the validity of the review given the type and range of study designs included?

The inclusion of non-randomised controlled trials means the possibility of selection bias (in terms of the methods used to select the intervention and control groups) cannot be ruled out. The validity level of results obtained from this type of study is therefore at best medium.

5. Were inclusion/exclusion criteria clearly stated?

The following inclusion/exclusion criteria appeared consistent with the review question:

Study design: Included:

- Studies that included a control group or comparison of groups experiencing different intervention strategies and reported both baseline and outcome measures

Population: Included:

- Young people (aged 8 to 25 years)

Intervention: Included:

- Evaluations of psycho-educational prevention measures designed to prevent or delay onset of drug use, lead to the cessation of drug use, or minimise the harm associated with drug use
- Generic drug education interventions directed towards reduction in the use of 'gateway' drugs (tobacco, alcohol & marijuana which it is felt can each provide a bridge towards more problematic drug use) were included when outcome measures for marijuana and other illicit substances were reported separately allowing an evaluation of intervention effectiveness upon them

Excluded:

- Therapeutic interventions involving individual or small group therapy or counselling

6. Was the search strategy adopted likely to have missed many potentially relevant studies?

Electronic databases searched (from 1980 to 1995):

- Medline
- Psychlit (search extended to April 1997)
- Current Contents (search extended to April 1997)
- ISDD Database (search extended to April 1997)
- Eric
- SciSearch

- Social SciSearch
- Health Periodicals Database
- HEA Unicorn Database
- Dissertation Abstracts
- Aidsline
- EMBASE

Other sources searched:

- Searches for work of identified authors
- Citation checking of identified reports
- Contributors to the 4th & 5th International Conferences on the Reduction of Drug Related Harm were contacted
- Research groups in UK & Netherlands contacted

This was a very comprehensive search strategy which encompassed both published and unpublished (grey) literature and did not impose a language restriction, thereby reducing the possibility of publication bias. Also, whilst the database search terms were not reported in the published review, the search strategy was available from the authors upon contact thereby enhancing the reproducibility of the review process.

7. How were inclusion/exclusion criteria applied?

In their search strategy the authors seemed to aim for a high level of sensitivity (i.e. they aimed to be as comprehensive as possible in the identification of all the 'included studies') and a low level of precision with regard to the relevance of some of the studies initially found.

Details of the number of studies retrieved and assessed the various stages of the review process were clearly reported thereby enhancing its potential reproducibility. Of the 4,876 studies initially located 140 reports examining 125 evaluations of programme effectiveness were found. Full data were extracted from these reports and inspected against the inclusion/exclusion criteria to ensure they satisfied criteria of relevance, outcome and design.

There may however be some potential for selection bias as whilst the authors stated that the reports selected for inclusion were read by two or more reviewers it is not clear who applied the inclusion/exclusion criteria and whether or not this part of the process was independently checked.

8. Was the validity of included studies assessed?

The study design criteria set by the reviewers for a study's inclusion within the review was that it should be methodologically adequate. A methodologically adequate study was defined as one that included a control group or a comparison of groups experiencing different intervention strategies and reported both baseline and outcome measures.

The reviewers then extended their assessment of the 'methodological rigour' of the included studies to categorize methodologically sound studies. They defined methodologically sound studies as ones that reported on the targeted outcome of the intervention (in this case an outcome relating to drug using behaviours); reported

subject refusal and attrition rates and discussed their possible impact on the findings; and included comparisons of baseline data for different study conditions and corrected for any baseline differences identified. The results obtained from these studies were combined in a meta-analysis.

9. Was the process of data abstraction adequate?

The data abstraction process appeared very thorough. Each report identified was reviewed against a standard data extraction sheet according to design, theoretical orientation of the intervention, the intervention setting, target audience, methods, population size, subject refusal rates, rates of attrition, content of intervention, outcome measures, length of follow-up, findings (including statistical power), the study author's view of effectiveness, the reviewers' judgement of effectiveness and their decision whether the inclusion criteria had been met. The reports selected for inclusion in the final review were read by two or more reviewers and any disagreements were resolved by discussion.

10. Were the important steps in the review reproducible and bias free?

The potential reproducibility and validity of the review was influenced by the following factors:

- A very comprehensive range of databases and additional sources was searched enhancing the validity of the review's findings. The inclusion of both published and unpublished studies and absence of a language restriction helped to reduce the possibility of publication bias. Also the availability of the search strategy terms (upon request from the authors) enhanced the potential reproducibility of the review process.

- The inclusion/exclusion criteria were clearly outlined as were details of the number of studies retrieved and assessed at the different stages of the review process. This enhanced the transparency and reproducibility of the review process. However there may have been some potential for selection bias as it was not clear in the report who applied the inclusion/exclusion criteria and whether or not this part of the process was independently checked.

- Study quality was assessed for methodological adequacy (this forming part of the inclusion criteria) and methodological rigour (to categorise methodologically sound studies the results of which were then combined in a meta-analysis). Both terms were clearly defined in the report enhancing its transparency and potential reproducibility.

- The data abstraction process was very thorough. Details of the items extracted were clearly stated and the availability of the standard data extraction form (upon request from the authors) enhanced the potential reproducibility of the review process. Also the potential for selection bias was reduced by the fact that each report selected for inclusion was read by two or more reviewers and any disagreements were resolved by discussion.

11. What was (were) the relevant and justifiable review bottom line(s) - as stated in the review?

- 71 studies examining 62 separate programme evaluations met the study inclusion criteria

- Of the 62 evaluations, 20 were categorised as methodologically sound and considered separately

- Information provided on the methodologically sound studies indicated that the programmes were time intensive: the number of sessions provided ranged from 5 to 30 and in some cases booster sessions were also provided

- Most programmes (89%) were directed towards adolescents and based in schools and colleges

- Only 7 (11%) programmes designed for delivery in non-school settings met the inclusion criteria

School based interventions

Trial characteristics

- 55 programmes based in schools were assessed

- Drugs targeted by the school based programmes were as follows:
    - 47% targeted marijuana only
    - 25% targeted marijuana and cocaine
    - 24% targeted 'drugs' without specifying which drugs
    - A significant minority assessed programme impact on knowledge, attitudes and intentions rather on drug use

- The studies assessing the programme impact on behaviour relied on self-reported use:
    - In all cases self-reported marijuana use was the outcome measure, although one evaluation also measured other drugs
    - Some programmes assessed behaviour at the end of the programme and others looked for longer continuing programme effects

- The effective and ineffective interventions incorporated a number of elements which aimed to increase knowledge of the effects of different substances and of the potential harm associated with them, change beliefs about the prevalence of drug use, provide the skills to resist the pressures to use drugs, provide peer support, enhance self-esteem, and provide alternative strategies for gaining peer approval

- Some programmes were more specific in their targeting and focused on one core skill, for example assertiveness, refusal skills or normative education

Results

- 64% of the evaluated interventions successfully modified attitudes

- Only 15 (27%) of the interventions successfully modified behaviour:
    - These 15 evaluations reported statistically significant programme gains in terms of reduced drug use

    - The effective interventions were a mix of focused and more general training
    - Only 10 of the 15 evaluations were methodologically sound
    - 8 of the effective, soundly evaluated programmes had 10 or more sessions devoted to the delivery of the programme
    - Of the 10 effective, soundly evaluated programmes, 8 included booster sessions or had additional elements that served a similar purpose

- Two meta-analyses of the methodologically sound studies assessed interventions whose evaluations had extended up to one year beyond the delivery of the programme, and longer term evaluations of 2 or more years:
    - Both meta-analyses showed that the effects of the interventions on illicit substance use were small and the effects declined somewhat with time
    - Weighted mean effect sizes were 0.037 ($p<0.002$) and 0.018 ($p=0.016$) respectively at the shorter and longer follow-up
    - 10 of the 11 interventions followed up to one year showed that the direction of effect favoured drugs education
    - 8 of the 10 interventions followed up for 2 or more years showed small but positive effects and the remaining 2 interventions showed marginal but insignificant counter effects

Interventions in non-school settings

Trial characteristics

- 7 programmes delivered in non-school settings were assessed

- 3 programmes used urine tests to validate the level of self reported drug use

Results

- 3 of the 7 programmes evaluated showed evidence of effectiveness

- 2 of the 3 effective programmes used urine tests to validate self-reported drug use and one programme relied on self-report

- Each of the 3 effective non-school based programmes was designed to meet the needs of a specific target audience:

    - A relapse prevention intervention directed at problem drug users' use of marijuana, cocaine, amphetamines and opiate showed initial benefits but these dissipated over the course of the year
    - A self-paced intervention aimed at young, black, pregnant women (where women worked through packages including activity-based work at their own rate) claimed a high degree of effectiveness in reducing marijuana use
    - An intervention directed at pregnant injecting drug users was effective in reducing self-reported needle sharing at 9-month follow-up but had no impact on drug use

12. Was the review up-to-date?

The review was published in 1998 with searches extending up to 1997. An update would be beneficial.

13. General comments

This comprehensive and generally well documented report was the highest quality systematic review located. It was however somewhat dated and an update taking into account developments in this area since 1997 would be beneficial. The review set broad parameters in terms of possible delivery settings and intervention lengths. In theory these parameters should have encompassed brief interventions in primary care settings. However the studies identified differed quite markedly from those of our target question as the programmes they evaluated were predominantly based in schools and generally very time intensive. The results of the review are therefore not generalisable to the type of brief primary care intervention that is the focus of our target question. However the review usefully explores the effectiveness of the main strategies employed to delay/prevent drug use amongst young people. Furthermore it highlights a lack of evidence on the effectiveness of brief interventions in primary care settings addressing these issues.

14. Recommendation for implementation of this review by purchasers

The evidence presented in this report indicates primary prevention programmes aimed at preventing/reducing the use of illicit substances or reducing the harm caused by the continuing use of illicit substances by young people are mainly delivered in schools and generally time-intensive. Clearly the type of programme and programme setting differ from those of our target question. However, given the absence of research evidence on the effectiveness of brief primary care interventions aimed at delaying/preventing drug use amongst young people, we feel the review provides an important overview of the effectiveness of the types of programmes generally adopted.

In summary the report indicates school based programmes have a small effect on illicit drug use in terms of a delay in the onset of substance use by non-users and a reduction in substance use by current users, but any programme gains dissipate with time. The majority of interventions with longer-term impact are intense interventions with the ability to reinforce their messages and programme gains with additional booster sessions. Whether or not this indicates that brief interventions in the complex area of drug prevention may have a relatively weaker effect is a matter of conjecture. To-date there is insufficient evidence on the effectiveness of brief interventions to prevent/reduce drug use amongst young people to either support or refute their use in primary care settings. Further research in the form of a well-conducted RCT in a UK setting is needed to address this question.

Critical appraisal of:

Ward D, Rowe B, Pattison H, Taylor R. Behavioural Interventions To Reduce The Risk of Sexually Transmitted Infections In Genitourinary Medicine Clinic Patients: A Systematic Review. The West Midlands Health Technology Assessment Collaboration, Department of Public Health and Epidemiology, University of Birmingham. 2004 June. Report No 50

By Wendy Greenheld

Purpose of this appraisal

Critical appraisals attempt to identify the strengths and weaknesses of pieces of information, often research literature, to enable readers to apply that information within identified limits. There are two important sets of limits:

1) The INTERNAL validity of the information i.e. the focus/clarity of the question posed by the researcher/reviewer and the extent to which this facilitates a systematic, unbiased retrieval and summary of the available evidence.

a) The EXTERNAL validity of the information i.e. the relevance of the information provided by the researcher/ reviewer to the specific question posed by the reader.

This appraisal checklist is specifically designed for reviews of research information. It is based on: Oxman AD. Checklists for review articles. *BMJ* 1994; **309**: 648-51, updated version in Chalmers I, Altman DG (eds). Systematic reviews. London: BMJ Publishing; 1995. This has in turn been modified on the basis of ARIF's experience reviewing many different types of reviews of research retrieved in its responses to requests for research information on the effects/effectiveness of health care interventions.

Implicit in the checklist is our belief that the following elements of a review are particularly important:

- Clear, explicit statement of method (in sufficient detail that another person undertaking the same review might be able to repeat the processes and arrive at the same conclusion AND make an assessment of any bias that the reviewers may have introduced in their identification and summary of the research).
- Comprehensive ascertainment of all the available research literature relevant to the question the reviewer sets out to answer.
- Processing the ascertained literature in a way that reduces bias or makes explicit any bias that has been introduced, so that the reviewer or reader can make allowance for this in their conclusions.
- An appropriate numerical summary of the size of any effect (or equivalent), including its confidence intervals.

If a review met the first three general criteria it would be a 'systematic review'. If a review met all four criteria it would be a 'systematic review with meta-analysis'.

A further belief this checklist seeks to incorporate is that reviews generally provide the most important means of accessing and interpreting research information. As such they are a valuable resource that should only be discarded lightly. Accordingly, the checklist attempts to define a range of uses for any particular review in addition to those that would require a 'systematic review with meta-analysis'. These uses

depend on whether the review has met some, rather than all of the above stated general criteria.

ARIF CRITICAL APPRAISAL CHECKLIST

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1.On first reading is there sufficient information to make a detailed appraisal?
Yes

2.Is this a highly contentious review on a topic of clear importance to the health service?
Yes

3.Is there no obvious alternative review of better quality available?
No

2. In relation to what question is this review being appraised (target question)?

The target question seeks to ascertain the effectiveness of brief interventions delivered by healthcare professionals at all levels, that promote a healthy lifestyle or lifestyle change, for all types of patients in any primary care setting.

3. Has a clear question been defined (review question)?

The authors sought to evaluate the effectiveness of behavioural interventions in reducing the risk of sexually transmitted infection or re-infection amongst patients attending genitourinary medicine (GUM) or sexual health clinics.

The review appeared to be conducted within the following parameters:

Question type: Effects/effectiveness

Population: Any person attending a GUM or equivalent sexual health clinic with an acute problem regardless of referral method

Intervention: Any behavioural intervention delivered to individuals or small groups that aimed to reduce the future likelihood of acquiring an STI

Comparators: Any

Outcomes: Subsequent rates of laboratory or clinically determined STIs; where these were unavailable, self-reported STI rates or quantifiable changes in sexual behaviour

The review question was sufficiently well defined to allow the review to be carried out in a systematic way i.e. it had internal validity. The review encompassed a wide range of interventions delivered in various clinical settings. However its inclusion of

some fairly brief behavioural interventions delivered to patients in primary care settings gave it a broad relevance to our target question (external validity).

4. What are the implications for the validity of the review given the type and range of study designs included?

The review aimed to provide a medium/high level of validity. It focused on randomised controlled trials thereby reducing the possibility of selection bias.

5. Were inclusion/exclusion criteria clearly stated?

The following inclusion/exclusion criteria were consistent with the review question:

Population: Included:
- Any person attending a GUM or equivalent sexual health clinic with an acute problem regardless of referral method

Excluded:
- Studies primarily aimed at those with known HIV or AIDS

Intervention: Included:
- Any behavioural intervention delivered to individuals or small groups that aimed to reduce the future likelihood of acquiring an STI

Excluded:
- Simple provision of educational materials
- Partner notification strategies
- Counselling when it was only a component of HIV testing

Comparators: Included:
- Any

Excluded:
- None

Outcomes: Included:
- Subsequent rates of laboratory or clinically determined STIs
- Self-reported STI rates or quantifiable changes in sexual behaviour (where there were no available clinical measures)

Excluded:
- Non-RCTs
- RCTs that had not finished recruiting
- RCTs that published only baseline characteristics
- RCTs that published results for only a small proportion of participants

6. Was the search strategy adopted likely to have missed many potentially relevant studies?

Sources searched:

- MEDLINE (1966 to week 3 January 2004)
- CINAHL (1982 to end December 2003)
- Embase (1980 to week 4 January 2004)
- PsychINFO (1985 to 30th January 2004)
- Applied Social Sciences Index an Abstracts (1987 to 30th January 2004)
- Cochrane library controlled clinical trials register (2004: Issue 1)
- National Research Register (2004: Issue 1)
- Local specialist clinicians contacted
- Citation lists of included studies checked

The authors searched a comprehensive range of databases. As there was no language restriction the possibility of publication bias was reduced. Also provision of full details of the search strategies used makes it possible to repeat the process if required.

7. How were inclusion/exclusion criteria applied?

The main reviewer used a standard inclusion criteria form (reflecting the criteria outlined in question 5) to assess all potential studies selected for review. All studies thought to meet the inclusion criteria, plus a 20% random sample of those that did not, were then independently assessed by a second reviewer and disagreements identified, discussed and resolved. The review protocol allowed for referral of ongoing disagreement to a third reviewer, but this was not necessary (inter-observer agreement was assessed using a Kappa (κ) statistic and the overall score was κ=0.70 indicating a good level of agreement).

A flow diagram provided details of the number of studies retrieved and assessed at the various stages of the review process. Information on the number of studies excluded and the reasons for their exclusion was also clearly documented.

In their search strategy the authors seemed to aim for a high level of sensitivity (i.e. they aimed to be as comprehensive as possible the identification of all the 'included studies') and a low level of precision with regard to the relevance of some of the studies initially located.

8. Was the validity of included studies assessed?

The Jadad scoring system which assesses randomisation, concealment of allocation, blinding, completeness of follow-up and the use of an intention to treat (ITT) analysis was used to assess trial quality. Two reviewers independently applied this system using a standard form and any disagreements were resolved by discussion (as outlined in question 7).

The authors also considered factors relating to the generalisability of the study results and their possible implementation in actual practice, and collected data on the recruitment rate of those eligible for inclusion and the rate to which they adhered to the experimental programme.

9. Was the process of data abstraction adequate?

The main reviewer extracted data on all included studies and a second reviewer checked a random sample of 20%, thereby reducing the possibility of selection bias. Publication of the data extraction form used ensured the transparency and reproducibility of the process.

10. Were the important steps in the review reproducible and bias free?

The potential reproducibility and validity of the review was enhanced by the following factors:

- A comprehensive range of databases and additional sources were searched, with no language restriction, thereby increasing the validity of the review. Also publication of the search strategies used meant the process could be repeated if necessary.
- The inclusion/exclusion criteria were clearly stated and details of the number of studies retrieved and assessed at the various stages of the process were clearly outlined in the form of a flow diagram. Also information on the number of studies excluded and the reasons for their exclusion was clearly documented.
- Study quality was assessed for potential sources of selection and assessment bias.
- The main reviewer extracted data on all included studies and, to reduce the possibility of selection bias, a second reviewer checked a sample of 20%. Also publication of the data extraction form used helped to ensure the transparency and reproducibility of the process.

11. What was (were) the relevant and justifiable review bottom line(s) - as stated in the review?

Trial characteristics

- 14 RCTs, published from 1989 to 2001, including over 14,000 subjects were identified.

- Trial size ranged from 117 to 5,758 with two multi-centre trials accounting for approximately two-thirds of those enrolled.

- 12 trials were conducted in North America, one in London, and one in Kenya.

- 3 trials recruited subjects from settings other than GUM or equivalent clinics: one included female patients from inner-city public STI clinics and health service organisations that delivered primary care and community services; one included adolescents recruited from family planning services; and one included young female patients from a children's hospital or inpatient facility.

- Mean trial follow-up was less than 9 months with a maximum period of 12 months, and most trials used monetary or other incentives to improve retention rates.

- 7 trials recruited both men and women (of which 2 recruited only heterosexual men and 4 did not specify their subjects sexuality); 4 trials recruited men only (of which one recruited only homosexual men, one recruited only heterosexual men, and 2 did not specify the men's sexuality); 3 trials recruited women only.

- 3 trials were concerned with adolescents and young people (14-23 years). The remaining trials were mostly concerned with adults and set a lower age limit between 16 & 20 years, although one large multi-centre trial included subjects as young as 14 years.

- The main ethic groups recruited by most studies comprised Black and African American subjects and Hispanic groups, reflecting the communities most represented in deprived inner city and urban American centres. In contrast a study of adolescents from Oregon, USA and a study of homosexual men from London recruited mainly subjects who labelled themselves as white.

- Most trials reported a high rate of new or recently diagnosed STIs at enrolment. 9 trials recruited only subjects with newly diagnosed STIs and/or their partners or subjects with a recent history of STI. 3 trials recruited only subjects reporting specific sexual behaviours seen to increase the risk of STIs. 2 trials excluded subjects who refused an HIV test.

- Study quality was frequently poor and recruitment, attendance and follow-up rates were generally low:
    - Jadad scores ranged from 0 to 3
    - Overall trials recruited fewer than half of those approached.
    - The proportion of individuals for whom data was available at follow-up was typically low, with a median across studies for the intervention group of 67.5% (range 50-93, n=12).

Aims

- 8 trials aimed to reduce the occurrence of new STIs, 5 of which placed this within a context of changing sexual behaviour (2 of these 5 trials specified increased condom use as the behavioural change desired).

- One trial aimed to increase the redemption of condom coupons.

- 5 trials aimed to reduce a range of high-risk sexual behaviours: whilst these trials did not focus specifically on condom use it appeared, from the content of their interventions, to be perceived as a key behaviour change for risk reduction.

Interventions

Interventions were delivered at either an individual or group level and were also varied in terms of length and content.

<u>Individual-level interventions:</u>

- 6 trials assessed individual face-to-face sessions.
- 2 trials assessed a single short session (≤30mins).
- The remaining 4 trials used between two (brief intervention) and five sessions (typically weekly) lasting a total of between 40 and 300 minutes.
- Themes explored included the perception of individual risks, barriers to safer sex, and personal risky or trigger situations.

    - Single session interventions emphasised an acceptance of condoms, promoting a positive attitude and negotiation of their use. Subjects were also encouraged to rehearse these skills through role-play and practised condom application using models.
    - Multiple session interventions emphasised personal goal setting and planning. 3 of the four trials used role-play and scenarios to rehearse skills such as communication and negotiation with partners and condom use.

Group-level interventions:

- 8 trials assessed group level interventions.
- 2 trials involved single contact only: a one-day workshop (homosexual males only); and a shared viewing of a video (both sexes).
- Other interventions comprised of between 3, 7, and in one case 26 sessions, lasting from approximately 5 to 26 hours in total.
- 6 of the 8 trials assessed single sex groups.
- 7 interventions (including 2 at the individual-level) included a video presentation.
- The video presentations were described as containing culturally specific content and actors, and illustrated living with HIV or condom use, portraying it as socially acceptable normative behaviour.
- Themes explored included the perception of individual risks and motivations, and the triggers of unprotected sex:
    - Some programmes also explored issues of self-esteem with some relating these issues to shared community values and the expectations of others.
    - Some programmes focussed on improving subjects self efficacy.
    - Problem solving and decision-making skills were seen as important elements of several interventions and these skills were practiced during role-play exercises.

Control group interventions:

- Choice of intervention for the control groups also varied. Many, described as usual care, typically consisted of one or two short individualised counselling sessions with a clinic doctor, nurse or trained advisor. These sessions were usually based on guidelines from the US Centres for Disease Control & Prevention (CDC) and consisted of:
    - Information giving and discussion.
    - Advice on risky sexual behaviour and appropriate methods for reducing risk.
    - Contact tracing.
    - Written material.
    - 3 trials also provided free condoms.
    - 2 trials employed longer & more in depth control interventions (one lasting 60 minutes and one 360 minutes).

Results

Primary outcome: STI rates

- 8 trials assessed laboratory confirmed STI rates at between 5 and 12 months:
    - 4 of the 8 trials (representing 80% of those enrolled) reported lower STI rates at follow-up for the intervention groups vs control groups. In 2 of these trials the results were statistically significant.

    - One trial suggested one case of STI was prevented for every 32 subjects receiving the intervention (Number needed to treat (NNT)).
    - One trial reported a NNT of 13.
    - One trial which reported laboratory confirmed cases of gonorrhoea in addition to all STIs showed the intervention had a greater impact on this diagnosis alone than for STIs as a whole (RR(relative risk): 0.61 vs 0.97; ARD(absolute risk difference): -1.4% vs 0.2%).
    - The remaining trials reported lower rates at follow-up for the control groups vs the intervention groups although the results were not statistically significant.
    - No clear pattern of intervention format or number of sessions and reported effects was noted.

- 4 trials used a broad-based definition of STI that included infections that may not exclusively be sexually transmitted and infections that may become latent so confusion as to whether an attack relates to a newly acquired STI or is the manifestation of an earlier episode may occur.
    - One trial reported a small non-statistically significant reduction in STI diagnosis amongst the intervention group vs the control group.
    - One trial found little evidence that a series of group sessions impacted on a range of specific STI diagnoses.
    - 2 trials found a greater incidence of STIs in the intervention vs control groups and in one case the results were statistically significant.

- One trial presented results for individual STI outcomes but did not say how these results were ascertained. A statistically significant reduction in the acquisition of gonococcal urethritis and urethral discharge, but not genital ulcers or HIV was reported in the intervention group.

- 3 trials reported data on self-reporting of STIs:
    - A question on STI acquisition was included in a self-completed questionnaire.
    - One trial found a significant reduction in reported symptoms amongst the intervention group compared with the control group (RR: 0.78; ARD: -0.59).
    - One trial found a non-significant reduction in reported symptoms amongst the intervention versus control group.
    - One trial found the intervention had no effect.

<u>Secondary outcomes: sexual behaviour change</u>

- Outcome data relating to sexual behaviour change were collected using self completed questionnaires or structured interviews. Reports of relevant behaviours related to specific time periods, typically the previous 1 to 3 months.

- 8 trials considered either the number or characteristics of sexual partners.

- 4 trials reported the number of new partners over the previous 3 to 6 months:
    - 3 trials showed a lower rate amongst the intervention groups (statistically significant in one trial)
    - One trial reported a lower rate in the control group.

- 4 trials provided information on the proportion of participants reporting multiple partners during the study period:

    - One trial noted a statistically significant decrease in the proportion of participants in the intervention group reporting multiple partners during the study period in comparison with the control group.
    - One trial found a non-statistically significant higher proportion of intervention group subjects reporting more than one partner per month.
    - 2 trials found the interventions had no apparent effect on rates of sexual contact with strangers or on the number of different partners engaging in unprotected sex.

- 3 trials reported the characteristics of sexual partners:
    - One trial (assessing US adolescents) found the intervention group significantly reduced their contacts with non-monogamous partners.
    - One trial (assessing homosexual men) found the intervention group who engaged in unprotected sex were just as likely to not know their partners HIV status as the control group.
    - One trial found a significantly greater proportion of women avoided sex with a symptomatic or incompletely treated partner with an STI after receiving a series of 3 small group sessions.

- 8 trials assessed consistent condom use (defined as always or nearly always using a condom) over the previous 1 to 6 months:
    - The results for all but one study were in a direction that favoured consistent condom use amongst the intervention group and in two (the largest studies) the result was statistically significant. Overall the pooled estimate, using a random effects model was also statistically significant with a RR of 1.16 (95%CI: 1.09-1.23) and ARD 6% (95% CI: 4-9). NB: An increased relative risk (RR) and absolute risk difference (ARD) is used here to denote increased condom use.
    - There was little evidence of a relationship between the number of sessions and effectiveness: the two largest effect estimates were reported from studies of a single individual session vs usual care amongst young women and two group sessions vs time matched information sessions in African American men.

- 4 trials reported information on the proportion of sexual encounters that were protected by condoms:
    - One large multi-centre indicated that receiving the intervention was associated with a greater increase in the proportion of sexual encounters protected by condoms.
    - One trial reported a non-significantly greater fall in the proportion of sexual encounters protected by condoms amongst the intervention group.
    - Two trials reported little difference between the groups.

- 4 trials reported the change in total number sexual acts for a specified period allowing changes in proportionate condom use to be put in the context of overall changes to sexual behaviour:
    - 3 trials reported either no difference or a greater fall in the number of sex acts in the control groups (although the difference was small).
    - One study reported a greater reduction in total sex acts in the intervention group.

12. Was the review up-to-date?

The review was published in August 2004 and searches were conducted up to January 2004.

13. General comments

This well executed systematic review provided an up to date evaluation of the effectiveness of behavioural interventions in reducing the risk of STIs amongst patients attending GUM or sexual health clinics. However the majority of the evidence reported came from US urban sexual health clinics. Therefore these results may not be directly applicable to UK GUM settings, given differences in the way that sexual health services are provided and perceived by the two countries. The interventions assessed by the review were also varied in terms of the length, number and content of sessions provided. Many of the interventions were, for example, much longer than the type of 'brief' intervention that is the focus of our target question. However the results of the review indicated that the success of the intervention was not apparently related to the number of intervention sessions or format. Finally the effectiveness of the experimental interventions needs to be interpreted within the context of the control group used. Most of the trials identified offered information and a brief personalised discussion of risk reduction according to the US CDC guidelines as a control. This approach goes beyond what is currently offered routinely in the UK and may have impacted on the relative magnitude of the results observed.

14. Recommendation for implementation of this review by purchasers

The evidence presented in this report does not consistently support the use of behavioural interventions as a means of reducing STI rates. Nor does it provide consistent evidence that behavioural interventions can reduce the number of new sexual partners or their risk characteristics. However the review does provide evidence that behavioural interventions are generally effective at increasing the proportion of subjects reporting consistent condom use. To-date the available evidence on the effectiveness of brief behavioural interventions, or indeed behavioural interventions per se, neither fully supports nor refutes their wholesale adoption in UK clinics. There is a need for further research in the form of a well-conducted RCT in a UK primary care setting to compare the effectiveness of brief behavioural interventions in reducing the risk or incidence of STIs with standard care or no intervention.

Critical appraisal of:

Marshall M, Crowther R, Almaraz-Serrano A, Creed F, Sledge W, Kluiter H, Roberts C, Hill E, Wiersma D. Day hospital versus admission for acute psychiatric disorders. *The Cochrane Database of Systematic Reviews* 2003, Issue 1. Art No: CD004026. DOI: 10.1002/14651858.CD004026

By Wendy Greenheld and Chris Hyde

Purpose of this appraisal

Critical appraisals attempt to identify the strengths and weaknesses of pieces of information, often research literature, to enable readers to apply that information within identified limits. There are two important sets of limits:

1) The INTERNAL validity of the information i.e. the focus/clarity of the question posed by the researcher/reviewer and the extent to which this facilitates a systematic, unbiased retrieval and summary of the available evidence.
2) The EXTERNAL validity of the information i.e. the relevance of the information provided by the researcher/ reviewer to the specific question posed by the reader.

This appraisal checklist is specifically designed for reviews of research information. It is based on: Oxman AD. Checklists for review articles. BMJ 1994; **309**: 648-51, updated version in Chalmers I, Altman DG (eds). Systematic reviews. London: BMJ Publishing; 1995. This has in turn been modified on the basis of ARIF's experience reviewing many different types of reviews of research retrieved in its responses to requests for research information on the effects/effectiveness of health care interventions.
Implicit in the checklist is our belief that the following elements of a review are particularly important:

- Clear, explicit statement of method (in sufficient detail that another person undertaking the same review might be able to repeat the processes and arrive at the same conclusion AND make an assessment of any bias that the reviewers may have introduced in their identification and summary of the research).
- Comprehensive ascertainment of all the available research literature relevant to the question the reviewer sets out to answer.
- Processing the ascertained literature in a way that reduces bias or makes explicit any bias that has been introduced, so that the reviewer or reader can make allowance for this in their conclusions.
- An appropriate numerical summary of the size of any effect (or equivalent), including its confidence intervals.

If a review met the first three general criteria it would be a 'systematic review'. If a review met all four criteria it would be a 'systematic review with meta-analysis'.
A further belief this checklist seeks to incorporate is that reviews generally provide the most important means of accessing and interpreting research information. As such they are a valuable resource that should only be discarded lightly. Accordingly, the checklist attempts to define a range of uses for any particular review in addition to those that would require a 'systematic review with meta-analysis'. These uses depend on whether the review has met some, rather than all of the above stated general criteria.

ARIF CRITICAL APPRAISAL CHECKLIST

1. Assessor's screening questions

1.*On first reading is there sufficient information to make a detailed appraisal?*
Yes

2.*Is this a highly contentious review on a topic of clear importance to the health service?*
Yes

3.*Is there no obvious alternative review of better quality available?*
No

2. In relation to what question is this review being appraised (target question)?

The target question seeks to ascertain the effectiveness/cost effectiveness of day hospitals in the treatment of people with mental illness in comparison with other NHS or social services models of provision. More specifically it seeks to address the following points:

- Do day hospitals extend life?
- Do they prevent admissions/readmissions?
- Do they improve quality of life?
- Are they cost effective?
- What are the alternatives?

3. Has a clear question been defined (review question)?

The authors aimed to systematically review the effects of psychiatric day hospitals for people with acute psychiatric disorders compared with inpatient care.
The main hypothesis was that admission to a day hospital would reduce the extent of hospital care and total costs of care without any deterioration in follow up rates or clinical and social functioning. Additionally the review attempted to determine the proportion of acutely ill patients for whom day hospital treatment was feasible; the recovery rate of day hospital patients (in terms of symptoms and social functioning) in comparison with that of inpatients; and the extent to which clinical and social recovery was affected by personal characteristics such as diagnosis, sex and age.
The review was conducted within the following parameters:

Question type: effects/effectiveness

Population: people with acute psychiatric disorders

Intervention: psychiatric day hospital

Comparator: standard inpatient care

Outcomes: feasibility of day hospital treatment, extent of hospital care, clinical & social outcomes, costs of care

The review question was sufficiently well defined to allow the review to be carried out in a systematic way i.e. it had internal validity. Furthermore the review appeared to reflect the main requirements of the target question i.e. it had external validity. However the review only addressed the day hospital/inpatient care comparison rather than the range of possible alternatives to psychiatric day hospitals therefore its relevance to the target question should be interpreted in terms of this specific focus.

4. What are the implications for the validity of the review given the type and range of study designs included?

The review aimed to provide a medium/high level of validity. It focused on randomised controlled trials and, following an assessment of trial quality, restricted its evaluation of outcome data to trials which had either an adequate or unclear method of concealment thereby reducing any possible selection bias.
It is unclear whether or not a language restriction was used. The authors had intended to address the question of publication bias but reported that there were insufficient data to produce a funnel graph to consider trial effect against trial size.

5. Were inclusion/exclusion criteria clearly stated?

The following inclusion/exclusion criteria were consistent with the review question:
Study design: Randomised controlled trials

Population: People with acute psychiatric disorders (all diagnoses) who would have been admitted to inpatient care, if acute day hospital care had not been available. Studies were excluded if they were restricted to, or included a majority of, patients who were aged under 18 or over 65, or who had a primary diagnosis of substance abuse and/or organic brain disorder.

Intervention: Acute psychiatric day hospital units that provided diagnostic and treatment services for acutely ill patients who would otherwise be treated on traditional psychiatric inpatient units.

Comparator: Standard inpatient care.

Outcomes: The four main outcome measures were:

1.Feasibility and engagement
1.1 Unsuitable for day patient care
1.2 Lost to follow up

2.Extent of hospital care
2.1 Duration of initial admission
2.2 Days in inpatient care
2.3 Days in day patient care
2.4 Days in inpatient or day patient care
2.5 Re-admitted to inpatient or day patient care after discharge

3.Clinical and Social outcomes
3.1 Mental state
3.2 Social functioning
3.3 Burden on carers
3.4 Deaths
3.5 Employed at end of study
3.6 Satisfaction with care
3.7 Quality of life
4.Costs of care
4.1 Cost of index admission
4.2 Cost of hospital care
4.3 Cost of psychiatric care
4.4 Cost of all care

6. Was the search strategy adopted likely to have missed many potentially relevant studies?

Sources searched:

- CINAHL (January 1982 - December 2000)
- The Cochrane Library (Issue 4, 2000)
- EMBASE (January 1980 - December 2000)
- MEDLINE (January 1966 – December 2000)
- PsycLIT (January 1967 – December 2000)
- Reference lists of the identified reviews and trials
- Contact with authors in the field to identify unpublished studies

Search strategy:
The Cochrane Schizophrenia Group's search strategy for randomised controlled trials was used in combination with the following key search terms and phrases: [((DAY adj2 HOSP*), (DAY adj2 CARE) or (DAY adj2 TREATMENT*) or (DAY adj2 CENT*) or (DAY adj2 UNIT*) or (PARTIAL adj2 HOSP*) or (DISPENSARY)) AND MENTAL DISORDERS]

The authors employed a comprehensive search strategy consistent with the review question. However as the authors did not report whether or not a language restriction was used it is possible that some potentially relevant studies may have been omitted.

7. How were inclusion/exclusion criteria applied?

The search criteria appeared to have a medium/high degree of sensitivity and medium level of precision. Two reviewers independently assessed abstracts of the studies identified by the search. The full papers for potentially relevant studies (i.e. studies in which a group of day hospital patients meeting the patient inclusion criteria were compared against a control group) were then ordered. The authors reported that 64 studies were excluded and provided details of the reasons for exclusion. Whilst precise numbers for the studies assessed at the various stages were not always reported (i.e. in the form of a flow diagram) the explanation of the process was generally clear thereby enhancing the reproducibility of the review.

8. Was the validity of included studies assessed?

Two independent reviewers undertook a quality assessment of the included studies. Disagreements were resolved by discussion or failing this contact with the authors. Trials were allocated to one of three categories of allocation concealment (where concealment was A) adequate, B) unclear or C) inadequate). Where outcome data was evaluated only category A or B trials were included. Trials were also rated on the independence and blinding of evaluators.

Data were excluded from the meta-analysis if they could not be analysed on an intention to treat (ITT) basis. Data were also excluded from studies where more than 50% of people were lost to follow up.

9. Was the process of data abstraction adequate?

Data reflecting the inclusion and exclusion criteria were extracted independently by two reviewers and cross checked. As it was found that the trials tended to present similar outcomes in slightly different formats individual patient data were sought so that outcomes could be reanalysed in a common format.

10. Were the important steps in the review reproducible and bias free?
In general, the main steps of the review were clearly reported and conducted in a way that helped to reduce bias:

- The search for all potentially relevant studies was comprehensive and consistent with the review question.
- The methods used to apply the inclusion/exclusion criteria were generally well explained. Although the report would have benefited from a more detailed account of the number of studies assessed at the various stages of the process.
- 2 reviewers independently assessed the validity and quality of the included studies.
- The data extraction process was adequately explained.

11. What was (were) the relevant and justifiable review bottom line(s) - as stated in the review?

9 trials involving 1568 randomised patients and 2268 patients who were assessed for suitability for day hospital treatment were included in the review. Feasibility of day hospital treatment was defined as the percentage reduction in acute inpatient admissions that could be achieved by diverting patients to an acute day hospital. There were 2 types of included trials which were analysed separately in view of their methodological differences however, as the interventions were similar, the findings of the two outcomes were reported together for each outcome:

1. Type 1 trials excluded before randomisation any patients who were considered ineligible for day patient treatment.
2. Type 2 trials randomised all patients presenting for admission but admitted to the inpatient ward any people who were too unwell for immediate day hospital treatment.

Proportion of patients suitable for patient care

Type 1 trials (N=7)
Best estimate of feasibility: 37.5% (n=1768, 95%CI 35.2, 39.8%)
Worst estimate of feasibility: 23.2% (n=2268, 95%CI 21.2, 25.2%)

Type 2 trials (N=2)
Estimate of feasibility: 18.4 to 39.1%

Meta-analyses of the outcomes for day hospital patients compared with patients admitted as inpatients were as follows:

Duration of initial admission (N=3 type 1 trials)
Patients randomised to day hospital care had a significantly longer index admission (defined as time from first admission to discharge to outpatient care):
n=465, weighted mean difference 10.9 days (95%CI 1.09,20.7)
Mann Whitney U, Z = -3.255, p=0.001
Significant heterogeneity: χ^2 20.17, df 2, p<0.01

Total number of days in hospital: all types of care (N=3 type 1 trials)
No difference between day hospital patient and controls:
n=465, WMD –0.38 days/month (95%CI –1.32,0.55)
Mann Whitney U, Z = -0.971, p=0.332

Total number of days in day hospital care (N=3 type 1 trials
Patients randomised to day hospital care spent significantly more days in day hospital care: n=265, WMD 2.34 days/month (95%CI 1.97, 2.70)
Mann Whitney U, Z = -14.33, p<0.001

Total number of days in inpatient care (N=3 type 1 trials)
Patients randomised to day hospital care spent significantly fewer days in inpatient care: n=265, WMD –2.75 days/month (95%CI -3.63, -1.87)
Mann Whitney U, Z = -11.89, p<0.001

Patients readmitted to hospital care: either inpatient or day hospital (N=5 type 1 trials)
No significant difference between day hospital and control groups:
n=667, RR 0.91 (95%CI 0.72, 1.15)

Mental state (N=3 type 1 trials)
For patients judged suitable for day hospital care individual patient data showed a significant time-treatment interaction indicating a more rapid improvement in mental state for day hospital patients compared with inpatients:
n=407, χ^2 9.66, p=0.002

Social functioning (N=3 type 1 trials)
For patients judged suitable for day hospital care individual patient data provided no evidence of a time-treatment interaction for day hospital patients compared with inpatients:
n=295, χ^2 0.006, p=0.941

Burden on carers (N=2 type 1 trials)
No difference in carer burden between day hospital and control groups at 2 weeks, 1,2,3 and 12 months.

Death: suicide/homicide/all causes (N=1 type 2 trial)
No difference in death rates between day hospital and control groups:
n=160, RR 0.74 (95%CI 0.17, 3.18)

Employment at end of study
One type 1 trial found no difference in number unemployed at 12 months:
n=179, RR 0.88 (95%CI 0.66, 1.19)
One type 2 trial found no difference in number unemployed at 24 months:
n=160, RR 0.95 (95%CI 0.87, 1.04)

Satisfaction with care: patients & relatives (N=1 type trial)
This trial reported data on number not satisfied with care which showed a significant difference in favour of day hospital care:
n=91, RR 0.46 (95%CI 0.27, 0.79), NNT=3

Costs of care
Four type 1 trials reported that day hospital care was cheaper than hospital care:

- index admission reductions ranged from 33.5 to 49.6%
- reductions in the cost of all psychiatric care (including hospital care) ranged from 20.9 to 36.9%

One type 2 trial found no significant difference between day and inpatient care although the trend favoured inpatient care.

12. Was the review up-to-date?

The review was published in 2003 and searches were conducted up to December 2000.

13. General comments

The review was clearly focused, well executed and contained a cogent statement of method sufficient to permit its repetition. Synthesis of the data also appeared appropriate with meta-analyses taking account of methodological differences in patient allocation.

14. Recommendation for implementation of this review by purchasers

The review indicates day hospitals provide a feasible and worthwhile alternative to inpatient care. At least 20% of patients currently admitted to inpatient care could realistically be treated in acute day hospitals. Whilst patients diverted to day hospitals spend the same number of days in hospital as inpatients overall, a significantly higher proportion of these days are spent in day hospitals. Given that day hospital care is cheaper than inpatient care this affords the possibility of substantial cost savings in the absence of a more suitable alternative. Furthermore this reduction in costs could be achieved without increasing the burden on relatives and carers as the review found there was no difference in carer burden between the day hospital and inpatient care groups.

The review indicates day hospital patients experience a greater sense of satisfaction with treatment. It also provides some evidence that they benefit from a more rapid improvement in their mental state (the results for this time/treatment improvement seem to be derived from the individual patient data multiple regression analysis however this seems to be an unusual approach).
Overall the results suggest day hospital care does not reduce readmission rates or lead to improvements in social functioning. However the studies included have limited statistical power and report wide 95% confidence intervals which include the possibility of both clinical benefits and harms.

The review focuses on the treatment of patients with acute psychiatric disorders who would normally be admitted as inpatients in the absence of day hospital availability. Its conclusions are therefore relevant to this specific group of acutely ill patients and should not be generalised to patients with other types of psychiatric illness i.e. chronic psychiatric illness. Furthermore the results of the review should be interpreted within the context of the specific treatment comparison: inpatient admission. The authors have not addressed the effectiveness of day hospitals in comparison with other forms of care however different types of care are touched upon in their concluding discussion of the implications for practice. Here the authors indicate day hospitals may not be as clinically or cost effective as, for example, community crisis intervention programmes. The reviewers conclude acute day hospitals are an attractive option in situations where the demand for inpatient care is high and facilities exist that are suitable for conversion. However the benefits are less clear when demand for inpatient care is low and effective alternatives are already available.

Critical appraisal of:

Marshall M, Crowther R, Almaraz-Serrano AM, Tyrer P. Day hospital versus out-patient care for psychiatric disorders. *The Cochrane Database of Systematic Reviews* 2001, Issue 2. Art No: CD003240. DOI: 10.1002/14651858.CD003240

By Wendy Greenheld

Purpose of this appraisal

Critical appraisals attempt to identify the strengths and weaknesses of pieces of information, often research literature, to enable readers to apply that information within identified limits. There are two important sets of limits:

1) The INTERNAL validity of the information i.e. the focus/clarity of the question posed by the researcher/reviewer and the extent to which this facilitates a systematic, unbiased retrieval and summary of the available evidence.

a) The EXTERNAL validity of the information i.e. the relevance of the information provided by the researcher/ reviewer to the specific question posed by the reader.

This appraisal checklist is specifically designed for reviews of research information. It is based on: Oxman AD. Checklists for review articles. *BMJ* 1994; **309**: 648-51, updated version in Chalmers I, Altman DG (eds). Systematic reviews. London: BMJ Publishing; 1995. This has in turn been modified on the basis of ARIF's experience reviewing many different types of reviews of research retrieved in its responses to requests for research information on the effects/effectiveness of health care interventions.

Implicit in the checklist is our belief that the following elements of a review are particularly important:

- Clear, explicit statement of method (in sufficient detail that another person undertaking the same review might be able to repeat the processes and arrive at the same conclusion AND make an assessment of any bias that the reviewers may have introduced in their identification and summary of the research).
- Comprehensive ascertainment of all the available research literature relevant to the question the reviewer sets out to answer.
- Processing the ascertained literature in a way that reduces bias or makes explicit any bias that has been introduced, so that the reviewer or reader can make allowance for this in their conclusions.
- An appropriate numerical summary of the size of any effect (or equivalent), including its confidence intervals.

If a review met the first three general criteria it would be a 'systematic review'. If a review met all four criteria it would be a 'systematic review with meta-analysis'.

A further belief this checklist seeks to incorporate is that reviews generally provide the most important means of accessing and interpreting research information. As such they are a valuable resource that should only be discarded lightly. Accordingly, the checklist attempts to define a range of uses for any particular review in addition to those that would require a 'systematic review with meta-analysis'. These uses depend on whether the review has met some, rather than all of the above stated general criteria.

ARIF CRITICAL APPRAISAL CHECKLIST

1. Assessor's screening questions

1.On first reading is there sufficient information to make a detailed appraisal?
Yes

2.Is this a highly contentious review on a topic of clear importance to the health service?
Yes

3.Is there no obvious alternative review of better quality available?
No

2. In relation to what question is this review being appraised (target question)?

The target question seeks to ascertain the effectiveness/cost effectiveness of day hospitals in the treatment of people with mental illness in comparison with other NHS or social services models of provision. More specifically it seeks to address the following points:

- Do day hospitals extend life?
- Do they prevent admissions/readmissions?
- Do they improve quality of life?
- Are they cost effective?
- What are the alternatives?

3. Has a clear question been defined (review question)?

The review assessed three types of day hospital care: day treatment programmes, day care centres and transitional day care. Its objectives were as follows:

1. To systematically review the effects of day treatment programmes as an alternative to continuing outpatient care for people with non-psychotic disorders:
   The main hypothesis was that admission to a day treatment programme would result in a better clinical outcome, in terms of improved mental state, social functioning and quality of life, without increasing costs of care. The review also considered satisfaction with care, engagement with treatment, the use of inpatient care and, for treatment programmes aimed at people with personality disorders, considered outcomes relating to self-harm.
2. To review the effectiveness of day care centres as an alternative to outpatient care for people with severe long term disorders:
   The main hypothesis was that day care centres would increase engagement in treatment; reduce readmission to hospital and duration of admission; improve clinical outcome; and reduce costs of care. The review also considered patients' satisfaction with care.
3. To review the effectiveness of transitional day care as an alternative to outpatient care for people discharged from inpatient care:
   The main hypothesis was that transitional day care would increase engagement in treatment; reduce readmission to hospital and duration of admissions; improve clinical outcome; and reduce costs of care. The review also considered patients' satisfaction with care.

The review was conducted within the following parameters:

Question type: effects/effectiveness

Population: 1. patients with non-psychotic disorders
2. patients with severe long term disorders
3. patients discharged from acute psychiatric wards

Intervention: 1. day treatment programmes (population 1)
2. day care centres (population 2)
3. transitional day care (population 3)

Comparator: standard outpatient care

Outcomes: engagement with treatment, readmission to hospital, clinical & social outcomes, costs of care

The review question was sufficiently well defined to allow the review to be carried out in a systematic way i.e. it had internal validity. Furthermore the review appeared to reflect the main requirements of the target question i.e. it had external validity. However the review only addressed the comparisons between different forms of day hospital and outpatient care rather than the range of possible alternatives to psychiatric day hospitals therefore its relevance to the target question should be interpreted in terms of this specific focus.

4. What are the implications for the validity of the review given the type and range of study designs included?

The review aimed to provide a medium/high level of validity. It focused on randomised controlled trials and, following an assessment of trial quality, restricted its evaluation of outcome data to trials which had either an adequate or unclear method of concealment thereby reducing any possible selection bias.

It is unclear whether or not a language restriction was used. The authors had intended to address the question of publication bias but reported that there were insufficient data to produce a funnel graph to consider trial effect against trial size.

5. Were inclusion/exclusion criteria clearly stated?

The following inclusion/exclusion criteria were consistent with the review question:

Study design: Randomised controlled trials

Population: 1. Patients with non-psychotic disorders (all diagnoses) who would have been treated in outpatient care had day care not been available (day treatment programmes).

2. Patients with severe long term disorders (predominantly schizophrenia and other psychoses) who would have been followed up in outpatient care had day hospital care not been available (day care centres).

3. Inpatients on acute psychiatric wards who would have been discharged to outpatient care had transitional care not been available (transitional day care).

Studies were excluded if they were restricted to, or included a majority of, patients who were aged under 18 or over 65, or who had a primary diagnosis of substance abuse and/or organic brain disorder.

Intervention: 1. Day treatment programmes: defined as psychiatric day hospitals offering intensive input to patients with non-psychotic disorders

2. Day care centres: defined as psychiatric day hospitals offering continuing care to patients with severe mental disorders

3. Transitional day hospitals: defined as psychiatric day hospitals offering time-limited care to patients discharged from inpatient care

Comparator: Standard outpatient care.

Outcomes: The four main outcome measures were:

1. Engagement with treatment
1.1 number lost to follow up

2. Readmission to hospital
2.1 number admitted to inpatient care
2.2 mean days in inpatient care

3. Clinical and Social outcomes
3.1 mental state
3.2 social functioning
3.3 quality of life
3.4 death
3.5 burden on relatives
3.6 satisfaction with care

4. Costs of care
4.1 mean monthly cost of psychiatric care
(comprising cost of hospital care plus cost of all ambulatory psychiatric care)
4.2 mean monthly cost of all care
(comprising cost of psychiatric care plus costs of other medical/social care, excluding wages, costs to relatives, and transfer payments)

6. Was the search strategy adopted likely to have missed many potentially relevant studies?

Sources searched:

- CINAHL (January 1982 - December 2000)
- The Cochrane Library (Issue 4, 2000)
- EMBASE (January 1980 - December 2000)
- MEDLINE (January 1966 – December 2000)
- PsycLIT (January 1967 – December 2000)
- Reference lists of the identified reviews and trials
- Contact with authors in the field to identify unpublished studies

Search strategy:
The Cochrane Schizophrenia Group's search strategy for randomised controlled trials was used in combination with the following key search terms and phrases: [((DAY adj2 HOSP*), (DAY adj2 CARE) or (DAY adj2 TREATMENT*) or (DAY adj2 CENT*) or (DAY adj2 UNIT*) or (PARTIAL adj2 HOSP*) or (DISPENSARY)) AND MENTAL DISORDERS]

The authors employed a comprehensive search strategy consistent with the review question. However as the authors did not report whether or not a language restriction was used it is possible that some potentially relevant studies may have been omitted.

7. How were inclusion/exclusion criteria applied?

The search criteria appeared to have a medium/high degree of sensitivity and medium level of precision. Two reviewers independently assessed abstracts of the studies identified by the search. The full papers for potentially relevant studies (i.e. those in which a group of day hospital patients meeting the patient inclusion criteria were compared against a control group) were then ordered. The authors reported that 65 studies were excluded and provided details of the reasons for exclusion. Whilst precise numbers for the studies assessed at the various stages were not always reported (i.e. in the form of a flow diagram) the explanation of the process was generally clear thereby enhancing the reproducibility of the review.

8. Was the validity of included studies assessed?

Two independent reviewers undertook a quality assessment of the included studies. Disagreements were resolved by discussion or failing this contact with the trialists. Trials were allocated to one of three categories of allocation concealment (where concealment was A) adequate, B) unclear or C) inadequate). Only category A or B trials were included in the review. Trials were also rated on the independence and blinding of evaluators.

Data were excluded from the meta-analysis if they could not be analysed on an intention to treat (ITT) basis. Data were also excluded from studies where more than 50% of people were lost to follow up.

9. Was the process of data abstraction adequate?

Data reflecting the inclusion and exclusion criteria were extracted independently by three reviewers and cross checked. Where further clarification was needed the authors of the trials were contacted to provide missing data.

10. Were the important steps in the review reproducible and bias free?

In general, the main steps of the review were clearly reported and conducted in a way that helped to reduce bias:

- The search for all potentially relevant studies was comprehensive and consistent with the review question.
- The methods used to apply the inclusion/exclusion criteria were generally well explained. Although the report would have benefited from a more detailed account of the number of studies assessed at the various stages of the process.
- 2 reviewers independently assessed the validity and quality of the included studies.
- The data extraction process was adequately explained.

11. What was (were) the relevant and justifiable review bottom line(s) - as stated in the review?

Eight studies were included in the review of which four were studies of day treatment programmes vs outpatient care; three were studies of day care centres vs outpatient care; and one was a study of transitional day hospital care vs outpatient care.

Comparison 1: Day treatment programmes vs outpatient care (N=2)

Number admitted to inpatient care (N=2)

No significant difference in number of patients admitted to hospital at 6-8 months (N=2)
RR 1.23 (95%CI 0.06, 25.5) random effects model
Very wide confidence intervals.
Evidence of heterogeneity.

No significant difference in admission rates at 24 months (N=1)
RR 1.81 (95%CI 0.54, 6.05)
Wide confidence intervals.

Mental state (N=2)

The results were equivocal:

One trial reported a statistically significant improvement in mental state scores (Standardised Psychiatric Interview) in favour of the day treatment programme:
day treatment median at baseline 35, at six months 21; control at baseline 36, at 6 months 32
P<0.001 Mann Whitney U test

One trial reported no significant difference in mental state scores at four and eight months, although there was a trend favouring the day treatment group.
Mean difference in change from baseline
at four months: -3.72(95% CI -8.69, 1.25)
at eight months: -3.39 (95%CI -8.96, 2.18)

Social functioning (N=1)

No significant difference in social functioning based on change scores from baseline although the direction of effect favoured the day treatment programme.
Mean difference in change from baseline
at four months: -3.24 (95%CI -8.07, 1.59)
at eight months: -4.38 (95% CI –9.95, 1.19)

Death: all causes (N=1)

One trial reported a non-significant increase in mortality in the day treatment group:
RR 2.42 (95%CI 0.23, 25.85)
Very wide confidence intervals

Satisfaction with care (N=2)

The results reported were equivocal.

One trial reported that patients were significantly more satisfied with day treatment and one reported that they were significantly less satisfied.

Comparison 2: Day care centres vs outpatient care for patients with severe long-term mental disorders (N=3)

Number admitted to outpatient care (N=2)

One trial found no significant difference at 3 months but confidence intervals were very wide:
RR 1.0 (95% CI 0.02, 47.4)

One trial found no significant difference in follow up rates at 12 or 24 months, although the direction of effect favoured the day centre group (12 months: RR 0.86 (95%CI 0.61, 1.23); 24 months: RR 0.82 (95% CI 0.64, 1.05)

Mean days in inpatient care (N=1)

One trial reported that day centre patients spent significantly fewer days in inpatient care over a 24 month period (day centre: 77.9; outpatient: 95.9) however the data were difficult to evaluate as no p-value, SD or confidence intervals were reported and the numbers of subjects in each group were unclear.

Mental state (N=2)

One study reported no significant differences at 3 months (Symptom Check List (SCL-90)). The effect favoured the control group but confidence intervals were very wide:
mean difference 0.31 (95%CI -0.20, 0.82)

One study reported a significant time by group interaction in favour day centre patients at 24 months ($p<0.01$, $F=8.08$).

Social functioning (N=2)

One group reported no difference in social functioning at 3 months (Community Adaption Scale (CAS)) but confidence intervals were wide:
mean difference –0.03 (95% CI –0.30, 0.24)

One study reported a significant time by group difference on social functioning in favour of the day centre group but univariate comparisons at 6, 12 18 and 24 months were not significant.

Death (N=1)

One study found no difference at 3 months but confidence intervals were very wide:
RR 1.0 (95%CI 0.02, 47.4)

Mean monthly cost of psychiatric care (N=1)

One trial reported a 32.8% increase in mean monthly costs for the day centre group. However these figures were only based on the costs of inpatient and day treatment and did not include costs of outpatient care.

Comparison 3: Transitional day hospital care vs outpatient care for patients just discharged from hospital (N=1)

Number admitted to inpatient care (N=1)

No significant differences reported but confidence intervals wide:
RR 1.26 (95%CI 0.53, 2.97)

Overall functioning (N=1)

No significant differences reported at 12 months:
mean difference 0.34 (95%CI -9.7, 10.4)

Mental state (N=1)

No significant differences reported at 12 months:
mean difference 0.17 (95% CI –0.39, 0.73)

Social functioning (N=1)

No significant differences reported (SAS scale):
mean difference 0.18 (95%CI –0.17, 0.53)

12. Was the review up-to-date?

The review was published in 2001 and searches were conducted up to December 2000.

13. General comments

The review was clearly focused, well executed and contained a cogent statement of method sufficient to permit its repetition. However the results obtained were based on a small number of studies and often displayed a large degree of variability.

14. Recommendation for implementation of this review by purchasers

The rationale for this paper is difficult to understand. The review essentially encompasses three specific populations each with its own specific intervention and thus might easily have formed the basis for three separate systematic reviews.

Overall there is insufficient evidence to determine whether any of the three types of day hospital care assessed in the review are better than outpatient care:

- There is insufficient evidence to judge whether day treatment programmes for patients with non-psychotic disorders are superior to outpatient care in terms of reducing deaths and numbers admitted to inpatient care, and improving overall mental state, social functioning or satisfaction with care.

- There is insufficient evidence to judge whether day care centres for patients with severe long term disorders are superior to outpatient care in terms of engagement with care, admission rates, clinical outcomes, patient satisfaction and costs.

- There is insufficient information upon which to make recommendations about the effectiveness of transitional day hospital in comparison with outpatient care for patients discharged from acute psychiatric wards.

In their discussion of the implications for research the authors state that as more community orientated forms of care have now largely superseded day care centres it is doubtful that further research is needed in this area. However the review highlights the need for rigorous research into the effectiveness of day treatment programmes and transitional day hospitals.

Critical appraisal of:

Forster A, Young J, Langhorne P for the Day Hospital Group. Medical day hospital care for the elderly versus alternative forms of care. *The Cochrane Database of Systematic Reviews* 1999; Issue 3. Art No: CD001730. DOI: 10.1002/14651858.CD00001730.

By Wendy Greenheld and Chris Hyde

Purpose of this appraisal

Critical appraisals attempt to identify the strengths and weaknesses of pieces of information, often research literature, to enable readers to apply that information within identified limits. There are two important sets of limits:

1) The INTERNAL validity of the information i.e. the focus/clarity of the question posed by the researcher/reviewer and the extent to which this facilitates a systematic, unbiased retrieval and summary of the available evidence.

a) The EXTERNAL validity of the information i.e. the relevance of the information provided by the researcher/ reviewer to the specific question posed by the reader.

This appraisal checklist is specifically designed for reviews of research information. It is based on: Oxman AD. Checklists for review articles. *BMJ* 1994; **309**: 648-51, updated version in Chalmers I, Altman DG (eds). Systematic reviews. London: BMJ Publishing; 1995. This has in turn been modified on the basis of ARIF's experience reviewing many different types of reviews of research retrieved in its responses to requests for research information on the effects/effectiveness of health care interventions.

Implicit in the checklist is our belief that the following elements of a review are particularly important:

- Clear, explicit statement of method (in sufficient detail that another person undertaking the same review might be able to repeat the processes and arrive at the same conclusion AND make an assessment of any bias that the reviewers may have introduced in their identification and summary of the research).
- Comprehensive ascertainment of all the available research literature relevant to the question the reviewer sets out to answer.
- Processing the ascertained literature in a way that reduces bias or makes explicit any bias that has been introduced, so that the reviewer or reader can make allowance for this in their conclusions.
- An appropriate numerical summary of the size of any effect (or equivalent), including its confidence intervals.

If a review met the first three general criteria it would be a 'systematic review'. If a review met all four criteria it would be a 'systematic review with meta-analysis'.

A further belief this checklist seeks to incorporate is that reviews generally provide the most important means of accessing and interpreting research information. As such they are a valuable resource that should only be discarded lightly. Accordingly, the checklist attempts to define a range of uses for any particular review in addition to those that would require a 'systematic review with meta-analysis'. These uses depend on whether the review has met some, rather than all of the above stated general criteria.

ARIF CRITICAL APPRAISAL CHECKLIST

1. Assessor's screening questions

1.On first reading is there sufficient information to make a detailed appraisal?
Yes

2.Is this a highly contentious review on a topic of clear importance to the health service?
Yes

3.Is there no obvious alternative review of better quality available?
No

2. In relation to what question is this review being appraised (target question)?

The target question seeks to ascertain the effectiveness/cost effectiveness of day hospitals in the treatment of the elderly in comparison with other NHS or social services models of provision. More specifically it seeks to address the following points:

- Do day hospitals extend life?
- Do they prevent admissions/readmissions?
- Do they improve quality of life?
- Are they cost effective?
- What are the alternatives?

3. Has a clear question been defined (review question)?

The authors aimed to systematically review the effects of medical day hospitals for elderly people compared with alternative forms of care. The primary research question was whether older patients attending a geriatric medical day hospital would experience better outcomes in terms of death, dependency or institutionalisation than those receiving alternative forms of care. Secondary questions focused on the impact of day hospital care on patient satisfaction and subjective health outcomes, carer distress, and resource use and costs.

The review was conducted within the following parameters:

Question type: effects/effectiveness

Population: elderly medical patients

Intervention: day hospital

Comparators: alternative forms of care

Outcomes: death, place of residence, dependency, global 'poor' outcome, activities of daily living (ADL) score, subjective health status, patient satisfaction, resource use

The review question was sufficiently well defined to allow the review to be carried in a systematic way i.e. it had internal validity. Furthermore the review appeared to reflect the requirements of the target question i.e. it had external validity.

4. What are the implications for the validity of the review given the type and range of study designs included?

The review aimed to provide a medium/high level of validity. It concentrated on studies with a prospective controlled design in which there was ideally random assignment of participants to alternative treatment groups (one of which involved day hospital care) without other major confounding treatments.

Factors such as the randomisation method, blinding of outcome assessment and the presence of an intention to treat analysis did not influence the decision to include a trial thereby introducing the possibility of bias and potentially reducing the validity of the review's findings. However these factors were taken into account in the authors' assessment of quality, statistical and sensitivity analyses.

5. Were inclusion/exclusion criteria clearly stated?

The following inclusion/exclusion criteria were consistent with the review question:

Study design: Prospective controlled design in which there was ideally random assignment of participants to alternative treatment groups (one of which involved day hospital care) without other major confounding treatments.

Population: Elderly (usually >60 years) medical patients.

Intervention: Day hospital: defined as an outpatient facility where older patients attend for a full or near full day and receive multidisciplinary rehabilitation in a health care setting. This definition excluded trials evaluating social day centres, other types of day hospitals such as psychiatric day hospitals and single condition hospitals.

Comparators: The following subgroup comparators were set prior to reviewing the trials:

Comprehensive elderly care: where control patients had access to a range of geriatric medical services (both inpatient and outpatient).

Domiciliary care: where control patients received an approximately equivalent rehabilitation input within their own home or social day centre.

No comprehensive elderly care: where control patients did not routinely have access to outpatient rehabilitation services.

Outcomes: Case fatality, need for institutional care, dependency, global 'poor' outcome (comprising death or one of the following in order of preference: resident in institutional care, severe dependency at end of follow-up, or deterioration in physical function during follow-up).

6. Was the search strategy adopted likely to have missed many potentially relevant studies?

Sources searched:

- MEDLINE
- SIGLE (System for Information on Grey Literature in Europe)
- BIDS ISI including Citation Index
- CINAHL
- The Cochrane Library
- Index Medicus
- Hand searches of UK & International dissertation abstracts
- Bibliographies of known trials
- Relevant articles and books
- Contact with authors of previous articles on day hospital care
- The reviewers' work was also publicised through presentations at geriatric symposia

Key search terms used:

- day care
- daycare
- out-patient clinic
- ambulatory care excluding child, children
- excluding surgery
- excluding substance abuse
- excluding HIV
- text word search of day hospital(s)

The authors employed a comprehensive search strategy consistent with the review question. However the authors did not report whether or not a language restriction was used raising the possibility that some potentially relevant studies may have been omitted. Furthermore as the review was published in 1999 and searches were conducted up to January 1997 an update is now required to take into account developments in service provision.

7. How were inclusion/exclusion criteria applied?

The search criteria appeared to have a high degree of sensitivity but low precision. The initial search identified 703 articles of which 613 were excluded upon reading the abstracts. An examination of the remaining 90 articles yielded 17 clinical trials that fulfilled the authors' predetermined definition of a geriatric day hospital. Of these 17 trials, a further 5 studies were excluded and reasons given. It is unclear who undertook the identification of the 12 studies included in the review. In general however the process was clearly reported thereby enhancing the reproducibility of the review.

8. Was the validity of included studies assessed?

The internal validity of the included studies was strengthened by their independent assessment by 3 reviewers to establish eligibility, agree sub-categories for the trials based on the treatments comparison, and extract data in line with pre-determined outcomes. The three reviewers also independently judged the quality of the reviews using a checklist that included assessments of the method of treatment allocation, performance bias, presence of an intention to treat analysis and blinding of outcome assessment.

9. Was the process of data abstraction adequate?

The data abstraction process strengthened the validity of the review and appeared consistent with the review question. Data was extracted in line with pre-determined outcomes (see question 5) and where necessary the surviving trial authors were contacted and asked to supply additional information.

10. Were the important steps in the review reproducible and bias free?

The main steps of the review were clearly reported enhancing its reproducibility and validity:

- The search for all potentially relevant studies was comprehensive and consistent with the review question.
- The methods used to apply inclusion/exclusion criteria were also clearly explained.
- 3 reviewers assessed the validity and quality of the included studies independently.
- The data extraction process was well documented and based on predetermined outcome measures thereby reducing bias.

11. What was (were) the relevant and justifiable review bottom line(s) - as stated in the review?

12 studies were reviewed involving 22 day hospitals and 2,867 patients. 5 studies compared day hospitals with comprehensive elderly care, 4 compared day hospitals with domiciliary care and 3 compared day hospitals with no comprehensive elderly care.

Meta-analyses of the primary outcomes for day hospitals for elderly people compared with alternative forms of care were as follows:

<u>Death by the end of follow up (n=12)</u>

- No significant differences between day hospital care and any of the comparators.
- Pooled odds ratio (OR) for all trials showed no difference between day hospitals & comparison groups: OR 1.02 (95% CI 0.82, 1.26)
- No significant heterogeneity between the results of individual trials or categories of trials.

<u>Death or institutional care by the end of follow up (n=11)</u>

- Overall there was no significant reduction in this combined outcome measure
- Results were calculated using a random effects model as there was some heterogeneity within and between the trial categories: OR 0.79 (95% CI 0.57, 1.11)
- The effects of day hospitals compared with comprehensive elderly services and domiciliary care were similar:
  Day hospitals vs comprehensive elderly services: OR 1.00 (95% CI 0.69, 1.44)
  Day hospitals vs domiciliary care: OR 0.97 (95% CI 0.44, 2.11)
- Patients using day hospitals were less likely to die or need institutional care than those receiving no comprehensive services: OR 0.53 (95% CI 0.36, 0.79), $p<0.001$

Death or deterioration in activities of daily living (n=7)

- Overall there was no difference between the groups:
  OR 1.07 (95% CI 0.76, 1.49) random effects model
- There was a trend towards day hospital care being better than no comprehensive care:
  OR 0.76 (95% CI 0.56, 1.05) random effects model

Death or poor outcome (n=12)

- Overall there was no significant difference between day hospital and alternative forms of care: OR 0.90 (95%CI 0.71, 1.14) random effects model
- The effects of day hospitals compared with comprehensive elderly services and domiciliary care were similar:
  Day hospitals vs comprehensive elderly services: OR 1.05 (95% CI 0.79, 1.40)
  Day hospitals vs domiciliary care: OR 1.06 (95% CI 0.56, 2.01)
- Patients using day hospitals were less likely to have a poor outcome than those receiving no comprehensive services: OR 0.72 (95% CI 0.53, 0.99), $p<0.05$

Institutional care (n=11)

- Overall there was a trend towards fewer day hospital survivors requiring long term institutional care than comparators (medium follow up 12 months):
  OR 0.77 (95% CI 0.52, 1.13) random effects model
- This trend was particularly apparent in the comparison between day hospital care and no comprehensive care: OR 0.50 (95% CI 0.26, 0.96), $p<0.05$
- On the basis of these data 15 patients (95% CI 10,34) would need to attend a day hospital as opposed to receiving no comprehensive service to prevent 1 admission to long term institutional care

Deterioration in activities of daily living amongst survivors (n=7)

- Overall there was no difference between day hospital care and alternative forms of care: OR 1.03 (95% CI 0.65, 1.65) random effects model
- Day hospital attendees appeared less likely to deteriorate than those receiving no comprehensive care: OR 0.60 (95% CI 0.38, 0.97), $p<0.05$

The secondary outcomes for day hospitals for elderly people compared with alternative forms of care were as follows:

Hospital bed use (n=12)

- This figure was calculated for individual trials, and for groups of trials by dividing the total number of bed days by the total number of patients.
- There was a small reduction in bed use by day hospital patients across all trials (15.0 vs 16.4 days with subgroup results as follows:
  Day hospital vs comprehensive elderly care: 20.5 vs 21.4
  Day hospital vs domiciliary care: 7.7 vs 11.1
  Day hospital vs no comprehensive care: 11.2 vs 11.7

Costs (n=9)

- Of the 9 trials that included a comparison of treatment costs only 2 included costs of nursing care
- 6 trials reported day hospital care was more expensive than the comparison treatment
- 2 trials reported the costs were similar
- 1 trial reported that day hospital attendance was considerably cheaper than inpatient care

Subjective health status
Patient satisfaction
Carer distress

The data was incomplete for these outcomes therefore no conclusions could be drawn.

12. Was the review up-to-date?

The review was published in 1999 and searches were conducted up to January 1997. An update would therefore be helpful to take account of developments in service provision.

13. General comments

A clearly focused, well executed review containing a cogent statement of method sufficient to permit its replication.

Whilst the review employed a comprehensive search strategy and the studies retrieved seemed to present the best available evidence at the time of its completion (January 1997) the evidence assessed mainly related to the 1980's and 1990's. The review therefore does not reflect more recent changes in health care provision and would benefit from an update. A further drawback relates to the heterogeneity of the included trials arising from the variations in subjects and the (unknown) interventions employed in the various day hospitals and comparison treatments. This together with the small scale of the included trials results in a lack of statistical power in the overall findings.

14. Recommendation for implementation of this review by purchasers

The review makes three distinct comparisons:

1. day hospitals vs comprehensive elderly care (inpatient/outpatient services)
2. day hospitals vs domiciliary care (rehabilitation at home or a social day centre)
3. day hospitals vs no comprehensive elderly care (no routine access to rehabilitation)

The differences between 'other forms of care' and 'no care' are especially apparent and the authors' decision to include the three comparisons within one overall meta-analysis seems inappropriate. The authors acknowledge the differences between the day hospital/other treatment and day hospital/no treatment comparisons in their report of the results however we feel the groups should have been more clearly separated at the outset.

In general, day hospitals appear to have similar effects on patient outcomes to other forms of elderly care such as inpatient, outpatient and domiciliary services. However as the included

studies have limited statistical power and report wide confidence intervals one cannot rule out a clinical benefit/disbenefit.

More favourable outcomes are demonstrated amongst patients attending day hospitals in comparison with those receiving no comprehensive elderly care.

Day hospital attendance may have a favourable impact on the need for long term institutional care. A trend illustrating fewer day hospital patients requiring long term institutional care than those receiving other forms of care was reported, this trend being particularly apparent in the day hospital care vs no comprehensive elderly care comparison. Furthermore a trend towards reduced use of hospital beds was evidenced amongst the day hospital attendees in comparison with those utilizing other services/no service.

Day hospitals appear to be more expensive than other forms of comprehensive elderly care however more stringent costing analyses are required to assess the extent to which these higher costs may be offset by reduced demands on hospital and institutional care resources.

In conclusion whilst the results of the review seem to represent the best available evidence at the time of its completion the studies included relate mainly to the 1980's and 90's and an assessment of their relevance to present service provision should take this into account. Furthermore the validity of the authors' conclusions may be questioned given the limited statistical power of the studies included in the review.