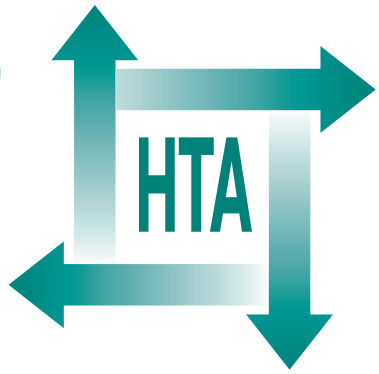
Health Technology Assessment 2006; Vol. 10: No. 31

Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation

N Woolacott, Y Bravo Vergel, N Hawkins, A Kainth, Z Khadjesari, K Misso, K Light, C Asseburg, S Palmer, K Claxton, I Bruce, M Sculpher and R Riemsma

September 2006



Health Technology Assessment
NHS R&D HTA Programme

How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation

N Woolacott,[1*] Y Bravo Vergel,[2] N Hawkins,[2] A Kainth,[1] Z Khadjesari,[1] K Misso,[1] K Light,[1] C Asseburg,[2] S Palmer,[2] K Claxton,[2] I Bruce,[3] M Sculpher[2] and R Riemsma[1]

[1] Centre for Reviews and Dissemination, University of York, UK
[2] Centre for Health Economics, University of York, UK
[3] ARC Epidemiology Unit, University of Manchester, UK

* Corresponding author

Declared competing interests of authors: R Riemsma is a member of the editorial board for *Health Technology Assessment* but he was not involved in the editorial process for this report

Published September 2006

This report should be referenced as follows:

Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, *et al*. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. *Health Technol Assess* 2006;**10**(31).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®*/Clinical Medicine.

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a short time period.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 04/04/01. The protocol was agreed in April 2004. The assessment report began editorial review in August 2005 and was accepted for publication in November 2005. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

Abstract

Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation

N Woolacott,[1*] Y Bravo Vergel,[2] N Hawkins,[2] A Kainth,[1] Z Khadjesari,[1] K Misso,[1] K Light,[1] C Asseburg,[2] S Palmer,[2] K Claxton,[2] I Bruce,[3] M Sculpher[2] and R Riemsma[1]

[1] Centre for Reviews and Dissemination, University of York, UK
[2] Centre for Health Economics, University of York, UK
[3] ARC Epidemiology Unit, University of Manchester, UK
* Corresponding author

Objectives: To evaluate the clinical effectiveness, safety, tolerability and cost-effectiveness of etanercept and infliximab for the treatment of active and progressive psoriatic arthritis (PsA) in patients who have inadequate response to standard treatment, including disease-modifying antirheumatic drug (DMARD) therapy.

Data sources: Electronic databases were searched up to July 2004.

Review methods: A systematic review evaluated the clinical efficacy and adverse effects of etanercept and infliximab. The efficacy of DMARDs in the treatment of PsA was also reviewed and treatments were compared using Bayesian evidence synthesis methods. Following evaluation of existing economic evaluations of etanercept and infliximab in PsA, a new economic model was developed (the York Model). This utilised the results from the evidence synthesis and data from a range of other sources.

Results: Across the two trials, at 12 weeks, around 65% of patients treated with etanercept achieved an American College of Rheumatology (ACR) 20 {pooled relative risk (RR) 4.19 [95% confidence interval (CI) 2.74 to 6.42]}, demonstrating a basic degree of efficacy in terms of arthritis-related symptoms. In addition, around 45% of patients treated with etanercept achieved an ACR 50 [pooled RR 10.84 (95% CI 4.47 to 26.28)] and around 12% achieved an ACR 70 [pooled RR 16.28 (95% CI 2.20 to 120.54)], demonstrating a good level of efficacy. The subgroup analyses conducted in one trial revealed that the effect of etanercept was not dependent upon patients' concomitant use of methotrexate. In addition, almost 85% of patients treated with etanercept achieved a Psoriatic Arthritis Response Criteria (PsARC) [pooled RR 2.60 (95% CI 1.96 to 3.45). The Psoriatic Area and Severity Index (PASI) results indicate some beneficial effect on psoriasis at 12 weeks; however, the data are sparse. The statistically significant reduction (improvement) in Health Assessment Questionnaire (HAQ) score with etanercept compared with placebo indicates a beneficial effect of etanercept on function. Similar results were seen at 24 weeks, except that the results for PASI 75 and PASI 50 now achieved statistical significance and data for Total Sharp Score annualised rate of progression were available; this was statistically significantly lower in etanercept-treated patients than in placebo-treated patients. Uncontrolled follow-up of patients indicates that treatment benefit may be maintained for at least 50 weeks. At 16 weeks, 65% of patients treated with infliximab achieved an ACR 20 [RR 6.80 (95% CI 2.89 to 16.01)], demonstrating a basic degree of efficacy in terms of arthritis-related symptoms. This level of efficacy was not dependent upon patients' concomitant use of methotrexate. Almost half the patients treated with infliximab achieved an ACR 50 [RR 49.00 (95% CI 3.06 to 785.06)] and over one-quarter achieved an ACR 70 [RR 31.00 (95% CI 1.90 to 504.86)] compared with none of the placebo group, demonstrating a good level of efficacy. In addition, 75% of patients treated with infliximab achieved a PsARC [RR 3.55 (95% CI 2.05 to 6.13)]. The beneficial treatment effect on psoriasis was also statistically significant with a mean difference in percentage change from baseline in PASI of –5 (95% CI –6.8 to –3.3), as was the percentage improvement from baseline in HAQ score with infliximab compared with placebo [mean difference 51.4 (95% CI 48.08 to 54.72)], indicating a beneficial effect of infliximab on functional status. Uncontrolled data from all measures of joint disease, psoriasis and HAQ collected up to 50

weeks of follow-up reflect those at 16 weeks. There were no radiographic assessments, so nothing can be determined about the potential or otherwise of infliximab to delay the progression of joint disease. Using the York cost-effectiveness model, infliximab was consistently dominated by etanercept because of its higher acquisition and administration costs without superior effectiveness. The incremental cost per quality-adjusted life-year (QALY) gained of etanercept compared with palliative care ranged from £14,818 (females, 40-year time horizon) to £49,374 (males, 1-year time horizon) if it is assumed that, when patients eventually fail on biological therapy, their disability (in terms of HAQ score) deteriorates by the same amount as it improved when they initially respond to treatment (rebound equal to gain). Results for etanercept ranged from £25,443 (females, 40-year time horizon) to £49,441 (males, 1-year time horizon) per QALY gained under the assumption that, when patients fail on therapy, their disability level returns to what it would have been had they never responded (rebound equal to natural history).

Conclusions: The limited data available indicated that etanercept and infliximab are efficacious in the treatment of PsA with beneficial effects on both joint and psoriasis symptoms and on functional status. Short-term data indicated that etanercept can delay joint disease progression, but long-term data are needed. There are no controlled data as yet to indicate that infliximab can delay joint disease progression. Treatment with both etanercept and infliximab for 12 weeks demonstrated a significant degree of efficacy, with no statistically significant difference between them. For both drugs, adverse events were common with mild injection/infusion reactions being the main treatment-related effect. The York model indicated that etanercept is more cost-effective than infliximab as it has a lower cost with little difference in outcomes. The cost-effectiveness of etanercept is also sensitive to assumptions made about the extent of disease progression when patients are responding to therapy. The number of years for which a patient can be safely on biologicals is uncertain so these results should be considered with caution. Further research should include long-term controlled trials to confirm benefits, review adverse events and to explore further the implications of biologic therapy.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Acitretin A synthetic derivative of vitamin A that is taken orally. It is indicated for severe psoriasis.

Adverse effect An abnormal or harmful effect caused by and attributable to exposure to a chemical (e.g. a drug), which is indicated by some result such as death, a physical symptom or visible illness. An effect may be classed as adverse if it causes functional or anatomical damage, causes irreversible change in the homeostasis of the organism or increases the susceptibility of the organism to other chemical or biological stress.

Ankylosing spondylitis A rheumatic disease that affects the spine and may lead to some degree of stiffness in the back. As the inflammation goes and healing takes place, bone grows out from both sides of the vertebrae and may join the two together; this stiffening is called ankylosis.

Arthritis A term meaning inflammation of the joint(s), but which is often used to include all joint disorders. Sometimes joints are damaged through the disease process of arthritis.

Articular Of or relating to the joints.

Autoimmune disease A disorder of the body's defence mechanism (immune system), in which antibodies and other components of the immune system attack the body's own tissue, e.g. lupus (SLE).

Biologic therapies (biologicals) Medical preparations derived from living organisms. Includes anti-TNF drug and other new drugs which target the pathologically active T cells involved in psoriasis, and psoriatic arthritis.

Confidence interval (CI) The typical ('Classical' or 'Frequentist') definition is the range within which the 'true' value (e.g. size of effect of an intervention) would be expected to lie if sampling could be repeated a large number of times (e.g. 95 or 99%).

Corticosteroid A synthetic hormone similar to that produced naturally by the adrenal glands that is available in pill, topical and injectable forms.

Cost–benefit analysis An economic analysis that converts the effects or consequences of interventions into the same monetary terms as the costs and compares them using a measure of net benefit or a cost–benefit ratio.

Cost-effectiveness analysis An economic analysis that expresses the effects or consequences of interventions on a single dimension. This would normally be expressed in 'natural' units (e.g. cases cured, life-years gained, additional strokes prevented). The difference between interventions in terms of costs and effects is typically expressed as an incremental cost-effectiveness ratio (e.g. the incremental cost per life-year gained).

Cost–utility analysis The same as a cost-effectiveness analysis but the effects or consequences of interventions are expressed in generic units of health gain, usually quality-adjusted life-years (QALYs).

Crohn's disease An inflammatory condition of the digestive tract; rheumatic diseases are often associated with it and ulcerative colitis is related to it.

continued

Glossary *continued*

C-reactive protein (CRP) Concentrations of this protein in the blood can be measured as a test of inflammation or disease activity, for example in rheumatoid arthritis.

Ciclosporin A medication originally developed to prevent the immune system from rejecting transplanted organs, which has also proved helpful in treating psoriasis.

Disease-modifying antirheumatic drugs (DMARDs) DMARDs are drugs capable of modifying the progression of rheumatic disease. The term is, however, applied to what are now considered to be traditional disease modifying drugs, in particular sulfasalazine, methotrexate and ciclosporin, in addition to azathioprine, cyclophosphamide, antimalarials, penicillamine and gold. The newer agent leflunomide may be included as a DMARD. The biologics such as etanercept and infliximab are not generally referred to as DMARDS.

Effect size A generic term for the estimate of effect for a study.

Emollient An agent that holds moisture in the skin and, by doing so, softens or soothes it.

Erythrocyte sedimentation rate (ESR) One of the tests designed to measure the degree of inflammation.

Fixed-effect model A statistical model that stipulates that the units under analysis (e.g. people in a trial or study in a meta-analysis) are the ones of interest, and thus constitute the entire population of units. Only within-study variation is taken to influence the uncertainty of results (as reflected in the confidence interval) of a meta-analysis using a fixed-effect model.

Heterogeneity In systematic reviews, heterogeneity refers to variability or differences between studies in the estimates of effects. A distinction is sometimes made between 'statistical heterogeneity' (differences in the reported effects), 'methodological heterogeneity' (differences in study design) and 'clinical heterogeneity' (differences between studies in key characteristics of the participants, interventions or outcome measures).

Immunomodulator A substance that alters the body's immune response.

Intention-to-treat An intention-to-treat analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not.

Joint A structure by which two bones are joined together. Normal joints consist of a smooth layer of cartilage overlying the bone end, which allows freedom of movement and acts as a shock absorber.

Methotrexate One of the oldest chemotherapy drugs used to treat cancer; used in the treatment of psoriasis.

Mixed treatment comparison Mixed treatment comparison is a form of meta-analysis used to strengthen inference concerning the relative efficacy of two treatments. It uses data based on direct comparisons (A versus B and B versus C trials) and indirect comparisons (A versus C trials); also, it facilitates simultaneous inference regarding all treatments in order to select the best treatments.

Monoclonal antibody An antibody produced in a laboratory from a single clone that recognises only one antigen.

Non-steroidal anti-inflammatory drugs (NSAIDs) NSAIDs consist of a large range of drugs of the aspirin family, prescribed for different kinds of arthritis, which reduce inflammation and control pain, swelling and stiffness.

Psoriasis Area and Severity Index (PASI) score A number representing the size, redness, thickness and scaliness of a person's psoriasis.

Placebo An inactive substance or procedure administered to a patient, usually to compare its effects with those of a real drug or other intervention, but sometimes for the psychological benefit to the patient through a belief that they are receiving treatment.

Plaque psoriasis The most common form of psoriasis, also known as psoriasis vulgaris, recognised by red, raised lesions covered by silvery scales. About 80% of psoriasis patients have this type.

continued

Glossary *continued*

Psoriasis A chronic skin disease characterised by inflammation and scaling. Scaling occurs when cells in the outer layer of skin reproduce faster than normal and pile up on the skin's surface. It is understood to be a disorder of the immune system.

Psoriatic arthritis (PsA) This disease is characterised by stiffness, pain and swelling in the joints, especially of the hands and feet. It affects about 23% of people with psoriasis. Early diagnosis and treatment can help inhibit the progression of joint deterioration.

Quality-adjusted life-year (QALY) An index of health gain where survival duration is weighted or adjusted by the patient's quality of life during the survival period. QALYs have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

Quality of life A concept incorporating all the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity and other factors which might affect their physical, mental and social well-being.

Random effects model A statistical model sometimes used in meta-analysis in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.

Randomised controlled trial (RCT) (synonym: randomised clinical trial) An experiment in which investigators randomly allocate eligible people into intervention groups to receive or not to receive one or more interventions that are being compared.

Relative risk (RR) (synonym: risk ratio) The ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. A relative risk of one indicates no difference between comparison groups. For undesirable outcomes, an RR that is less than one indicates that the intervention was effective in reducing the risk of that outcome.

Remission A lessening or abatement of the symptoms of a disease.

Rheumatoid arthritis A chronic autoimmune disease characterised by pain, stiffness, inflammation, swelling and, sometimes, destruction of joints.

Sensitivity analysis An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Statistical significance An estimate of the probability of an association (effect) as large or larger than what is observed in a study occurring by chance, usually expressed as a *p*-value.

Squamous cell carcinoma A form of skin cancer that is more aggressive than basal cell carcinoma. People who have received PUVA (psoralens plus long-wavelength UV radiation) may be at risk of this type of skin cancer.

Systemic Affecting the entire body internally.

Systemic treatment A treatment such as a pill or an injection.

T cell A type of white blood cell that is part of the immune system that normally helps protect the body against infection and disease.

Thrombocytopenia A disorder sometimes associated with abnormal bleeding in which the number of platelets (cells that help blood to clot) is abnormally low.

Topical agent A treatment such as a cream, salve or ointment that is applied to the surface of the skin.

Toxicity The potential of a drug or treatment to cause harmful side-effects.

Tumour necrosis factor (TNF) One of the cytokines, or messengers, known to be fundamental to the disease process that underlies psoriasis. It often plays a key role in the onset and the continuation of skin inflammation.

Variance A measure of the variation shown by a set of observations, defined by the sum of the squares of deviations from the mean, divided by the number of degrees of freedom in the set of observations.

continued

Glossary *continued*

Visual analogue scale Direct rating where raters are asked to place a mark at a point between two anchor states appearing at either end of the line. It is used as a method of valuing health states.

Weighted mean difference (in meta-analysis) A method of meta-analysis used to combine measures on continuous scales, where the mean, standard deviation and sample size in each group are known. The weight given to each study is determined by the precision of its estimate of effect and is equal to the inverse of the variance. This method assumes that all of the trials have measured the outcome on the same scale.

List of abbreviations

ACR	American College of Rheumatology
ANA	anti-nuclear antibodies
BNF	British National Formulary
BSA	body surface area
BSR	British Society for Rheumatology
CEAC	cost-effectiveness acceptability curve
CHF	congestive heart failure
CI	confidence interval
CRP	C-reactive protein
CSA	ciclosporin
DIP	distal interphalangeal
DMARD	disease-modifying anti-rheumatic drug
ERAS	Early RA Study
EQ-5D	EuroQol-5D
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
HAQ	Health Assessment Questionnaire
HCHS	Hospital and Community Health Services
HEED	Health Economic Evaluation Database
HRG	healthcare resource group
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio (i.e. incremental cost per QALY gained)
IP	interphalangeal
LFT	liver function test
MS	multiple sclerosis
MTP	metatarsophalangeal
MTX	methotrexate
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NSAID	non-steroidal anti-inflammatory drug
OLS	ordinary least-squares
OMERACT	Outcome Measures in Rheumatoid Arthritis (Rheumatology) Clinical Trials
PASI	Psoriasis Area and Severity Index
PhGA	physician global assessment
PsA	psoriatic arthritis
PSA	probabilistic sensitivity analysis

continued

List of abbreviations *continued*

PsARC	Psoriatic Arthritis Response Criteria
PtGA	patient global assessment
PUVA	psoralens plus long-wavelength UV radiation
QALY	quality-adjusted life-year
QoL	quality of life
RA	rheumatoid arthritis
RCT	randomised controlled trial
RF	rheumatoid factor
RR	relative risk
SE	standard error
SF-36	Short Form with 36 Items
SLE	systemic lupus erythematosus
SPC	summary of product characteristics
SJC	swollen joint count
SSZ	sulfasalazine
TB	tuberculosis
TJC	tender joint count
TNF	tumour necrosis factor
TSS	Total Sharp Score
U&E	urea and electrolytes
VAS	visual analogue scale
WMD	weighted mean difference
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable amount of data that were supplied by Wyeth and Schering-Plough and which are deemed commercial-in-confidence. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of commercial-in-confidence data removed and replaced by the statement 'CiC removed' is available on the NICE website www.nice.org.uk

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences and tables have been removed. Readers should bear in mind that the discussion and conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Executive summary

Objective

The aim of this review was to evaluate the clinical effectiveness, safety, tolerability and cost-effectiveness of etanercept and infliximab for the treatment of active and progressive psoriatic arthritis (PsA) in patients who have inadequate response to standard treatment, including disease-modifying antirheumatic drug (DMARD) therapy.

Background

PsA is defined as an inflammatory arthropathy associated with psoriasis, which is usually negative for rheumatoid factor (RF) [an antibody produced by plasma cells and found in around 70% of cases of rheumatoid arthritis (RA)]. It is a hyperproliferative and inflammatory arthritis that is distinct from RA and closely associated with psoriasis. Overall, because PsA involves both skin and joints, it can result in significant quality of life impairment, joint deformity and psychosocial disability. Owing to the lack of a precise definition and diagnostic marker for psoriatic arthritis, it is difficult to gauge its prevalence. The UK adjusted prevalence of PsA in the primary care setting has been estimated to be 0.3%. In the UK both etanercept (Enbrel®) and infliximab (Remicade®) are recently licensed drugs for the treatment of adults with active and progressive PsA in patients who have responded inadequately to DMARDs. Both etanercept and infliximab are new biological agents, which target pathological T cell activity (anti-tumour necrosis factors drugs). Other therapies available for the treatment of psoriatic arthritis are DMARDs such as sulfasalazine, methotrexate and ciclosporin, all of which have limitations to their use owing to limited efficacy or serious long-term adverse effects. There is also a new DMARD, leflunomide, which is the only drug other than etanercept and infliximab licensed for the treatment of psoriatic arthritis.

Methods

A systematic review, based on literature searches conducted between April and July 2004, evaluated the clinical efficacy and adverse effects of etanercept and infliximab. The efficacy of DMARDs in the treatment of PsA was also reviewed and, where data allowed, treatments were compared utilising Bayesian evidence synthesis methods. Following evaluation of existing economic evaluations of etanercept and infliximab in psoriatic arthritis, a new economic model was developed (the York Model). This utilised the results from the evidence synthesis and data from a range of other sources.

Results

Number and quality of studies

The review of the clinical evidence identified 40 studies: three trials of the efficacy of the interventions of interest (two for etanercept and one for infliximab), 23 studies of the adverse effects of the interventions and 14 trials of the efficacy of the DMARDs.

The trials of the efficacy of the interventions were all double-blind and placebo-controlled trials and were rated 'Good' by the quality assessment. A total of 265 patients were included in the etanercept trials and 104 in the infliximab trial.

Efficacy of the interventions

Across the two trials, at 12 weeks, around 65% of patients treated with etanercept achieved an American College of Rheumatology (ACR) 20 {pooled relative risk (RR) 4.19 [95% confidence interval (CI) 2.74 to 6.42]}, demonstrating a basic degree of efficacy in terms of arthritis-related symptoms. In addition, around 45% of patients treated with etanercept achieved an ACR 50 [pooled RR 10.84 (95% CI 4.47 to 26.28)] and around 12% achieved an ACR 70 [pooled RR 16.28 (95% CI 2.20 to 120.54)], demonstrating a good level of efficacy. The subgroup analyses conducted in one trial revealed that the effect of etanercept was not dependent upon patients' concomitant use of methotrexate. In addition, almost 85% of patients treated with etanercept achieved a Psoriatic Arthritis Response Criteria (PsARC) [pooled RR 2.60 (95% CI 1.96 to 3.45)], which is the only joint disease outcome measure

that has been specifically defined for psoriatic arthritis. The Psoriatic Area and Severity Index (PASI) results indicate some beneficial effect on psoriasis at 12 weeks; however, the data are sparse. The statistically significant reduction (improvement) in Health Assessment Questionnaire (HAQ) score with etanercept compared with placebo indicates a beneficial effect of etanercept on function. Similar results were seen at 24 weeks, except that the results for PASI 75 and PASI 50 now achieved statistical significance and data for Total Sharp Score (TSS) annualised rate of progression were available; this was statistically significantly lower in etanercept-treated patients than in placebo-treated patients. Uncontrolled follow-up of patients indicated that treatment benefit may be maintained for at least 50 weeks.

At 16 weeks, 65% of patients treated with infliximab achieved an ACR 20 [RR 6.80 (95% CI 2.89 to 16.01)], demonstrating a basic degree of efficacy in terms of arthritis-related symptoms. This level of efficacy was not dependent upon patients' concomitant use of methotrexate. Almost half the patients treated with infliximab achieved an ACR 50 [RR 49.00 (95% CI 3.06 to 785.06)] and over one-quarter achieved an ACR 70 [RR 31.00 (95% CI 1.90 to 504.86)] compared with none of the placebo group, demonstrating a good level of efficacy. In addition, 75% of patients treated with infliximab achieved a PsARC [RR 3.55 (95% CI 2.05 to 6.13)]. The beneficial treatment effect on psoriasis was also statistically significant with a mean difference in percentage change from baseline in PASI of –5 (95% CI –6.8 to –3.3), as was the percentage improvement from baseline in HAQ score with infliximab compared with placebo [mean difference 51.4 (95% CI 48.08 to 54.72)], indicating a beneficial effect of infliximab on functional status.

Uncontrolled data from all measures of joint disease, psoriasis and HAQ collected at up to 50 weeks of follow-up reflect those at 16 weeks. There were no radiographic assessments, so the potential or otherwise of infliximab to delay the progression of joint disease could not be assessed.

Adverse effects

Injection site reactions appear to be the most common adverse effects of etanercept. Overall, etanercept appeared to be well tolerated in short- and long-term use, although much of the long-term data are not from patients with psoriastic arthritis. As identified in earlier reviews, the main areas of concern relate to uncommon but serious adverse events the significance of which is not readily discernible from the published reports of clinical trials.

Overall, infusion reactions, the development of antibodies and infections appear to be the most common adverse effects of infliximab, although it is unclear whether they occur more frequently than on placebo. In the long term, the possible risk of serious adverse effects requires caution and further monitoring and investigation.

Importantly, both biologics are new drugs with which there is only very limited experience and long-term monitoring. Therefore, review and further investigations of their safety are warranted.

DMARDs

The available drug treatments for psoriatic arthritis, with the exception of sulfasalazine and possibly leflunomide, have not been investigated thoroughly. The available limited data indicate some degree of efficacy for all DMARDs, but the evidence for intramuscular gold and azathroprine is particularly weak and may not be reliable.

Evidence synthesis

A Bayesian evidence synthesis was undertaken to complete the clinical evaluation and to estimate relevant parameters for the economic model. The need to populate the economic model indicated a focus on response rates to therapy in terms of PsARC and changes in HAQ conditional on whether the patient responds to therapy. The synthesis relates to etanercept, infliximab and placebo as these are the comparators in the economic model. The probability of responding to infliximab treatment was estimated to be 0.7705, and for etanercept this probability is also estimated as 0.7705. The RR of infliximab versus etanercept of 1.0 (95% CI 0.82 to 1.18) also highlighted that, as far as response rates are concerned, the evidence synthesis suggested the two treatments are very similar. The evidence synthesis showed that responders to either treatment experienced a statistically significant improvement in HAQ scores. Incremental to the natural progression baseline change in HAQ of 0.0166 (95% CI 0.002 to 0.031), responders to etanercept treatment experienced an additional change in HAQ of –0.72 (95% CI –0.83 to –0.61), and responders to infliximab treatment of –0.67 (95% CI –0.84 to –0.49). Both of these HAQ changes are significantly different from the incremental HAQ change experienced by placebo responders, of –0.28 (95% CI –0.39 to –0.18), but

do not differ substantially between the two active treatments.

Cost-effectiveness

Cost-effectiveness models were submitted by Wyeth and Schering-Plough. Wyeth's model estimated the incremental cost per quality-adjusted life-year (QALY) gained for etanercept (compared with a composite comparator) to range from £28,189 for a 10-year time horizon to £66,580 for a 6-month time horizon. Schering-Plough presented two models. The 'Active Joint' model estimated an incremental cost per QALY gained for infliximab of £36,786 (5-year time horizon). The 'Chronic Active Joint' model estimated an incremental cost-effectiveness ratio (ICER) of £33,877 (30-year time horizon).

Given some potential limitations of the manufacturers' models and their failure to compare the two biological therapies directly and with palliative care, a new model was developed (the York Model). Results were estimated over a range of time horizons and based on a number of alternative assumptions. Infliximab is consistently dominated by etanercept because of its higher acquisition and administration costs without superior effectiveness. The incremental cost per QALY gained of etanercept compared with palliative care ranges from £14,818 (females, 40-year time horizon) to £49,374 (males, 1-year time horizon) if it is assumed that, when patients eventually fail on biological therapy, their disability (in terms of HAQ score) deteriorates by the same amount as it improved when they initially respond to treatment (rebound equal to gain). The ICERs of etanercept range from £25,443 (females, 40-year time horizon) to £49,441 (males, 1-year time horizon) if it is assumed that, when patients fail on therapy, their disability level returns to what it would have been had they never responded (rebound equal to natural history).

Sensitivity analyses

Probabilistic sensitivity analysis showed that etanercept and palliative care have the highest probabilities of being cost-effective. At lower levels of the threshold value of cost-effectiveness, palliative care has the higher probability of being cost-effective. As the threshold increases, so does the probability that etanercept is optimal. Scenario analysis was undertaken to assess the sensitivity of the results to other assumptions in the model. The most important analysis indicates that the ICER of etanercept increases markedly if it is assumed that etanercept only improves symptoms and does not retard disease progression. We also examined an alternative specification of the prior distribution in the evidence synthesis used to reflect between-trial variation in the placebo response rate, but no substantive change in the results was observed.

Limitations of the calculations (assumptions made)

A number of parameters in the model are based on very limited evidence. This applies, in particular, to the long-term withdrawal rate (based on a non-randomised observational study and assumed to be the same for the two biological therapies), the natural history HAQ progression (based on an unpublished cohort study of 24 PsA patients reported in the Wyeth submission) and the HAQ progression in patients responding to therapy (assumed to be zero based on some evidence for the open-label continuation studies after etanercept and infliximab).

Other important issues regarding implications

The model considered the cost-effectiveness of etanercept and infliximab compared with each other and with palliative care. This is equivalent to assuming that the biological therapies would be used 'end of line' once DMARD therapies have been tried and failed. The York Model was not able to incorporate the possible quality of life impact of the biological therapies on patients' skin. This assumption also had to be made in the two manufacturers' models. The York Model uses HAQ score as the measure of disability, which drives both quality of life and costs in the model. This is consistent with both the Wyeth models in PsA and many cost-effectiveness models of biological therapies in RA, but the use of radiological measures of disease progression may be more appropriate should data become available.

Notes on the generalisability of the findings

The efficacy data used in the clinical evaluation, evidence synthesis and the economic models were very limited, being derived from just three trials and 369 patients, with only 134 patients treated with etanercept and 52 treated with infliximab. Furthermore, these trial populations were not precisely representative of those for whom etanercept and infliximab are licensed: neither population was made up exclusively of patients who had failed to respond to at least two DMARDs. Other parameters within the economic models were also based on very limited evidence.

Conclusions

The limited data available indicated that both etanercept and infliximab are efficacious in the treatment of psoriatic arthritis with beneficial effects on both joint and psoriasis symptoms and on functional status. Short-term data indicated that etanercept can delay joint disease progression but further long-term data are required to confirm and consolidate the evidence base for this. There are no controlled data as yet to indicate that infliximab can delay joint disease progression. Further data are required to confirm the findings of the currently available trials and to demonstrate that response is maintained and that disease progression is delayed in the long term.

Treatment with both etanercept and infliximab for 12 weeks demonstrated a significant degree of efficacy, with no statistically significant difference between them.

For both etanercept and infliximab, adverse events were common with mild injection/infusion reactions being the main treatment-related effect. Concerns exist over uncommon serious and long-term adverse effects and, in the authors' opinion, further monitoring of the safety profiles of both drugs is required.

The York Model indicated that etanercept is more cost-effective than infliximab as it has a lower cost with little difference in outcomes. The incremental cost per QALY gained of etanercept compared with palliative care (i.e. to no active therapy) ranged from £14,818 (females, 40-year time horizon) to £49,374 (males, 1-year time horizon) under the assumption of rebound equal to gain. It ranged from £25,443 (females, 40-year time horizon) to £49,441 (males, 1-year time horizon) under the assumption of rebound equal to natural history progression. The cost-effectiveness of etanercept was also sensitive to assumptions made about the extent of disease progression when patients are responding to therapy. The number of years for which a patient can be safely on biologicals is uncertain so these results should be considered with caution.

Recommendations for further research

The following areas are recommended for future research (all are of equal importance).

- Long-term controlled trials are required to confirm that symptomatic benefits for joint and skin disease and improvements in function are maintained. Data on long-term HAQ progression while responding to biologics is required.
- Long-term controlled trials on the effects of biologics on joint disease progression are also required.
- Further research on the effects of biologics on both arthritis and psoriasis and their combined effects on quality of life is required, including in terms of a generic preference based (utility) instrument.
- A 2-year controlled trial of etanercept versus best care (probably methotrexate or leflunomide) is warranted; such a trial should gather comparative data on HAQ and radiographic progression with leflunomide.
- Randomised controlled trials investigating the effects of the biologics in combination with methotrexate, with reference to any synergistic effect and the possibility of tachyphylaxis, are warranted.
- Long-term monitoring studies of adverse events and regular reviews of the significance of serious adverse events are essential. Research should establish whether long-term patterns of adverse events are similar to those in RA. The setting up of a Biologics Registry for the treatment of psoriatic arthritis is advisable.
- Long-term information on withdrawal rates from biologics for lack of efficacy and adverse events is important.
- Research to establish whether intermittent biologic therapy is a reasonable option for the treatment of psoriatic arthritis would be of value.

Chapter 1

Aim of the review

The aim of this review was to evaluate the clinical effectiveness, safety, tolerability and cost-effectiveness of etanercept and infliximab for the treatment of active and progressive psoriatic arthritis (PsA) in patients who have inadequate response to standard treatment [including disease modifying antirheumatic drug (DMARD) therapy].

Chapter 2
Background

Description of underlying health problem

Epidemiology

There are difficulties in defining PsA[1] and, owing to the lack of a precise definition and diagnostic marker for PsA, it is difficult to estimate its prevalence. A study within the primary care population in north-east England that involved six general practices (population 26,348) estimated the UK adjusted prevalence of PsA in the primary care setting to be 0.3%.[2] The same study identified that PsA had a significant and measurable impact on all areas of health but was less well documented in primary care than was psoriasis. Another study using data from 77 GP practices in the Norwich Health Authority (population 413,421) reported prevalence rates per 100,000 of 3.5 for males and 3.4 for females.[3]

Aetiology, pathology and prognosis

PsA is defined as an inflammatory arthropathy associated with psoriasis which is usually negative for rheumatoid factor (RF) [an antibody produced by plasma cells and found in around 70% of cases of rheumatoid arthritis (RA)]. It is a hyperproliferative and inflammatory arthritis that is distinct from RA and closely associated with psoriasis.[1,4] Overall, because PsA involves both skin and joints, it can result in significant quality of life (QoL) impairment and joint deformity and psychosocial disability.[4,5] PsA is diagnosed when a patient with psoriasis has a distinctive pattern of peripheral and or spinal arthropathy.[5] Most, but not all, of these patients will test negative for RF. PsA differs from RA in that the absolute number of joints affected is less and the pattern of joint involvement is commonly asymmetric and involves the distal interphalangeal joints and nail lesions.[6] In PsA dactylitis, spondylitis and sacroiliitis are common whereas in RA they are not.[6] In PsA the involved joints are tighter, contain less fluid and are less tender than those in RA and there is a propensity for inflammation of the enthesal sites. In addition to distinct clinical features, PsA and RA show differences in the inflammatory reaction that accompanies each form of arthritis.[6] Most patients with PsA will have developed psoriasis first but joint involvement appears first in 19%, and concurrently with psoriasis in 16% of cases.[5] There are, however, still some difficulties in defining PsA.[1]

PsA is a progressive disorder ranging from mild synovitis to severe progressive erosive arthropathy.[7] Studies have found that patients presenting with oligoarticular disease progress to polyarticular disease and a significant percentage of patients develop joint damage and deformities, which progress over time.[8] Even in early PsA, despite current DMARD treatment, PsA results have shown radiological damage in up to 47% of patients at a median interval of 2 years.[9] Although remission might occur in PsA, especially in patients with Health Assessment Questionnaire (HAQ) score levels <1,[10] of those who can sustain clinical remission only a small fraction can discontinue medication with no evidence of damage.[11] Joint damage can occur early in the disease, often before functional limitation.[8,12] This appears to be associated with the development of inflamed entheses close to peripheral joints, although the link is still largely unclear.[7] Studies indicate that there is an association between polyarthritis and functional disability, with higher mean HAQ score than oligoarthritic patients.[13,14] With regard to disease progression, it has been shown that a polyarticular onset of PsA is an important risk factor that predicts progressive joint deformity.[15,16]

A classification scheme for PsA based on joint involvement has been proposed:[8,17] Distal interphalangeal arthritis can occur as the sole presentation or in combination with other symptoms. It can be symmetric or asymmetric and can involve a few or many joints. Adjacent nails may demonstrate psoriatic changes and joint erosions are common.

- Arthritis mutilans is a very severe presentation of the disease with osteolysis of the phalanges, metatarsals and metacarpals.
- Symmetric polyarthritis appears similar to RA, with inflammation of the metacarpals and the proximal interphalangeal joints being prominent. However, it is generally milder than RA and almost always patients are RF negative.

- Oligoarthritis is the most common form of psoriatic arthritis. It is characterised by asymmetric involvement of a small number of joints (less than four).
- Spondylitis or sacrolytis resembles ankylosing spondylitis but is generally less severe and less disabling.

Despite this classification, the forms of PsA overlap and evolve from one form to another as the disease progresses and as diagnostic investigations become more thorough.[7] A common feature of PsA is dactylis, where the whole digit appears swollen due to inflammation of the tendons and periosteum in addition to the joints. Radiographic features include bone erosions, new bone formation, bony ankylosis, bony outgrowths in the axial skeleton, osteolysis and enthesopathy.

Significance in terms of ill health

The health burden of PsA can be considerable. It is a life-long condition but its severity and hence its impact fluctuate over time.[18] A comparison of health-related quality of life (HRQoL) between patients with PsA and patients with RA, using the Medical Outcomes Study Short Form with 36 Items (SF-36) health survey and the HAQ, found that both patient populations experienced lower physical health compared with that of a general population sample.[19] The patients with RA demonstrated more active inflammatory disease at the time of assessment than the patients with PsA and patients with PsA reported higher levels of vitality than patients with RA. However, patients with PsA reported more role limitations due to emotional problems and more bodily pain after adjusting for the difference in vitality and other covariates. It appeared that there may be unique disabilities associated with the psoriasis dimension of PsA. These findings were reflected in another comparison of disability and QoL in RA and PsA; this study found that despite greater peripheral joint damage in patients with RA, function and QoL scores were the same for both groups.[20] As in RA, joint damage in PsA results in a significant reduction in a patient's HRQoL. Ideally, PsA should be diagnosed early and treated aggressively in order to minimise joint damage.[12]

In addition to its impact on QoL, PsA carries about a 60% higher risk of mortality relative to the general population.[18,21,22]

There is little information on the economic costs of PsA, with only one US study available.[23] Although the economic costs of PsA have not been studied in the UK, they are likely to be proportional to those of RA. In studies that analyse the indirect costs of RA, in general these are higher than direct costs, largely as a consequence of extensive work disability.[24] In RA, productivity losses represent the predominant economic burden of the disease[25,26] and the economic cost rises with both age and disease severity.[24,27] In the UK, direct healthcare costs have been shown to represent about one-quarter of all costs and these are dominated by inpatient and community day care.[28] One recent study reports that in the UK, drugs currently represent a minor cost: 3–4% of total costs and 13–15% of direct costs.[29]

Assessment of treatment response in psoriatic arthritis

Assessment of the effectiveness of treatments for PsA relies on there being outcome measures that accurately and sensitively measure disease activity. Overall response criteria have not yet been clearly defined; they are currently being developed by an international collaboration on outcome measures in rheumatology [Outcome Measures in Rheumatoid Arthritis (Rheumatology) Clinical Trials (OMERACT)]. There are many different parameters of disease activity in arthropathies, including number of swollen joints, number of tender joints, pain, level of disability, patient's global assessment, physician's global assessment and biochemical markers in the blood. Selecting which to assess in clinical trials and which to appoint as the primary variable can be difficult. Different ways of combining the various outcome measures have been suggested including a simple 'pooled index'.[30] In recent years, the compound response criterion, the American College of Rheumatology (ACR) 20, has gained general acceptance for the assessment of treatments for RA and this has been adopted for PsA. Another compound measure, Psoriatic Arthritis Response Criteria (PsARC), was developed specifically for a trial in PsA.[31]

ACR response criteria

The ACR response criteria were developed after the identification of a set of core disease activity measures. ACR 20 requires a 20% reduction in the tender joint count, a 20% reduction in the swollen joint count and a 20% reduction in three of five additional measures, including patient and physician global assessment, pain, disability and an acute-phase reactant. In patients with RA, the ACR 20 has been confirmed as being able to discriminate between a clinically significant and a

clinically insignificant improvement.[32,33] It is not yet clear if the ACR 20 has the same discriminatory validity in PsA.[34] The ACR 20 is generally accepted to be the **minimal** clinically important difference that indicates some response to a particular intervention. The ACR 50 reflects significant and important changes in a patient's disease status that may well be acceptable to both clinician and patient in long-term management. The ACR 70 represents a major change and approximates in most minds to a near remission. Differences between PsA and RA mean that when the ACR response criteria are used in trials of treatment for PsA, the distal interphalangeal (DIP) joints must be included.

PsARC

PsARC was developed for a trial of sulfasalazine (SSZ) in PsA.[31] Four assessment measures were selected: patient self-assessment; physician assessment; joint pain/tenderness score; and joint swelling score. Treatment response was then defined as an improvement in at least two of these four measures, one of which had to be joint pain/tenderness score or joint swelling score, with no worsening in any of the four measures. PsARC has not been validated but responses assessed by it do parallel those identified with ACR 20. A limitation of PsARC is that although developed for assessment of PsA, it does not incorporate an assessment of psoriasis. The Working Group producing the British Society for Rheumatology (BSR) guidelines for the use of anti-tumour necrosis factor (TNF) drugs in PsA[35] elected to use the PsARC as the primary joint response to anti-TNF therapy, although it advocates some extra data collection such as a patient self-assessed disability (HAQ) and a biochemical marker of disease activity such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

Radiological assessments

In all arthropathies, progression of the disease can only be truly measured by assessment of joint damage; radiological assessments include the Steinbrocker, Sharp and Larsen methods. A modification of the Steinbrocker method which assigns a score for each joint has been validated for PsA. The Sharp method grades all the joints of the hand separately for erosions and joint space narrowing, each erosion being assigned a score of 0–5 and each joint space narrowing a score of 0–4. A total score (maximum 149) is calculated. The Sharp method, modified to include the DIP and metatarsophalangeal (MTP) joints of the feet and interphalangeal (IP) joint of the first toe, was used in the Mease trial of etanercept.[36] None of these methods, which were developed for RA, score additional radiographic changes specific to PsA. A new score has been tested by Wassenberg and colleagues,[37] but this has not yet been validated in clinical trials. Whichever method is selected, it is important that trials are stratified by baseline radiographic findings.

HAQ

The HAQ score is a well-validated tool in the assessment of patients with RA.[34] It focuses on two dimensions of health status: physical disability (eight scales) and pain, generating a score of 0 (least disability) to 3 (most severe disability). Modifications of the HAQ for spondylarthropathies (HAQ-S) and for psoriasis (HAQ-SK) have been recently developed but, when tested against HAQ, their scores were almost identical,[38] suggesting either can be used in PsA.[34] The HAQ is one component of the ACR 20 (50 or 70) response criteria.

HAQ has been tested in patients with PsA, showing a moderate to close correlation with disease activity as measured by the actively inflamed joint count and some measures of clinical function (including the ACR functional class).[39] Although the HAQ has been used as a disability measure and is a common outcome measure in PsA therapy trials, it may not sufficiently incorporate all aspects of disease activity (i.e. deformity or damaged resulting from disease process, especially in late PsA),[40] so the clinical assessment of disease activity and both clinical and radiological assessments of joint damage remain important outcome measures in PsA.

Overall, the advantage of the HAQ as an instrument is that it can estimate the functional and psychological impact of the disease. HAQ is a measure conventionally used as a driver of QoL scores and costs in main economic evaluations on the use of anti-TNF drugs and DMARDs in RA.[41–43]

PASI

In evaluating the efficacy of interventions in the treatment of PsA, the outcomes measures used must assess disease activity in both the joints and the skin.[34] In clinical trials of patients with psoriasis, assessment of the response to treatment is usually based on the Psoriasis Area and Severity Index (PASI). PASI is also used in trials of PsA, although given the various degrees of severity of psoriasis in these patients not all patients may be evaluable for assessment of response; at least 3% of the body surface area (BSA) has to be affected

by the skin disease in order for the PASI measure to be used.[34] Although it is widely used, it is acknowledged to have many deficiencies: its constituent parameters have never been properly defined; it is insensitive to change in mild to moderate psoriasis; estimation of disease extent is notoriously inaccurate; and the complexity of the formula required to calculate the final score further increases the risk of error. It combines an extent and a severity score for each of four body areas (head, trunk, upper extremities and lower extremities). The extent score of 0–6 is allocated according to percentage skin involvement such that 0 and 6 represent no psoriasis and 90–100% involvement, respectively. The severity score of 0–12 is derived by adding scores of 0–4 for each of the qualities erythema (redness), induration and desquamation representative of the psoriasis within the affected area. It is probable but usually not specified in trial reports that most investigators take induration to mean plaque thickness without adherent scale and desquamation to mean thickness of scale rather than severity of scale shedding. The severity score for each area is multiplied by the extent score and the resultant body area scores, weighted according to the percentage of total BSA which that body area represents (10% for head, 30% for trunk, 20% for upper extremities and 40% for lower extremities), are added together to give the PASI score. Although PASI can theoretically reach 72, scores in the upper half of the range (above 36) are uncommon even in severe psoriasis.

Although the optimum assessment outcomes for PsA trials are yet to be defined, those selected as the primary measures of efficacy in this review, namely PsARC, ACR 20, 50, 70, HAQ and PASI based measures, all have discriminatory capability and are generally accepted for the assessment of treatment effect. HAQ has been chosen as our main outcome variable for the economic evaluation because it makes it technically feasible to evaluate the impact of retarding and/or halting the progression of the disease, both in an economic sense and in terms of QoL.

Current service provision

Effective treatment for PsA needs to consider both skin and joint disease, especially if both are affected significantly. Both dermatologists and rheumatologists manage PsA, each focusing on their specialism.[8] Most treatments for PsA have been borrowed from those used for RA, and non-steroidal anti-inflammatory drugs (NSAIDs) are widely used.[5] There is a concern that NSAIDs may provoke a flare of the psoriasis component of the disease, but this may not be of clinical significance.[7] Local corticosteroid injections are also frequently used,[5] although there is a significant risk of a serious flare in psoriasis when corticosteroids are withdrawn. Disease that is unresponsive to NSAIDs and particularly polyarticular disease should be treated with DMARDs in order to reduce joint damage and prevent disability.[7] It has also been suggested that aggressive treatment of early-stage progressive psoriatic arthritis should be implemented in order to improve prognosis.[7] Again, the treatments used are based on experience in RA rather than knowledge of the pathophysiology of PsA or trial-based efficacy. Currently, methotrexate (MTX) and SSZ are considered the DMARDs of choice, although the evidence for MTX is largely empirical and the effects of SSZ appear modest.[7] A review of the experience of 100 patients treated with DMARDs for PsA[44] reported that of those treated with SSZ, gold, MTX or hydroxychloroquine, over 70% had discontinued owing to lack of efficacy or adverse events (range 35% with MTX to 94% with hydroxychloroquine).

Recently (2004), a new DMARD, leflunomide, has been licensed for use in PsA; it is the only non-biologic licensed in PsA. Leflunomide inhibits *de novo* pyrimidine synthesis and because activated lymphocytes require a large pyrimidine pool, it preferentially inhibits T cell activation and proliferation. Controlled clinical trials have demonstrated efficacy in RA[45] and PsA.[46] Other drugs investigated for the treatment of PsA are auranofin, etretinate, fumaric acid, intramuscular gold, azathioprine and Efamol marine[47] and infliximab. Ciclosporin (CSA), penicillamine and leflunomide are also sometimes used in clinical practice.

Costs of current service

The cost to the NHS of treating PsA includes direct costs such as the cost of drugs, clinician (nurse, GP and hospital physician) time, the cost of day care therapies such as intravenous infusions and the costs of administering and monitoring drugs. Patients may also require inpatient care with an average stay of 3 days.[48] Based on prices from the British National Formulary (BNF),[49] weekly treatment costs with the most commonly used DMARDs in PsA, SSZ and MTX are approximately £2 and less than £0.50, respectively. The weekly cost of CSA is approximately £40–80 per week. Figures for the actual total costs of DMARDs for PsA are not readily available,

relevant data being subsumed within those for all rheumatic diseases.[50] In the UK in 2003 there were approximately 347,600 prescriptions for drugs that suppress the rheumatoid disease process with a total net ingredient cost of £6,602,400 and with an average cost per prescription item of £19.00.[50] In addition to the cost of these drugs, the cost of NSAIDs is considerable.

No economic evaluations of the treatment of PsA in the UK have been published.

Variation in service

No surveys of UK service models for PsA have been conducted. Although PsA is a disease of joints and skin, it is treated mainly by rheumatologists. A study conducted with patients with confirmed PsA in The Netherlands found a considerable variation in the delivery of care amongst rheumatologists, 29% of whom failed to diagnose PsA, mainly owing to their failure to enquire about skin lesions.[51] Of those who did correctly diagnose PsA, only 43% referred patients to a dermatologist and 66% ordered laboratory tests. The median costs for imaging and laboratory investigations were higher in the patients correctly diagnosed with PsA than in the remaining patients who were incorrectly diagnosed.

Description of new intervention

Numerous chemokines and cytokines are believed to play an important role in triggering cell proliferation and sustaining joint inflammation in PsA. Cytokines stimulate inflammatory processes that result in the migration and activation of T cells which then release tumour necrosis factor α (TNFα). TNFα is one of several pro-inflammatory cytokines that have been implicated in the pathogenesis of both psoriasis and PsA.[52,53] Newer strategies for the treatment of PsA have focused on modifying T cells in this disease through direct elimination of activated T cells, inhibition of T cell activation or inhibition of cytokine secretion or activity.[54] Etanercept and infliximab are among a number of these new biologic agents that have been developed and investigated for the treatment of various diseases, including psoriasis and PsA. Etanercept is a human dimeric fusion protein that binds specifically to TNF and blocks its interaction with cell surface receptors.[5] Infliximab is a murine/human chimeric anti-TNF monoclonal γ-immunoglobulin that inhibits the binding of TNF to its receptor.[5] Etanercept and infliximab have gained European Agency for the Evaluation of Medicinal Products approval for clinical use in the treatment of PsA that is unresponsive to DMARDs. They were granted their UK product licences in 2003 and 2004, respectively.

Anticipated costs of biologic interventions

Based on the recommended dose regimen (25-mg injections administered twice weekly as a subcutaneous injection), the initial 3-month acquisition cost of etanercept is £2145.12, and the annual cost thereafter is £9295.52. The recommended dose for infliximab is 5 mg/kg given as an intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter, each dose corresponding to three or four vials of infliximab depending on the patient's body weight. The initial 3-month acquisition cost of infliximab is estimated to be £5414.40 and the annual cost thereafter is £11,731.20.

Chapter 3
Methods

Search strategy

Searches were undertaken on the following databases to identify relevant clinical and cost-effectiveness research. Full details of the search strategies are reported in Appendix 1.

- MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/)
- EMBASE (OVID Online – http://www.ovid.com/)
- National Research Register (NRR) (CD-ROM)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm)
- CenterWatch (Internet – http://www.centerwatch.com/index.html)
- Current Controlled Trials (Internet – http://controlled-trials.com/)
- ClinicalTrials.gov (Internet – http://clinicaltrials.gov/)
- NHS Economic Evaluation Database (NHS EED) (CRD administration database)
- Health Economic Evaluation Database (HEED) (CD-ROM)
- EconLit (SilverPlatter on the web via ARC2 WebSPIRS – http:/arc.uk.ovid.com/)
- ISI Science and Technology Proceedings (Web of Knowledge – http://wos.mimas.ac.uk/)
- Social Science Citation Index (Web of Science – http://wos.mimas.ac.uk/)
- Science Citation Index (Web of Science – http://wos.mimas.ac.uk/)

All databases were searched from their inception to the date of the search. No language or other restrictions were applied.

Searches were also undertaken on several Internet resources, which are documented in Appendix 1.

Searches took place over a period from April to July 2004 (see Appendix 1 for dates of individual searches).

Terminology

The terms for the search strategies were identified through discussion between an Information Officer and the research team, by scanning the background literature and by browsing the MEDLINE Medical Subject Headings (MeSH).

Management of references

As several databases were searched, some degree of duplication resulted. To manage this issue, the titles and abstracts of bibliographic records were downloaded and imported into Endnote bibliographic management software to remove duplicate records.

Handsearching

The bibliographies of all included studies and industry submissions made to the National Institute for Health and Clinical Excellence (NICE) were reviewed to identify further relevant studies. Handsearching continued throughout the project.

Additional searches

Additional searches (including citation searches on key papers) were completed as required. See Appendix 1 for full details.

Inclusion and exclusion of studies

Study selection

Two reviewers selected the studies for the review. Discrepancies were resolved by consensus and a third reviewer was consulted when necessary. Each reviewer's decision and a final decision were recorded in the Endnote library.

All titles and abstracts identified by the search were screened and any references that were considered relevant by either reviewer were obtained.

No language restrictions were applied to study selection. Trials reported as full publications or unpublished full reports were included in the review. Trials reported as abstracts only were included if adequate information was provided. All of the data submitted by Wyeth and Schering-Plough were considered in the review.

Inclusion/exclusion criteria

Studies were included in the review according to the inclusion criteria described below.

Efficacy of interventions

The review addressed the following questions about the efficacy of etanercept and infliximab in the treatment of PsA:

- Is treatment effective at all?
- How effective is the treatment?
- Is the drug effective long term?
- Is there evidence of effect on disease progression?
- Is there evidence that treatment has a beneficial effect on the psoriasis component of the disease?
- Is there evidence that treatment improves the functional status of patients?

Intervention

Etanercept administered by subcutaneous injection and infliximab administered by intravenous infusion were the interventions of interest. Comparisons with either placebo or any other active agent were eligible for inclusion. Trials that compared different regimens of the same DMARD or compared a DMARD with or without a concomitant agent were not included in the review; all such trials identified are listed under excluded studies in Appendix 3.

Participants

Studies of adults with PsA were included.

Study design

Randomised controlled trials (RCTs) were included in the evaluation of efficacy.

Outcomes

The outcomes of primary interest were those of disease activity (those derived from the ACR joint count, the PsARC and the PASI based measures), those of function and QoL (HAQ) and those of radiological assessment of disease progression. Other outcomes measures of disease activity, function and QoL and disease progression were considered as necessary given the available trials.

Adverse events of interventions

Adverse events data were summarised from key sources and existing reviews. This was supplemented by a systematic review of adverse events data from clinical studies.

Intervention

Subcutaneous Etanercept and infliximab intravenous infusion were the interventions of interest. Studies with any comparator (placebo or any other active agent) or no comparator were eligible for inclusion.

Participants

Studies of adult patients receiving treatment for any of the following indications were eligible: PsA, psoriasis, RA, Crohn's disease and spondyloarthropathy.

Study design

Long-term experimental and observational studies of at least 24 weeks' duration and including a minimum of 100 patients were included in the review. Studies or data without a denominator were excluded from the review.

Outcomes

All adverse event data were considered in the review.

DMARDs for treatment of psoriatic arthritis

Treatments

The following oral systemic agents were included in the review: CSA, MTX, SSZ, auranofin, intramuscular gold, azathioprine, penicillamine, leflunomide and hydroxychloroquine and were also considered relevant comparators. All of the above therapies were considered as monotherapy only. Only trials that included etanercept, infliximab, placebo or any of the above comparator agents as a control were eligible.

Participants

Studies of adults with PsA were included.

Study design

RCTs were included in the evaluation of DMARDs.

Outcomes

The outcomes of primary interest were those derived from the ACR PsARC, PASI and HAQ.

Economic evaluations – systematic review

Studies were eligible for inclusion if they assessed both the costs and benefits (i.e. a full economic evaluation[55]) of either etanercept or infliximab and compared findings with an appropriate comparator treatment.

Data extraction strategy

All data were extracted by one reviewer and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus and by consulting with a third reviewer if necessary. Data were extracted on to pre-designed forms. Data from studies with multiple publications were extracted and reported as from a single study.

Any 'commercial-in-confidence' data are clearly marked in the NICE report (*underlined and followed*

by an indication of the relevant company name, e.g. in brackets) and removed from the subsequent submission to the HTA. They are indicated here by [**Confidential information removed**].

For the efficacy trials, the following details were extracted from each trial:

- study details (author, year, country, type of publication, other publications/reports, funding, study design, setting, duration of trial follow-up, frequency of follow-up, sample size calculation, analyses)
- participant details (number randomised and treated, age, gender, PsA history, duration of PsA and psoriasis, concurrent therapies)
- details of intervention
- results and outcomes.

For the adverse effects studies, the following details were extracted from each study:

- study details (author, year, country, type of publication, other publications/reports, funding, study design, duration of trial follow-up, study objective)
- participant details (indication, inclusion criteria, number of participants, age, gender, concurrent therapies)
- details of intervention
- adverse event results (non-infectious adverse events, infectious adverse events including any serious infections, other non-infectious serious adverse events, deaths, withdrawals due to adverse events, positive test for anti-etanercept or anti-infliximab antibodies, other important adverse event results).

As DMARDs are not the primary focus of the review, we undertook only limited data extraction of these trials. The following details were extracted from each trial: study details (author, year, study design); participant details (definition of PsA, positive for RF factor excluded?, previous therapy, concomitant therapy, adult status, number of participants); details of treatment; results and outcomes.

For economic studies, data were extracted into a standard template, covering the timeframe used, types of costs included and their sources, measures of benefit and methods used to derive these, modelling undertaken and key findings.

Quality assessment strategy

The quality of studies was assessed by one reviewer and independently checked by a second reviewer. Disagreements were resolved through consensus, consulting a third reviewer if necessary.

Efficacy of interventions

The efficacy trials were assessed for quality using a checklist compiled from criteria specified in CRD Report No. 4.[56] The quality of each study was summarised as a quality rating, classifying trials as Excellent, Good, Satisfactory, or Poor. The checklist and quality ratings are detailed in Appendix 2.

Adverse effects of interventions

Owing to the range of study designs included in the assessment and the limitation of the review to long-term large studies, the quality of adverse events studies was not assessed.

DMARDs for treatment of psoriatic arthritis

Owing to time constraints, the quality of trials of DMARDs was not assessed.

Economic evaluations – systematic review

Data were extracted into a standard quality assessment template, covering selection of alternatives, treatment of costs and benefits (including any modelling undertaken), use of discounting, allowance for uncertainty and presentation of results. The template is updated from that presented in Drummond and colleagues.[55]

Data analysis

Efficacy of interventions

Full data extraction and quality assessment have been presented for each efficacy trial of etanercept and infliximab.

Results have been summarised in tables and the effect of trial quality on the efficacy findings is discussed. Relative risks (RRs) and mean differences were calculated for the primary outcomes with 95% confidence intervals (CIs); the primary outcome variables were ACR 20, ACR 50, ACR 70, PsARC, HAQ and PASI.

Clinical diversity of the trials regarding adult status, minimum PASI score and concomitant medication was considered. Where the trials were not clinically diverse (heterogeneous), the data were pooled. Statistical heterogeneity was investigated using the χ^2 test; where it was statistically significant, data were not pooled. Where pooling was appropriate, pooled RRs (95% CI) or weighted mean differences (WMDs) (95% CI) were calculated using a fixed-effect model. A fixed-effect model was selected because a small

number of trials were included in the meta-analysis and a fixed-effect model was therefore considered most appropriate owing to the smaller estimation of between-study variance.[57]

In order to generate appropriately pooled estimates of clinical parameters for the cost-effectiveness modelling, an evidence synthesis was conducted. The exact specification of the synthesis depended on the nature of the trial evidence and the details of the cost-effectiveness models; unless head-to-head trials comparing etanercept and infliximab are identified, the synthesis would be likely to take the form of a mixed treatment comparison.[58,59] The detailed methods of the evidence synthesis are described in Chapter 4 (p. 30).

Adverse effects of interventions

Results have been summarised in tables and the findings are discussed in a narrative synthesis. Adverse events data have been grouped by duration of follow-up.

DMARDs for treatment of psoriatic arthritis

Data extraction has been presented for each comparator trial. Results have been summarised in tables and the findings are discussed. RRs and mean differences were calculated for the primary outcomes with 95% CIs; the primary outcome variables were ACR 20, ACR 50, ACR 70, PsARC, tender joint count (TJC) (mean change from baseline), ESR (mean change from baseline mm/h), pain [mean change from baseline, visual analogue scale (VAS)], swollen joint count (SJC) (mean change from baseline), patient global assessment (PtGA) (mean change from baseline), physician global assessment (PhGA) (mean change from baseline), HAQ (mean change from baseline) and PASI (mean change from baseline).

The findings were not pooled statistically owing to the clinical diversity of the trials and the small numbers of studies investigating the same treatment comparison.

Economic evaluations – systematic review

Any published economic evaluations were to be described but no formal synthesis was planned. This also applied to submitted analyses from manufacturers, although additional analyses using their electronic models were to have been considered. In the event, no published economic evaluation on anti-TNF drugs for the treatment of PsA was identified.

Chapter 4
Clinical evaluation

Quantity of research available

The search strategies for efficacy, adverse events and comparator trials generated 2173 references. Of these, 325 references were ordered and 66 references met the inclusion criteria for the efficacy, adverse events or DMARDs section of the review. These references provided information on 40 studies: three trials of the efficacy of the interventions of interest, 23 studies of the adverse effects of the interventions and 14 trials of the efficacy of the DMARDs. The company submissions did not include any additional RCTs but did provide detailed information to complement that from the published articles.

Efficacy of interventions

Efficacy of etanercept

The literature search identified two RCTs of etanercept for the treatment of PsA.[36,60] Both trials were double-blind and placebo-controlled and both were rated as Good on the quality assessment rating (*Table 1*). Both trials, in addition to being presented in publications, were available as industry trial reports.

Both trials were of adults (aged 18–70 years) with active PsA (defined in both trials as >3 swollen joints and >3 tender or painful joints, although only the more recent trial[36] specified stable plaque psoriasis). Patients in both trials had demonstrated an inadequate response to NSAIDs. Patients taking stable doses of MTX or corticosteroids were permitted to continue with that dose and randomisation was stratified for MTX use at baseline.

The baseline characteristics of the trial population are summarised in *Table 2*. Neither trial required patients to have demonstrated an inadequate response to DMARDs. However, over 70% of the patients in the larger trial (Mease, 2004)[36] had previously used at least one DMARD. Over 80% of patients in the Mease (2004) trial[36] had polyarticular disease indicating that overall the disease was severe.. The proportion of patients with spine involvement and arthritis mutilans at baseline was reported only for the larger trial,

TABLE 1 *Results of quality assessment for trials of etanercept*

Quality assessment criteria	Mease, 2000[60]	Mease, 2004[36]
Eligibility criteria specified?	Y	Y
Power calculation?	Y	Y
Adequate sample size?	Y	Y
Number randomised stated?	Y	Y
True randomisation?	Y	Y
Double-blind?	Y	Y
Allocation of treatment concealed?	Y	Y
Treatment administered blind?	Y	Y
Outcome assessment blind?	Y	Y
Patients blind?	Y	Y
Blinding successful?	NS	NS
Adequate baseline details presented?	Y	Y
Baseline comparability?	Y	Y
Similar co-interventions?	Y	Y
Compliance with treatment adequate?	Y	Y
All randomised patients accounted for?	Y	Y
Valid ITT analysis?	Y	Y
≥ 80% patients in follow-up assessment?	Y	Y
Quality rating	Good	Good

ITT, intention-to-treat; Y, yes; NS, not stated.

TABLE 2 *Summary of trial population characteristics*

	Mease, 2000[60]		Mease, 2004[36]	
	Etanercept (*n* = 30)	**Placebo (*n* = 30)**	**Etanercept (*n* = 101)**	**Placebo (*n* = 104)**
Median age (range) (years)	46.0 (30.0–70.0)	43.5 (24.0–63.0)	47.6 (18–76)	47.3 (21–73)
Male (%)	53	60	57	45
Duration of PsA (mean) (years)	9.0	9.5	9.0	9.2
Duration of psoriasis (mean) (years)	19.0	17.5	18.3	19.7
Proportion with >3% BSA psoriasis (%)	63	63	65	60
Number of prior DMARDS (mean)	1.5	2.0	1.6	1.7
Proportion of patients with numbers of previous DMARDs	–	–	27% = 0 40% = 1 20% = 2	21% = 0 50% = 1 19% = 2
Concomitant therapies during study (%)				
Corticosteroids	20	40	19	15
NSAIDs	67	77	88	83
MTX	47	47	45	49
Type of PsA (%)				
DIP joints in hand and feet	–	–	51	50
Arthritis mutilans	–	–	1	2
Polyarticular arthritis	–	–	86	83
Asymmetric peripheral arthritis	–	–	41	38
Ankylosing arthritis	–	–	3	4
TJS[a]: median (25th–75th percentiles)	22.5 (11, 32)	19.0 (10, 39)	20.4	22.1
SJS[a]: median (25th–75th percentiles)	14.0 (8, 23)	14.7 (7, 24)	15.9	15.3
HAQ (0–3)[a]: median (25th–75th percentiles)	1.3 (0.9, 1.6)	1.2 (0.8, 1.6)	1.1	1.1

where such patients made up only a small proportion of the trial population. These details were not available for the smaller of the two trials so the severity of disease across that population is unknown. However, given the similarity between the trials for other measures of joint disease activity (TJC, SJC, HAQ at baseline and baseline and previous medication), significant differences between the populations in terms of joint disease severity are unlikely. The proportion of patients in the two trials who had significant active psoriasis (defined as affecting more than 3% of BSA) was around 63%. Overall, the baseline characteristics demonstrate that the trial populations are similar and are likely to be representative of a population with PsA requiring DMARD or biologic therapy. It should be noted, however, that the populations in these trials of etanercept are not representative of the patients for whom etanercept is licensed for use: these patients would, according to the British Society of Rheumatology,[35] have demonstrated a lack of response to at least two DMARDS.

In both trials, etanercept was administered by subcutaneous injection twice weekly at a dose of 25 mg. Treatment with active drug or placebo was administered for 12 weeks in the smaller trial (Mease, 2000)[60] and for 24 weeks in the larger trial (Mease, 2004).[36] In both trials, the controlled phase was followed by a follow-up period during which etanercept was administered in an open-label fashion to all patients.

Outcome data derived under RCT conditions are available from both trials for PsARC, ARC 20, ACR 50 and ACR 70 and HAQ at week 12. The primary outcome variable in the Mease (2000) trial[60] was PsARC whereas in the Mease (2004) trial[36] it was ACR 20. Published data on PASI at week 12 are available from the small (Mease, 2000)[60] trial only. RCT outcome data for PsARC, ARC 20, ACR 50 and ACR 70, HAQ, PASI and radiographic assessment of progression at week 24 are available from the larger (Mease 2004) trial[36] (n = 205). In addition, a subgroup analysis by concomitant MTX use provided additional PsARC, ACR 20, 50 and 70 data at weeks 12 and 24. As the subgroup analyses were in already fairly small trials, the findings generated must be interpreted with some caution. They are, however, useful to explore the influence that concomitant MTX has on the main treatment effect. All outcome data are summarised in *Table 3*, with pooled 12 week data in *Table 4*.

Uncontrolled data on all outcomes are also available at 36 weeks or 12 months (uncontrolled follow-up data). These data are summarised in *Table 5*.

TABLE 3 *Etanercept efficacy outcomes – RCT data*

Trial	Duration	Outcomes	Etanercept	Placebo	RR or mean difference (95% CI)
Mease, 2000[60]	12 weeks	PsARC[a]	26/30 (87%)	7/30 (23%)	3.71 (1.91 to 7.21)
		ACR20	22/30 (73.0%)	4/30 (13%)	5.50 (2.15 to 14.04)
		ACR50	15/30 (50.0%)	1/30 (3%)	15.00 (2.11 to 106.49)
		ACR70	4/30 (13%)	0/30 (0%)	9.00 (0.51 to 160.17)
		HAQ improvement from baseline (mean) (%)	(n = 29) 64.2	(n = 30) 9.9	**[Confidential information removed]**
		PASI 75	5/19 (26%)	0/30 (0%	11.00 (0.65 to 186.02)
		PASI 50	8/19 (42%)	4/19 (21%)	2.00 (0.72 to 5.53)
Mease, 2004[36]	12 weeks	PsARC			
		All pts	73/101 (72%)	32/104 (31%)	2.35 (1.72 to 3.21)
		+MTX	32/42 (76%)	14/43 (33%)	2.34 (1.47 to 3.72)
		–MTX	41/59 (69%)	18/61 (30%)	2.35 (1.54 to 3.60)
		ACR20[a]			
		All pts	60/101 (59%)	16/104 (15%)	3.86 (2.39 to 6.23)
		+MTX	26/42 (62%)	8/43 (19%)	3.33 (1.70 to 6.49)
		–MTX	34/59 (58%)	8/61 (13%)	4.39 (2.22 to 8.7)
		ACR50			
		All pts	38/101 (38%)	4/104 (4%)	9.78 (3.62 to 26.41), $p < 0.001$
		+MTX	17/42 (40%)	1/43 (2%)	17.40 (2.42 to 124.99)
		–MTX	21/59 (36%)	3/61 (5%)	7.24 (2.28 to 22.98)
		ACR70			
		All pts	11/101 (11%)	0/104 (0%)	23.68 (1.41 to 396,53), $p < 0.001$
		+MTX	4/42 (10%)	0/43 (0%)	9.21 (0.51 to 165.93)
		–MTX	7/59 (12%)	0/61 (0%)	15.5 (0.91 to 265.46)
		HAQ improvement from baseline (mean) (%)	(n = 96) 53.5	(n = 99) 6.3	**[Confidential information removed]**
		PASI 50	**[Confidential information removed]**		
		PASI 75	**[Confidential information removed]**		
	24 weeks	PsARC			
		All pts	71/101 (70%)	24/104 (23%)	3.05 (2.10 to 4.42)
		+MTX	31/42 (74%)	11/43 (26%)	2.89 (1.68 to 4.95)
		–MTX	40/59 (68%)	13/61 (21%)	3.18 (1.90 to 5.32)
		ACR20			
		All pts	50/101 (50%)	14/104 (13%)	3.68 (2.17 to 6.22)
		+MTX	23/42 (55%)	8/43 (19%)	2.94 (1.49 to 5.83)
		–MTX	27/59 (46%)	6/61 (10%)	4.73 (2.10 to 10.63)
		ACR50			
		All pts	37/101 (37%)	4/104 (4%)	9.52 (3.52 to 25.75)
		+MTX	16/42 (38%)	3/43 (7%)	5.46 (1.72 to 17.37)
		–MTX	21/59 (36%)	1/61 (2%)	21.71 (3.02 to 156.30)
		ACR70			
		All pts	9/101 (9%)	1/104 (1%)	9.27 (1.20 to 71.83)
		+MTX	2/42 (5%)	0/43 (0%)	5.12 (0.25 to 103.50)
		–MTX	7/59 (12%)	0/61 (0%)	15.50 (0.91 to 265.46)
		HAQ improvement from baseline (mean) (%)	(n = 96) 53.6	(n = 99) 6.4	**[Confidential information removed]**
		PASI 75	15/66 (23%)	2/62 (3%)	7.05 (1.68 to 29.56)
		PASI 50	31/66 (47%)	11/62 (18%);	2.65 (1.46 to 4.80)
		PASI 90	4/66 (6%)	2/62 (3%)	1.88 (0.36 to 9.90)
		TSS mean (SD) annualised rate of progression			
		All pts	–0.03 (0.73)	0.53 (1.39)	–0.56 (–0.86 to –0.26)

TSS, Total Sharp Score.
[a] Primary outcome variable in the respective trials.

Efficacy at 12 weeks treatment

In the Mease (2000)[60] trial, the RR for the primary outcome measure PsARC was 3.71 (95% CI: 1.91 to 7.21) and in the Mease (2004)[36] trial the RR for the primary outcome measure ACR 20 was 3.86 (95% CI: 2.39 to 6.23); both treatment differences were statistically significant in favour of etanercept. In both trials, all secondary outcome measures of the effect on joint disease were also statistically significantly in favour of etanercept with the exception of ACR 70 in the Mease (2000)[60] trial, probably owing to the small number of patients in this trial resulting in few data. The results for the effect on psoriasis, PASI 75 and PASI 50 both showed a treatment difference in favour of etanercept, but statistical significance was not reached, probably because of the small number of patients evaluable for psoriasis ($n = 38$).

Pooled estimates of effect (*Table 4*) demonstrate a statistically significant benefit of etanercept for all joint disease and HAQ score outcomes. There was no statistical heterogeneity for any outcome.

Across the two trials at 12 weeks, almost 85% of patients treated with etanercept achieved a PsARC, which is the only joint disease outcome measure that has been specifically defined for PsA. In addition, around 65% of patients treated with etanercept achieved an ACR 20, demonstrating a basic degree of efficacy in terms of arthritis-related symptoms. Around 45% of patients treated with etanercept achieved an ACR 50 and around 12% achieved an ACR 70, demonstrating a good level of efficacy. The subgroup analyses conducted on the Mease (2004)[36] data revealed that the effect of etanercept was not dependent on patients'

TABLE 4 *Pooled etanercept efficacy data – outcomes at 12 weeks*

Trial	Outcomes	Etanercept	Placebo	RR or mean difference (95% CI)
	PsARC			
Mease, 2000[60]		26/30 (87%)	7/30 (23%)	3.71 (1.91 to 7.21)
Mease, 2004[36]		73/101 (72%)	32/104 (31%)	2.35 (1.72 to 3.21), $p < 0.001$
	Pooled RR (95% CI), p p for heterogeneity			2.60 (1.96 to 3.45), $p < 0.00001$ $p = 0.22$
	ACR20			
Mease, 2000[60]		22/30 (73.0%)	4/30 (13%)	5.50 (2.15 to 14.04)
Mease, 2004[36]		60/101 (59%)	16/104 (15%)	3.86 (2.39 to 6.23), $p < 0.001$
	Pooled RR (95% CI), p p for heterogeneity			4.19 (2.74 to 6.42), $p < 0.00001$ $p = 0.51$
	ACR50			
Mease, 2000[60]		15/30 (50.0%)	1/30 (3%)	15.00 (2.11 to 106.49)
Mease, 2004[36]		38/101 (38%)	4/104 (4%)	9.78 (3.62 to 26.41), $p < 0.001$
	Pooled RR (95% CI), p p for heterogeneity			10.84 (4.47 to 26.28), $p < 0.00001$ $p = 0.70$
	ACR70			
Mease, 2000[60]		4/30 (13%)	0/30 (0%)	9.00 (0.51 to 160.17)
Mease, 2004[36]		11/101 (11%)	0/104 (0%)	23.68 (1.41 to 396,53), $p < 0.001$
	Pooled RR (95% CI), p p for heterogeneity			16.28 (2.20 to 120.54), $p = 0.006$) $p = 0.63$
	HAQ change from baseline: mean (SD) (%)			
Mease, 2000[60]	**[Confidential information removed]**			
Mease, 2004[36]	**[Confidential information removed]**			
	Pooled WMD (95% CI), p p for heterogeneity			48.99 (38.53 to 59.44), $p < 0.00001$ $p = 0.56$

TABLE 5 *Etanercept efficacy outcomes – uncontrolled follow-up data*

Trial	Type of data	Duration	Outcomes	
Mease, 2000[60]	Uncontrolled	36 weeks	PsARC	26/30 (87%)
			ACR20	26/30 (87%)
			ACR50	19/30 (63%)
			ACR70	10/30 (33%)
			HAQ change from baseline: mean (median) (%)	**[Confidential information removed]**
			PASI 75	7/19 (37%)
			PASI 50	11/19 (58%)
Mease, 2004[36]	Controlled	12 months	ACR results, etc. only as brief text	Maintained as at 24 weeks
			TSS mean (SD) annualised rate of progression	
			All pts	(n = 101) –0.03

concomitant use, or not, of MTX. The PASI results indicate some beneficial effect on psoriasis at 12 weeks. The improvement in HAQ score with etanercept compared with placebo was statistically significant, indicating a beneficial effect of etanercept on functional status.

Efficacy after 24 weeks treatment

At 24 weeks, the treatment effect for all joint disease outcome measures was statistically significantly greater with etanercept than with placebo. As at 12 weeks, the subgroup analyses conducted on the Mease (2004)[36] data revealed that the effect of etanercept was not dependent on patients' concomitant use, or not, of MTX. The size of treatment effect did not appear greater at 24 than at 12 weeks.

At 24 weeks, the mean Total Sharp Score (TSS) annualised rate of progression was statistically significantly lower in etanercept-treated patients compared with placebo patients. However, 24 weeks is a barely adequate duration for radiographic assessment of disease progression.

At 24 weeks, the treatment effect on psoriasis favoured etanercept with RRs for PASI 75 of 7.05 (95% CI: 1.68 to 29.56), PASI 50 of 2.65 (95% CI: 1.46 to 4.80) and PASI 90 of 1.88 (95% CI: 0.36 to 9.90). The results for PASI 75 and PASI 50 were statistically significant despite there being only 66 patients on etanercept evaluable for psoriasis.

Long-term follow-up

The results for long-term follow-up are summarised in *Table 5*. The data from the Mease (2000)[60] trial are uncontrolled and therefore cannot be taken as reliable. In general, they do indicate that the improvements in patients' joint and skin symptoms and HAQ score achieved during the controlled phase of the trials are maintained in the medium term. At 1 year, the mean TSS annualised rate of progression for all patients was –0.03, indicating that on average no clinically significant progression of joint erosion had occurred.

Summary of the efficacy of etanercept in the treatment of psoriatic arthritis

- There is evidence from double-blind placebo-controlled trials of a good level of efficacy for etanercept in the treatment of PsA.
- There is evidence from two RCTs that etanercept treatment improves patients' functional status as assessed using the HAQ score.
- There is evidence from two RCTs that etanercept treatment has a beneficial effect on the psoriasis component of the disease.
- Uncontrolled follow-up of patients indicates that treatment benefit is maintained for at least 50 weeks; however, these data may not be reliable.
- There are radiographic data from controlled trials for etanercept in PsA that demonstrate a beneficial effect on progression of joint disease at 24 weeks. This is a very short time over which to identify a statistically significant effect of therapy and indicates a rapid onset of action of etanercept. Follow-up data indicate that on average disease progression may be halted for at least 1 year.

Efficacy of infliximab

The literature search identified a single RCT of infliximab (the IMPACT trial) for the treatment of PsA.[61] In addition to published reports of this trial, we had access to the industry trial report. The IMPACT trial was rated as Good by the quality assessment (*Table 6*). The industry submission[62] also included brief details of one

TABLE 6 *Results of quality assessment for trials of infliximab*

Quality assessment criteria	Antoni, 2005[61]
Eligibility criteria specified?	Y
Power calculation?	Y
Adequate sample size?	Y
Number randomised stated?	Y
True randomisation?	–[a]
Double-blind?	Y
Allocation of treatment concealed?	–[a]
Treatment administered blind?	Y
Outcome assessment blind?	Y
Patients blind?	Y
Blinding successful?	–[a]
Adequate baseline details presented?	Y
Baseline comparability?	Y
Similar co-interventions?	Y
Compliance with treatment adequate?	Y
All randomised patients accounted for?	Y
Valid ITT analysis?	Y
≥ 80% patients in follow-up assessment?	Y
Quality rating	Good

Y, yes; [a] [**Confidential information removed**].

ongoing trial (IMPACT2), which has since been published[63] but was too late for inclusion in our assessment report.

This was a double-blind, placebo-controlled trial of 104 adult patients with active PsA. All patients had been diagnosed at least 6 months previously with PsA and active peripheral polyarticular disease including 5+ swollen and 5+ tender joints and to have tested negative for RF. All patients must have failed on at least one DMARD. **[Confidential information removed]**. The proportion of patients with spine involvement, arthritis mutilans and erosions at baseline was not reported so the severity of disease across the populations is unknown. At baseline, 42% of infliximab patients and 32% of placebo patients had active psoriasis (defined as a baseline PASI score of at least 2.5). The baseline characteristics of the trial population are summarised in *Table 7*. These demonstrate that the trial population is likely to be representative of a population with fairly severe PsA requiring further DMARD or biologic therapy[35] and that the treatment and placebo groups were well balanced.

In the RCT phase of the trial, infliximab (5 mg/kg) or placebo was infused at weeks 0, 2, 6 and 14 with follow-up at week 16. Further infusions of infliximab were administered to all patients in an open-label fashion at 8-week intervals, with further follow-up at week 50.

The primary outcome variable in this trial was ACR 20 at 16 weeks. Outcome data are also available for ACR 50 and ACR 70, PsARC, HAQ and PASI at week 16 (RCT data). A subgroup analysis by concomitant MTX use provided additional ACR 20 data. As the subgroup analyses were in a fairly small trial, the findings generated must be interpreted with caution. They are, however, useful to explore the influence that concomitant MTX has on the main treatment effect. Data on these outcomes are also available at 50 weeks (uncontrolled trial data). All data are summarised in *Table 8*.

At 16 weeks, 75% of patients treated with infliximab achieved a PsARC which is the only outcome measure that has been specifically defined for the joint disease of PsA. The RR for ACR 20 at 16 weeks was 6.80 (95% CI: 2.89 to 16.01) and 65% of patients treated with infliximab achieved an ACR 20, demonstrating a clear degree of efficacy in terms of arthritis-related symptoms. This level of efficacy was not dependent on patients' concomitant use of MTX. Almost half the patients treated with infliximab achieved an ACR 50 and over one-quarter achieved an ACR 70 compared with none of the placebo group, demonstrating a good level of efficacy.

TABLE 7 *Summary of trial population characteristics*

	Infliximab (*n* = 52)	**Placebo (*n* = 52)**
Mean age (SD) (years)	45.7 (11.1)	45.2 (9.7)
Male (%)	58	58
Duration of psoriatic arthritis: mean (SD) (years)	11.7 (9.8)	11.0 (6.6)
Duration of psoriasis: mean (SD) (years)	36.9 (10.9)	19.4 (11.6)
TJS[a]: mean (SD)	23.7 (13.7)	20.4 (12.1)
SJS[a]: mean (SD)	14.6 (7.5)	14.7 (8.2)
HAQ (0–3): mean (SD)	1.2 (0.7)	1.2 (0.7)

SD, standard deviation.

TABLE 8 *Summary of outcome data for infliximab versus placebo*

Type of data	Duration (weeks)	Outcomes	Infliximab	Placebo	RR or mean difference (95% CI) (p, χ^2 test)
RCT	16	PsARC	39/52 (75.0%)	11/52 (21.2%)	3.55 (2.05 to 6.13), $p < 0.01$.
		ACR 20			
		All pts	34/52 (65.4%)	5/52 (9.6%)	6.80 (2.89 to 16.01), $p < 0.01$.
		ACR 50	24/52 (46.2%)	0/52 (0%)	49.00 (3.06 to 785.06), $p < 0.01$
		ACR 70	15/52 (28.8%)	0/52 (0%)	31.00 (1.90 to 504.86), $p < 0.01$
		HAQ mean (SD) improvement from baseline (%)	49.8 (8.2)	–1.6 (8.3)	51.4 (48.08 to 54.72)
		PASI mean (SD) change from baseline	(n = 42) –4.1 (3.9)	(n = 38) 0.9 (3.7)	–5 (–6.8 to –3.3)
Uncontrolled	50	ACR 20			
		All pts	34/49 (69.4%)		
		+MTX	72.7%		
		–MTX	66.7%		
		ACR 50	26/49 (53.1%)		
		ACR 70	19/49 (38.8%)		
		PsARC	36/49 (73.5%)		
		HAQ mean (SD) change from baseline (%)	–42.5 (8.8)		
		PASI mean (SD) change from baseline (%)	(n = 35) –4.8 (5.9)		

The beneficial treatment effect on psoriasis was statistically significant with a mean difference in percentage change from baseline in PASI of –5 (95% CI: –6.8 to –3.3).

The statistically significant percentage change from baseline in HAQ score with infliximab compared with placebo [mean difference 51.4 (95% CI 48.08 to 54.72)] indicates a beneficial effect of infliximab on functional status.

The data for all measures of joint disease, psoriasis and HAQ collected after 50 weeks of treatment reflect those at 16 weeks. These data are uncontrolled and may therefore be unreliable. However, they do indicate that the level of efficacy achieved with infliximab after 16 weeks of treatment appears to be maintained in the medium term.

There are limitations of these data as evidence of the efficacy of infliximab in the treatment of PsA. Controlled data were only available for 16 weeks of treatment; which is a very short period over which to assess changes in arthritis symptoms. Also, no radiographic assessment was made, so nothing can be determined about the potential or otherwise of infliximab to delay the progression of joint disease.

Data from ongoing trials

Data from an ongoing trial were reported in the company submission.[62] This was a placebo-controlled RCT of 200 patients with active PsA (defined as five or more swollen and tender joints and at least one plaque of psoriasis at least 2 cm in diameter), who had had the disease for at least 6 months and had had an inadequate response to NSAIDs or DMARDs. Patients were randomised to receive infusions of placebo or infliximab 5 mg/kg at weeks 0, 2, 6, 14 and 22, with assessments at weeks 14 and 24.

The reported results indicated that the proportion of patients achieving an ACR 20 response in the infliximab group was significantly greater than in the placebo group ($p < 0.001$) at both week 14 (58.0 and 11.0%, respectively) and week 24 (54.0 and 16.0%, respectively). In the 83 patients with psoriasis that involved 3% or more of their BSA, treatment with infliximab resulted in 64% of patients achieving a PASI 75% or greater improvement at week 14. It was reported that dactylitis and enthesopathy improved significantly

with infliximab treatment compared with placebo (no actual data) and that arthritis and psoriasis responses were maintained over time.

These trial results appear to provide additional evidence of the efficacy of infliximab in the treatment of PSA.

Summary of the efficacy of infliximab in the treatment of psoriatic arthritis

- There is evidence from a single, short-term trial of a good level of efficacy for these drugs in the treatment of PsA, with beneficial effects on joint disease, psoriasis and functional status as assessed by HAQ.
- Conclusions to be drawn from these data are limited by the small sample size and by the short duration of the controlled trial; controlled data to evaluate long-term effects are not available.
- Uncontrolled follow-up of patients indicate that short-term benefit is maintained for at least 50 weeks; however, these data may not be reliable.
- There are no radiographic data from controlled trials for infliximab in PsA. Hence there is no good-quality evidence that these drugs delay the progression of joint disease in PsA.

Adverse events

Adverse effects of etanercept

Information regarding the adverse effects of etanercept was reviewed in three ways: information from standard reference texts was summarised, information from existing reviews was summarised and a systematic review of RCTs of etanercept in PsA and clinical studies in other indications that were of at least 24 weeks' duration and had included at least 100 patients was conducted.

Information from standard reference texts

A list of adverse effects associated with etanercept was generated from standard reference texts. This is presented in Appendix 6, section 'Information from standard reference texts' (p. 173). The list appears very comprehensive but provides only limited information on the significance of individual events.

Information from existing reviews of etanercept

In addition to the standard reference texts, a large number of articles and reviews have been published regarding the adverse effects of etanercept.[64–73] Most of the clinical experience and trial and study data drawn upon for these reviews were from patients with RA, with a smaller body of evidence from patients with psoriasis and PsA. To date the main areas of concern relate to the potential of etanercept to increase the risk of infections, malignancy, heart failure, conditions secondary to the development of autoimmune antibodies, haematological disorders and demyelinating disease. Further details are presented in Appendix 6, section 'Information from existing reviews of etanercept' (p. 173).

Adverse events for etanercept: data from included studies

Ten clinical studies that provided data on the adverse events of etanercept were identified.[36,74–83] Details of all studies are presented in the data extraction tables [Appendix 4, section 'Data extraction tables: intervention efficacy – etanercept', (p. 110)]. Each of these 10 studies had included at least 100 patients and provided at least 24 weeks' data. Five of these studies were of patients treated with etanercept for RA, two were of patients with psoriasis, one was of patients with psoriatic arthritis, one was of patients with ankylosing spondylitis and one was of patients with either RA, PsA or ankylosing spondylitis.

Overall there are data available on the adverse effects of etanercept over 24 weeks (6 months), 1 year and 2 years or more. These data are presented in Appendix 6, section 'Adverse events for etanercept: data from included studies (p. 175). The adverse events reported most frequently during 24 weeks of treatment with etanercept are listed in *Table 9*.

Treatment for 24 weeks with etanercept 25 mg twice weekly was also associated with a high rate of

TABLE 9 *Adverse events reported most frequently during 24 weeks of treatment with etanercept*

Time	Adverse event
24 weeks[a]	Any non-infectious Injection site reaction Headache Any infection Upper respiratory tract infection Serious adverse event[b] Withdrawals due to adverse event

[a] Some data uncontrolled.
[b] Serious adverse event including serious infection, cancer, death and any other non-infectious adverse event.

adverse events, but this rate was not demonstrably higher than that seen in placebo-treated patients. Withdrawals across the trials were not consistently higher than on placebo. The highest withdrawal rate over 24 weeks of treatment was 5.6%, reported in an uncontrolled study of RA.[80] Only injection site reactions (including ecchymosis, bruising or bleeding at the injection site) and possibly an increase in respiratory tract infections are clearly linked to etanercept. The overall rate of infections with etanercept is high but not necessarily higher than that on placebo. Serious infections have been reported at a rate of approximately 3% of patients and represent a concern with etanercept therapy. In clinical trials, the rate of withdrawals due to adverse events was no higher than with placebo, indicating that generally the drug was well tolerated. Data from one study indicate that the higher dose of etanercept (50 mg twice weekly) is also well tolerated.

Data regarding anti-etanercept antibodies are also scarce, with few studies reporting them. The rates reported indicated that up to 6% of patients might develop antibodies.

Most long-term data for 2 years or more for etanercept are from patients with RA. Furthermore, published long-term data are poorly reported and hence of limited value. With longer term use, neurological adverse events are reported and haematological effects such as neutropenia appear. However, it is unclear how treatment-related such effects are.

Summary of adverse events for etanercept

Injection site reactions appear to be the most common adverse effects of etanercept. Otherwise, etanercept appears to be well tolerated in short- and long-term use, although many of the long-term data are not from patients with PsA. Adverse events, particularly mild infections, are common but not more so than on placebo. As identified from earlier reviews, the main areas of concern relate to uncommon but serious adverse events: the potential of etanercept to increase the risk of serious infections, malignancy, heart failure, conditions secondary to the development of autoimmune antibodies, haematological disorders and demyelinating disease. Their significance is not readily discernible from the published reports of clinical trials. Etanercept is a new drug with which there is only limited experience, particularly in patients with PsA; long-term monitoring, review and further investigation of its safety are warranted.

Adverse effects of infliximab

Information from standard reference texts

The adverse effects of infliximab were summarised from standard reference sources[84–86] and Centocor and Remicade SPC (Summary of Product Characteristics) July 2004, and are listed in Appendix 6, section 'Information from standard reference texts's (p. 185). The long list of adverse effects generated by this process appears comprehensive but does not really provide useful information on the significance of individual events.

Information from existing reviews of infliximab

In addition to the standard reference texts, a number of articles and reviews have been published regarding the adverse effects of infliximab[72,87–91] and its safety has been reviewed by FDA advisory committees.[92,93] The data on the adverse effects of infliximab have been gathered mainly from patients treated for RA and Crohns' disease. This is summarised in Appendix 6, section 'Information from existing reviews of infliximab' (p. 185). To date, one of the main areas of concern relates to the potential of infliximab to trigger the development of autoimmune antibodies. The development of these antibodies is associated with acute infusion reactions (anaphylactic or anaphylactoid reactions, delayed hypersensitivity-type reactions) and altered drug pharmacokinetics with diminution of clinical efficacy. In addition, some patients develop anti-nuclear antibodies and anti-double-stranded DNA antibodies. The clinical significance in terms of the risk of developing lupus-like syndromes or demyelination disorders is unclear: there have been cases of demyelinating disease associated with infliximab and very rare reports of a drug-induced lupus-like syndrome associated with positive antibodies. Immediate and delayed infusion reactions are the most common adverse event associated with infliximab. Some reports link them with the development of antibodies, their frequency increasing with subsequent infusions, whereas others indicate that they are most frequent with a first infusion. Infusion reactions are usually mild, with symptoms such as fever or chills. More serious reactions result in chest pain, hypotension and dyspnoea and there have been some cases of anaphylaxis. Delayed hypersensitivity reactions have also been reported.

The possibility that infliximab increases the risk of infections is also a concern. In general, the infections are not serious and in clinical trials the rate of infection with infliximab has not been found to be higher than with placebo. Serious

infections have been reported and infliximab does appear to carry an increased risk of tuberculosis (TB) such that testing patients for latent TB and the treatment of any TB is required prior to initiating therapy with infliximab. Although cases of malignancy have occurred in patients treated with infliximab, it is unclear that the rates are above that in the patient population. Congestive heart failure is a contraindication to infliximab use.

Adverse events for infliximab: data from included studies

Against the background information on the adverse effects profile of infliximab, we reviewed systematically all long-term (longer than 24 weeks) studies of at least 100 patients for further information on the adverse effects of infliximab.

A total of 15 studies that met the review's inclusion criteria for adverse events data were identified.[61,76,94–106] Details of these studies are presented in the data extraction tables in Appendix 5, section 'Data extraction tables: intervention adverse events – infliximab' (p. 150) and the adverse events data is presented in Appendix 6, section 'Adverse events for infliximab: data from included studies' (p. 187).

One of these studies was the main efficacy trial of infliximab in PsA.[61] This was the only study of exclusively patients with PsA. The 16-week RCT data in this trial were supplemented by a 36-week long open-label follow-up in which all patients were treated with infliximab. Only one other included study contained patients with a diagnosis of PsA; this was a prospective observational study of patients with spondyloarthropathy.[94] Three studies of infliximab in patients with RA provide data on patients in most of whom infliximab was used in combination with at least one DMARD.[76,98,105] One trial in patients with psoriasis[106] provided data for the use of infliximab alone compared with placebo in patients similar to a PsA population. Finally, there were nine long-term studies of infliximab in patients with Crohn's disease.[95–97,99–104] This population is in many ways different from those with PsA and even within the trials for Crohn's disease patients are divided into those with active non-fistulising disease and those with fistulising disease.

The most frequently reported adverse events with infliximab are summarised in *Table 10*.

The number of patients experiencing severe infusion reactions, infection and infestations, upper respiratory tract infection (not just treatment related), serious infection and withdrawals due to adverse events were derived from commercial-in-confidence data and so cannot be presented here.

The treatment-related adverse events that were reported by at least four patients during the first 16 weeks of treatment with infliximab were headache (four infliximab, three placebo), bronchitis (three infliximab, four placebo), upper respiratory tract infection (one infliximab, five placebo), influenza-like symptoms (one infliximab, four placebo), rhinitis (three infliximab, two placebo) and rash (three infliximab and two placebo patients). Serious adverse events reported in the first 16 weeks of the study were one case of rectal bleeding due to diverticulitis (placebo) and one case of synovitis suspected of being infectious that was culture negative (infliximab).

Between 16 and 50 weeks (when all patients received infliximab), the most common adverse event was upper respiratory tract infection (23 patients), then headache (seven patients), dizziness (six patients) influenza-like symptoms (five patients), non-productive cough (five patients),

TABLE 10 *Adverse events reported most frequently during 16–50 weeks of treatment with infliximab*

Time (weeks)	Adverse event	Infliximab 5 mg/kg	Placebo
16[a]	Any	38/52 (73%)	33/51 (65%)
	Infusion reactions	4 (8%)	5 (10%)
	Serious adverse events	1 (2%)	1 (2%)
	Severe adverse events	3 (6%)	2 (4%)
36–50[b]	Any	41/49 (84%)	–
	Infusion reactions	4 (8%)	–
	Serious adverse events	8 (16%)	–
	Severe adverse events	6 (12%)	–

[a] Data from patients with PsA.
[b] Data from patients with PsA or RA.

rhinitis (four patients), hypertension (four patients) and sinusitis (four patients). Serious adverse events that occurred during this phase of the study were surgery for inguinal hernia, angina pectoris, atrial fibrillation, urinary retention, chest pain, cerebrovascular event, fever, acute gastroenteritis, pyelonephritis and leg weakness.

Overall, studies of 16–50 weeks with a range of indications have demonstrated that adverse events are common with infliximab, but they are not necessarily more common than on placebo treatment. These studies have identified clearly the problem of infusion reactions with infliximab. These reactions are usually not serious but the possibility of serious infusion reactions is real. These data and longer term data indicate that infections are common in patients treated with infliximab, but it is unclear if this represents an increased rate caused by infliximab. Infliximab therapy is associated with a risk of developing antibodies, with a high proportion of patients testing positive after treatment. The presence of antibodies appears to be associated with a progressive diminution of efficacy with continued infliximab therapy rather than any safety concerns.

With longer term data, one would like to answer the questions of how significant infusion reactions are: does the rate and or severity of infusion reactions increase or decrease with increasing number of infusions? The data from the studies that met our inclusion criteria have not helped answer these questions. Similarly, we have been unable to shed light on the clinical significance of reports of cancer, infections, heart failure and other serious adverse events.

Summary of adverse effects of infliximab

Overall, infusion reactions, the development of antibodies and infections appear to be the most common adverse effects of infliximab, although it is unclear whether they occur more frequently than on placebo. In the long term, the possible risk of lymphomas, systemic lupus erythematosus (SLE) and multiple sclerosis (MS) requires caution and further monitoring and investigation. The data indicate that the combination of infliximab and MTX is generally as well tolerated as MTX alone; however, mild infusion reactions, infections and possibly the risk of malignancy are higher with the combination therapy. Importantly, infliximab is a new drug with which there is only very limited experience and long-term monitoring, review and further investigations of its safety are warranted.

DMARDs for the treatment of psoriatic arthritis

Efficacy of DMARDs

The search for RCTs of the DMARDs identified one Cochrane review[47] and four additional trials,[46,107–109] giving a total of 14 trials to be included in the review. *Table 11* summarises the details of these trials; full data extraction is presented in Appendix 6. No RCTs of penicillamine or hydroxychloroquine were found.

The trials were of adult patients with PsA. The inclusion criteria for 10/14 trials specified arthritis symptoms in at least three (or even five) joints and two specified at least one joint. Only one trial specified a minimum degree of psoriasis. Ten of the 14 trials excluded patients who were positive for RA; whether this was so for the remaining four trials was not reported. Eight trials included only patients who had taken previous DMARDs or who had failed to previous DMARDs; five trials failed to report this information. In the one trial of leflunomide,[46] almost 40% of patients had not taken any DMARD; this population would appear to be less severely affected than those in the other trials. The number of patients in the trials ranged from 12 to 221.

Most trials assessed patient outcome after at least 6 months of treatment, with only two short-term trials, one of 8 weeks[110] and one of 12 weeks.[111]

The various DMARDs represented in the trials were not studied evenly. SSZ was the most studied drug, being included in seven trials,[110,112–116] one of which was the largest and longest of all the trials (221 patients and a follow-up period of 36 months).[112] MTX, azathroprine and leflunomide were each included in only one placebo-controlled trial and CSA was compared with 'standard therapy'. In addition, MTX and CSA were compared with each other[109] and also their combination was compared with MTX alone.[107]

Interpretation of the findings of the trials is hampered by the wide range of outcome measures used and by the fact that a beneficial effect on any single facet of the disease cannot be taken alone as evidence of efficacy. PsARC and ACR 20 have become accepted as an indicator of a basic level of efficacy in arthritis and are used in more recent trials of PsA. Unfortunately, most of the included trials were performed prior to the acceptance of these compound measures of response. In addition, the psoriasis aspect of PsA has been neglected in most of the trials. Only four trials

TABLE 11 *Characteristics of RCTs of comparator drugs for the treatment of psoriatic arthritis*

	Kaltwasser, 2004[46]	**Clegg, 1996[31] linked to Ref. 112**	**Dougados, 1995[113]**	**Fraser, 1993[114]**	**Combe, 1996[115]**	**Farr, 1990[116]**	**Gupta, 1995[110]**	**Palit, 1990[117]**	**Carette, 1989[118]**	**Levy, 1972[119]**	**Willkens, 1984[111]**	**Fraser, 2003[107]**	**Salvarani, 2001[108,120]**	**Spadaro, 1995[109]**
Indication	PsA and psoriasis	PsA	PsA	PsA	PsA	PsA	PsA	PsA	PsA	PsA	PsA	PsA	PsA	PsA
Number of patients	186	221	136	39	117	30	24	82	138	12	37	72	99	35
Study duration	24 weeks	36 weeks	6 months	24 weeks	24 weeks	6 months	8 weeks	24 weeks	6 months	6 months	12 weeks	12 months	24 weeks	12 months
Intervention	Leflunomide	SSZ	SSZ	SSZ	SSZ	SSZ	SSZ	Auranofin and i.m. gold	Auranofin	Azathioprine	MTX	MTX + CSA	CSA, SSZ	CSA
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	MTX + placebo	Symptomatic therapy	MTX
Outcomes for which data available in review	ACR 20 PsARC HAQ TJC SJC PASI	PsARC ESR TJC SJC	Pain (VAS) PtGA PhGA	Pain (VAS) ESR	Pain (VAS) TJC	Pain (VAS) ESR	TJC SJC PtGA PhGA	Pain (VAS) ESR TJC	Pain (VAS) TJC SJC		TJC SJC PtGA PhGA	TJC Pain (VAS) ESR PASI PtGA HAQ	ACR 20 ACR 50 ACR 70 Pain (VAS) TJC SJC ESR PASI	TJC SJC PtGA PhGA ESR PASI

use any measure of psoriasis as an outcome measure.[46,107–109]

Data from the placebo-controlled trials were synthesised in the Cochrane review.[47] The Cochrane review identified five outcome measures for which adequate data were available to make a comparison with placebo [change from baseline in pain (VAS), ESR, TJC, SJC, PtGA and PhGA. We extracted these data from the four additional trials identified by our searches. In addition, we extracted data on the outcome measures PsARC, ACR 20, ACR 50, ACR 70 and HAQ where available. These data are presented in *Tables 12–14*. In summarising the results, the 'standard therapy' controlled trial of SSZ and CSA[120] is included as a placebo-controlled trial.

Sulfasalazine

All trials of SSZ reported a positive but not statistically significant effect on TJC.[31,108,110,113–116] All trials also reported a positive effect on ESR but only one reported statistical significance. Statistically significant positive effects were seen for PtGA and PhGA but not SJC or PASI score. In the one small trial in which it was assessed, a significantly higher proportion of patients achieved ACR 20 and ACR 50 than did those on placebo. Overall there is some limited evidence of efficacy with SSZ in the treatment of PsA.

Intramuscular gold

Intramuscular gold has been studied in only one small trial.[117] A statistically significant positive effect was seen for TJC but not for ESR or pain. Hence there is almost no evidence of efficacy with intramuscular gold in the treatment of PsA.

Auranofin

Auranofin has been studied in two trials.[117,118] Overall it appeared to have no effect on TJC or ESR, but the larger of the two trials found statistically significant benefits on pain and SJC.

Azathioprine

Azathioprine has been studied in one very small trial (n = 12) that reported marked or moderate improvement in joint and skin symptoms in all six patients treated with azathioprine but no improvement in any placebo-treated patient.[119]

Leflunomide

The one double-blind RCT of leflunomide in 190 patients provided some evidence of efficacy in the treatment of PsA.[46] About 36% of patients on leflunomide achieved a (modified) ACR 20 and this was statistically significant compared with placebo. Statistically significant effects on the proportion of patients achieving PsARC, PASI 50, PASI 75 and reduction in PASI score and a reduction in HAQ were also reported.[46]

Methotrexate

When compared with placebo in a short-term trial (12 weeks), MTX failed to demonstrate any significant beneficial effect on TJC or SJC.[111] However, both the PtGA and the PhGA were improved statistically significantly more than they were by placebo, providing some very weak evidence of effect.

Ciclosporin

CSA has been compared with placebo (supportive care) in only one small trial.[108] Statistically significant effects in favour of CSA were found for the proportion of patients achieving ACR 20 and ACR 50, and reductions in ESR, pain and PASI score. No significant benefit was found on TJC or SJC, but overall the results do indicate a degree of efficacy.

When compared with each other, MTX and CSA were found to be equally efficacious except that MTX had a statistically significantly greater beneficial effect on PhGA, whereas CSA produced a statistically significantly greater reduction in PASI score.[109]

The one trial that investigated the benefit of adding CSA to MTX found no evidence of benefit except for a possible improvement in PASI score with the combination.[107]

Summary

In summary, the available drug treatments for PsA, with the exception of SSZ and possibly leflunomide, have not been investigated thoroughly. The available limited data indicate some degree of efficacy for all DMARDs but the evidence for intramuscular gold and azathroprine is particularly weak and may not be reliable. Further trial evidence on all agents using the outcome measures proportion of patients achieving PsARC, ACR 20, ACR 50, ACR 70 and the mean reduction from baseline in PASI and HAQ score would be desirable. Such trials should include only those patients who have failed to respond to NSAIDs and should have a minimum duration of 6 and preferably 12 months.

Adverse effects of DMARDs

Sulfasalazine

Headache and hypersensitivity reactions including skin rash, itching, aching of joints and fever,

TABLE 12 *Summary of continuous data from placebo controlled trials*

Outcome	Treatment	Trial	Treatment		Placebo		Mean difference (95% CI)
			Mean (SD)	*n*	Mean (SD)	*n*	
TJC (mean change from baseline)	SSZ	Clegg, 1996[31]	–10.3 (22.4)	109	–7.8 (19.1)	112	–2.5 (–8.0 to 3.0)
		Combe, 1996[115]	–4.4 (4.5)	53	–3.5 (6.6)	64	–0.9 (–2.9 to 1.1)
		Gupta, 1995[110]	–13.0 (21.8)	9	2.0 (29.1)	14	–15.0 (–35.9 to 5.9)
		Salvarani, 2001[108,120]	–4.8 (6.7)	32	–1.5 (8.1)	31	–3.3 (–7.0 to 0.38)
	i.m. gold	Palit, 1990[117]	–8.9 (9.7)	21	–2.3 (7.2)	18	–6.6 (–11.9 to –1.28)
	Auranofin	Palit, 1990[117]	0.1 (6.8)	24	–2.3 (7.2)	18	2.4 (–1.9 to 6.7)
		Carette, 1989[118]	–12.0 (4.2)	93	–11.1 (4.05)	95	–0.90 (–2.8 to 0.3)
	Azathroprine	Levy, 1972[119]	–12.0 (3.5)	6	0.0 (6.0)	6	–12.0 (–17.6 to –6.4)
	MTX	Willkens, 1984[111]	–4.2 (15.4)	16	-5.2 (17.0)	21	1.01 (–9.5 to 11.5)
	Ciclosporin	Salvarani, 2001[108,120]	–6.9 (8.8)	36	–1.5 (8.1)	31	–5.4 (–9.5 to 1.35)
ESR (mean change from baseline) (mm/h)	SSZ	Clegg, 1996[31]	–6.4 (14.9)	109	1.1 (15.0)	112	–7.5 (–11.4 to –3.6)
		Combe, 1996[115]	–10.7 (21.7)	53	–4.1 (17.4)	64	-6.6 (–13.8 to 0.63)
		Farr, 1990[116]	–23.1 (17.0)	15	–16.4 (14.0)	15	–6.7 (–17.9 to 4.5)
		Fraser, 1993[114]	–17.0 (20.4)	17	–4.0 (25.2)	20	–13.0 (–27.7 to 1.7)
		Salvarani, 2001[108,120]	–12.9 (25.7)	32	–0.9 (23.3)	31	–12.0 (–24.1 to 0.11)
	i.m. gold	Palit, 1990[117]	–9.3 (22.8)	21	–2.2 (24.6)	18	–7.1 (–22.1 to 7.9)
	Auranofin	Palit, 1990[117]	–2.1 (16.5)	24	–2.2 (24.6)	18	0.1 (–13.0 to 13.24)
	CSA	Salvarani, 2001[108,120]	–12.4 (19.5)	36	–0.9 (23.3)	31	–11.5 (–21.9 to –1.1)
Pain (mean change from baseline) (VAS)	SSZ	Combe, 1996[115]	–22.9 (27.7)	53	–12.6 (30.2)	64	–10.3 (–20.8 to 0.21)
		Farr, 1990[116]	–43.1 (26.0)	15	–35.8 (21.0)	15	–7.3 (–24.2 to 9.61)
		Fraser, 1993[114]	–22.5 (18.9)	17	–30.4 (27.6)	20	7.9 (–7.2 to 23.0)
		Dougados, 1995[113]	–21.5 (25.6)	70	–7.1 (22.0)	66	–14.4 (–22.5 to –6.4)
		Salvarani, 2001[108,120]	–17.3 (18.0)	32	–12.5 (22.8)	31	–4.8 (–15.0 to 5.4)
	i.m. gold	Palit, 1990[117]	–21.2 (24.3)	21	–26.5 (21.8)	18	5.3 (–9.2 to 19.77)
	Auranofin	Palit, 1990[117]	–4.5 (23.1)	24	–26.5 (21.8)	18	21.9 (8.2 to 35.6)
		Carette, 1989[118]	–5.0 (0.75)	93	–2.0 (0.9)	95	–3.0 (–3.2 to –2.8)
	CSA	Salvarani, 2001[108,120]	(–31.9)	36	–12.5 (22.8)	31	–14.7 (–27.9 to –1.6)
SJC (mean change from baseline)	SSZ	Clegg, 1996[31]	–7.8 (12.8)	109	–8.0 (13.7)	112	0.2 (–3.3 to 3.7)
		Gupta, 1995[110]	–7.0 (7.54)	9	–6.0 (4.4)	14	–1.0 (–6.4 to 4.4)
	Auranofin	Carette, 1989[118]	–2.4 (1.1)	93	–2.0 (1.3)	95	–0.4 (–0.7 to –0.1)
	MTX	Willkens, 1984[111]	–2.6 (10.5)	16	–2.4 (11.5)	21	–0.2 (–7.3 to 6.9)
	Leflunomide	Kaltwasser, 2004[46]	–6.8 (16.8)	95	–4.2 (13.6)	91	–2.6 (–7.0 to 1.8)
PtGA (mean change from baseline)	SSZ	Dougados, 1995[113]	–0.8 (0.8)	70	–0.3 (0.7)	66	–0.5 (–0.7 to –0.2)
		Gupta, 1995[110]	–0.9 (1.0)	9	0.3 (1.1)	14	–1.2 (–2.1 to –0.4)
	MTX	Willkens, 1984[111]	–0.6 (0.26)	16	–0.2 (0.7)	21	–0.4 (–0.7 to –0.1)

continued

TABLE 12 *Summary of continuous data from placebo controlled trials (cont'd)*

Outcome	Treatment	Trial	Treatment		Placebo		Mean difference (95% CI)
			Mean (SD)	*n*	Mean (SD)	*n*	
PhGA (mean change from baseline)	SSZ	Dougados, 1995[113]	–0.6 (0.7)	70	–0.4 (0.7)	66	–0.2 (–0.4 to 0.0)
		Gupta, 1995[110]	–1.2 (0.8)	9	0.3 (1.9)	14	–1.5 (–2.6 to –0.4)
	MTX	Willkens, 1984[111]	–0.7 (0.45)	16	0.2 (0.6)	21	–0.9 (–1.2 to –0.5)
HAQ (mean change from baseline)	Leflunomide	Kaltwasser, 2004[46]	–0.19 (0.51)	94	–0.05 (0.46)	90	–0.14 (–0.4 to 0.0)
PASI (mean change from baseline)	Leflunomide	Kaltwasser, 2004[46]	–2.1 (5.9)	92	–0.6 (6.1)	90	–1.5 (–3.2 to 0.2)
	SSZ	Salvarani, 2001[108,120]	–2.3 (3.4)	32	–0.4 (3.9)	31	–1.9 (–3.7 to –0.1)
	CSA	Salvarani, 2001[108,120]	–3.6 (3.7)	36	–0.4 (3.9)	31	–3.2 (–5.0 to –1.4)

TABLE 13 *Summary of dichotomous data from placebo controlled trials*

Outcome	Treatment	Trial	Treatment *n/N*	Placebo *n/N*	RR (fixed-effect model) (95% CI)
Proportion achieving PsARC	SSZ	Clegg, 1996[31]	63/109	50/112	1.29 (1.00 to 1.68)
Proportion achieving ACR 20	Leflunomide	Kaltwasser, 2004[46]	29/80	16/80	1.81 (1.07, 3.07
	SSZ	Salvarani, 2001[108,120]	14/32	11/31	1.23 (0.67 to 2.28)
	CSA	Salvarani, 2001[108,120]	16/36	11/31	1.25 (0.69 to 2.28)
Proportion achieving ACR 50	SSZ	Salvarani, 2001[108,120]	4/32	1/31	3.88 (0.46 to 32.77)
	CSA	Salvarani, 2001[108,120]	9/36	1/31	7.75 (1.04 to 57.81)
Proportion achieving ACR 70	SSZ	Salvarani, 2001[108,120]	0/32	0/31	Not calculable
	CSA	Salvarani, 2001[108,120]	5/36	0/31	9.51 (0.55 to 165.5)
	Leflunomide	Kaltwasser, 2004[46]	56/95	27/91	1.99 (1.39 to 2.84)

TABLE 14 *Summary of continuous data from methotrexate controlled trials*

Outcome	Treatment	Trial	Treatment		Methotrexate		Mean difference (95% CI)
			Mean (SD)	*n*	Mean (SD)	*n*	
TJC (mean change from baseline)	MTX plus CSA	Fraser, 2003[114]	–12.0 (45.3)	38	–16.9 (36.0)	34	4.9 (–13.9 to 23.7)
	CSA	Spadaro, 1995[109]	–14.0 (17.3)	17	–11.1 (7.2)	18	–2.9 (–11.8 to 5.8)
ESR (mean change from baseline) (mm/h)	MTX plus CSA	Fraser, 2003[114]	0.9 (SD not reported)	38	–1.6 (SD not reported	34	–
	CSA	Spadaro, 1995[109]	–9.3 (25.2)	17	–19.5 (26.7)	18	10.2, (–7.0 to 27.4)
Pain (mean change from baseline) (VAS)	MTX plus CSA	Fraser, 2003[114]	–0.8 (SD not reported)	38	–0.2 (SD not reported)	34	–
PtGA (mean change from baseline)	MTX plus CSA	Fraser, 2003[114]	–1.0 (SD not reported)	38	–0.5 (SD not reported)	34	–
	CSA	Spadaro, 1995[109]	30.0 (23.1)	17	22.7 (41.6)	18	7.3 (–14.9 to 29.5)
PhGA (mean change from baseline)	CSA	Spadaro, 1995[109]	16.0 (20.2)	17	30.8 (17.0)	18	–14.8 (–27.2 to –2.4)
HAQ (mean change from baseline)	MTX plus CSA	Fraser, 2003[114]	–0.1 (SD not reported)	38	–0.2 (SD not reported)	34	–
PASI (mean change from baseline)	MTX plus CSA	Fraser, 2003[114]	–1.2 (1.9)	38	–0.3 (SD not reported)	34	–
	CSA	Spadaro, 1995[109]	–7.6 (8.3)	17	–2.6 (2.6)	18	–5.0 (–9.1 to –0.9)

photosensitivity and serum sickness-like syndrome are reported frequently with SSZ.[86,121] Gastrointestinal disturbances (nausea and vomiting) are also common but medical attention is required only if symptoms persist.[86,122] Liver enzyme and haematological abnormalities are also considered common adverse effects of SSZ but serious hepatic and haematological toxicity is uncommon.[121,122] There have been occasional cases of reversible leucopenia or agranulocytosis.[122]

Leflunomide

Bronchitis, respiratory infection, urinary tract infection, hepatotoxicity and hypertension are frequently reported adverse events with leflunomide.[86,123] Diarrhoea, nausea and alopecia are also associated with the use of leflunomide.[86,122] Medical attention is necessary if these complaints and others such as abdominal and back pain, dizziness, dyspepsia, headache, vomiting, skin rash and weight loss are found to be troublesome.[86] There is a lack of long-term adverse event data.[122]

Intramuscular gold

Skin lesions are the most common side-effects of gold.[121] Nitritoid reactions and temporary joint pain following injection are associated with intramuscular gold.[86] Mucous membrane reactions (gingivitis, glossitis, stomatitis and a metallic taste in the mouth) are also common.[86,121] The gastrointestinal effects seen with oral gold (auranofin) are less common with intramuscular gold, but if diarrhoea or nausea are severe they may be indicative of overdose. Nitritoid reactions and temporary joint pain following injection are associated with some preparations of intramuscular gold.[86]

Auranofin

Adverse events associated with the use of auranofin are largely gastrointestinal, including diarrhoea,[86,122] cramping, constipation, nausea and indigestion.[86] Stomatitis, proteinuria, and conjunctivitis are also common.[86] The serious adverse events associated with injectable gold formulations are rare with auranofin.[122]

Azathioprine

Serious adverse events associated with the use of azathioprine are leucopenia, infections and megaloblastic anaemia.[86] Gastrointestinal and mucocutaneous side-effects have also been reported,[86,122] There have been reports of hepatotoxicity, and long-term treatment with azathioprine may increase the risk of liver function abnormalities and cancer.[121,122] Appetite loss, nausea and vomiting are common but require medical attention only if symptoms persist.[86] Bone marrow depression has been observed after the discontinuation of medical treatment.[86]

Penicillamine

Adverse events are common with penicillamine.[122] Allergic reaction, fever, pemphigus folaceus or vulgaris and stomatitis have been reported frequently in patients receiving penicillamine, who should receive medical attention.[86] Other reported effects of penicillamine are mucocutaneous reactions, proteinuria, haematological effects, myositis and autoimmune induced disease.[122] Adverse events that require medical attention if troublesome include diarrhoea, loss/lessening of taste, nausea or vomiting, appetite loss and stomach pain.[86]

Hydroxychloroquine

Of particular concern with hydroxychloroquine in the treatment of PsA is the risk of exacerbation of psoriasis.[124] Gastrointestinal disturbances are associated with the use of hydroxychloroquine, and medical attention should be sought if symptoms persist.[86,122] Ocular toxicity, namely corneal opacities, keratopathy and retinopathy, renal abnormalities and skin reactions have been reported occasionally.[86,122] Medical attention is necessary if patients experience ciliary muscle dysfunction, headache and itching on a frequent basis or any change in vision.[86]

Ciclosporin

Hypertension and nephrotoxicity are well known side-effects of long-term use of CSA.[86,121] Gastrointestinal disturbances (including dyspepsia, nausea and abdominal discomfort), headache, hirsutism and paraesthesia are also associated with the use of CSA.[86,122] Gingival hyperplasia and tremor occur in transplant patients treated with CSA.[86,122]

Methotrexate

Long-term therapy with MTX has been associated with significant liver damage, but the risk of this can be minimised by careful selection and management of patients.[121] There is some evidence that patients with psoriasis may be more susceptible to liver toxicity.[125,126] Other adverse events reported with the use of MTX include mucocutaneous, haematological or gastrointestinal problems.[86,122] Concomitant folic acid can reduce the risk of mucocutaneous and gastrointestinal complaints.[122] Pulmonary toxicity and infections can also occur with MTX.[122] Less serious but possibly bothersome side-effects include repeated

occurrence of acne, appetite loss, boils, nausea, skin rash or itching, pale skin and vomiting.[86] There have been reports of lymphomas and other malignancies associated with MTX therapy, but it is unclear if there is a causative link.[121]

Evidence synthesis

Aim

Three RCTs have been undertaken that each compared etanercept or infliximab individually with placebo, but no studies were identified that compared infliximab and etanercept directly. An estimation of the relative efficacy of the available treatments for PsA is required to complete the clinical evaluation of the biologic interventions under review. It is also necessary to populate the economic model, and hence derive estimates of the cost-effectiveness of etanercept and infliximab.

For this evidence synthesis, a single outcome measure was required. As described in the background section and seen in the earlier clinical efficacy sections of this review, identifying the single most relevant outcome measure for PsA is not a simple matter. As described earlier, for the purposes of the economic evaluation the HAQ score is the best available outcome measure, and therefore this, in combination with response rates determined by PsARC, is the outcome measure used in this evidence synthesis.

This evidence synthesis aims to use the methods of indirect comparison to generate estimates of the absolute short-term benefits of etanercept, infliximab and the placebo effect observed in the trials (no active therapy). Ideally, the evidence synthesis would also include all the treatments available for PsA. Unfortunately, no DMARD trials provided the necessary data. In any case, given the licences of etanercept and infliximab, which indicate that they should be given only after DMARDs have failed, it is reasonable that the evidence synthesis and economic model will not compare them with DMARDs but will include a palliative therapy option (i.e. no active therapy).

Outcomes of interest

PsA is characterised by progressive disabilities, the severity of which can be measured on the HAQ scale. The clinical review has shown that both treatments aim to reduce the HAQ score. However, not all patients respond to each treatment.

This evidence synthesis consists of two linked meta-analyses that estimate the respective response rates of infliximab and etanercept treatments on the one hand and mean reductions (improvements) in HAQ score conditional on response to treatment on the other.

In RCTs where placebo is one of the treatment options, the placebo treatment itself often has some beneficial effect. To take this into account in the evidence synthesis, we also estimate from the clinical trials the response rate and mean reduction in HAQ score of the placebo treatment.

Evidence

Three RCTs reported the number of subjects responding to each treatment out of the number of subjects randomised to receive each treatment. One trial (IMPACT, 2003)[127] reports results after 14 weeks, the other two trials (Mease, 2000[60] and Mease, 2004)[36] report after 12 weeks. The data on response rates are summarised in *Table 15*.

In addition to probabilities of response, the clinical review also identified and extracted data from the trial reports on the mean changes in HAQ, which inform the evidence synthesis regarding HAQ score. However, the reports of the

TABLE 15 *Response rates (in terms of PsARC) reported in the trials and used in the evidence synthesis*[a]

Trial	Arm of RCT		
	Infliximab treatment	**Etanercept treatment**	**Placebo**
IMPACT, 2003;[127] 14 weeks	40 out of 52		7 out of 52
Mease, 2000;[60] 12 weeks		26 out of 30	7 out of 30
Mease, 2004;[36] 12 weeks		73 out of 101	32 out of 104

[a] The 2-week difference in the definition of trial end-points is ignored, and it is assumed that both intervals are equivalent to the 3 months used in the cost-effectiveness model. The 14- rather than the 16-week response rate has been used for infliximab as this is closer to the 12-week response rate data reported for etanercept. The 16-week response rate was 39/52 [see the section Efficacy of infliximab (p. 17)], so the difference is minimal.

TABLE 16 *Indirect information on the change in HAQ that applies to treatment responders and treatment non-responders*

HAQ data		Infliximab treatment	Etanercept treatment	Placebo
Mease, 2000[60]	Baseline HAQ	–	1.2	1.2
	Change	–	–64.2% (SE 7.2)	–9.9% (SE 7.8)

SE, standard error.

TABLE 17 *Change in HAQ score without treatment*

Disease progression	Annual[a] HAQ change
Leeds PsA cohort study, Prof. Emery, as detailed in Wyeth submission	+0.07 (SE 0.03)

SE, standard error.
[a] Our short-term model is deemed to extend over one-quarter of a year.

above trials give aggregate change in HAQ (average change as a percentage from the baseline, combined for both responders and non-responders), whereas additional data from Wyeth and Schering-Plough give evidence on absolute change in HAQ conditional on response to treatment for the IMPACT (2003)[127] and Mease (2004)[36] trials. These data cannot be presented in this report because of commercial confidentiality. These data were used in the evidence synthesis.

For the Mease (2000) trial,[60] additional data have not been made available, and only aggregate data on percentage change of HAQ by treatment arm can be used. Because the mean change in HAQ for each treatment arm is related to the HAQ change for responders and to the HAQ change for non-responders, weighted by the probability of responding to the treatment, these aggregate data from the Mease (2000) trial[60] contain indirect information on the change in HAQ that applies to treatment responders and treatment non-responders, respectively (*Table 16*).

Finally, we used data from one unpublished study to inform the change in HAQ score experienced by subjects that are not undergoing treatment (*Table 17*).

Key assumptions for the evidence synthesis

- The probability of response was modelled separately, and change in HAQ score conditional on response.
- For each clinical trial, we assumed a random baseline probability of response to the placebo treatment.
- We modelled the treatment effects on probability of response as fixed effects that are additive to the placebo probability of response on the log-odds scale.
- We used a fixed-effects model to describe the change in HAQ score for treatment responders, together with a random-effect baseline for the natural progression.
- The effect of placebo response on HAQ change is the same for all trials, regardless of the treatment alternative. The effects of treatment response and non-response on HAQ change are treatment specific.
- Mean changes in HAQ score, as reported in the trials, are assumed to follow a normal distribution around the mean HAQ change predicted by the model. The standard errors of these distributions are assumed to be known.

As part of the sensitivity analysis, in the section 'Alternative assumptions' (p. 51) we examine an alternative specification of the prior distribution in the evidence synthesis used to reflect between-trial variation in the placebo response rate. No substantive changes in the results were observed.

Formal model description

The evidence synthesis model was fitted using WinBUGS 1.4.1. Let $i = I, E$ denote the treatments infliximab and etanercept. Let $j = 1, 2, 3$ denote the IMPACT (2003),[127] Mease (2004)[36] and Mease (2000)[60] trials, respectively. For each trial j, let T_j denote the treatment administered on the treatment arm.

Regarding the **evidence synthesis model of probabilities of responding** to treatment (or

placebo), let r_j^t and n_j^t be the responders and the number of subjects in the treatment arm of trial j, respectively. Let r_j^c and n_j^c be the responders and number of subjects in the placebo arm of trial j. Let π_j^t and π_j^c denote the probabilities of responding to the treatment and to the placebo in trial j. Let Π denote the underlying probability of responding to treatment i, let P_i denote the log-odds increment in response rates due to treatment i and let Π denote the underlying probability of response to placebo. For the probabilities of response, we assume the following model: $r_j^t \sim Bin(\pi_j^t, n_j^t)$ and $r_j^c \sim Bin(\pi_j^c, n_j^c)$ for the three trials j, with $\alpha/(\alpha + \beta) = \Pi_c$, $\pi_j^c \sim Beta(\alpha, \beta)$ describing the random baseline probabilities of responding to the placebo treatment and $\log[\pi_j^t/(1 - \pi_j^t)] = \log[\pi_j^c/(1 - \pi_j^c)] + P_{T_j}$ defining the probabilities of responding to treatment.

We apply the following prior distributions to the unknown parameters: $\alpha + \beta \sim Unif\ (0, 50000)$, $\Pi_c \sim Unif\ (0, 1)$ and $P_i \sim N(0, 10000^2)$. These priors are taken to be uninformative, and the robustness of the results to particular parameterisations of these priors has been tested.

In reporting the results of this evidence synthesis, we calculate treatment response rates Π_i as $\log[\Pi_i/(1 - \Pi_i)] = \log[\Pi_c/(1 - \Pi_c)] + P_i$.

Regarding the **evidence synthesis model of HAQ changes**, let N_j denote the natural progression in HAQ for trial population j. Furthermore, let $\delta_j^{t,\text{resp}}$, $\delta_j^{t,\text{noresp}}$, $\delta_j^{c,\text{resp}}$ and $\delta_j^{c,\text{noresp}}$ denote the reported mean changes in HAQ score on the treatment and placebo arms of trial j, with associated standard errors $\tau_j^{t,\text{resp}}$, $\tau_j^{t,\text{noresp}}$, $\tau_j^{c,\text{resp}}$ and $\tau_j^{c,\text{noresp}}$. Corresponding to each δ_j, let ∂_j denote the corresponding underlying effects. Because the ∂_j are fixed effects, we can replace the indices j by an indicator of treatment (I or E), and we have the following simplifications:

$\partial_1^{t,\text{resp}} = \partial_I^{t,\text{resp}}$, $\partial_2^{t,\text{resp}} = \partial_3^{t,\text{resp}} = \partial_E^{t,\text{resp}}$ (treatment responders)

$\partial_1^{t,\text{noresp}}$, $\partial_I^{t,\text{noresp}}$, $\partial_2^{t,\text{noresp}} = \partial_2^{t,\text{noresp}} = \partial_3^{t,\text{noresp}} = \partial_E^{t,\text{noresp}}$ (treatment non-responders)

$\partial_1^{c,\text{resp}}$, $\partial_2^{c,\text{resp}} = \partial_3^{c,\text{resp}} = \partial^{c,\text{resp}}$(placebo responders)

$\partial_1^{c,\text{noresp}}$, $\partial_2^{c,\text{noresp}} = \partial_3^{c,\text{noresp}} = 0$ (placebo non-responders)

All these fixed effects ($\partial_I^{t,\text{resp}}$, $\partial_E^{t,\text{resp}}$, $\partial_I^{t,\text{noresp}}$ $\partial_E^{t,\text{noresp}}$ and $\partial^{c,\text{resp}}$) are incremental to the natural progression baseline, N_j.

Finally, let ∂_d denote the HAQ change associated with the natural progression of the disease, and let δ_{4d} be the data on annual change, with its associated standard error τ_{4d}.

Our evidence synthesis model for the HAQ change (conditional on being a treatment responder or not) can be expressed as follows. For all trials we model the baseline change in HAQ as a random effect $N_j \sim N(\partial_d, \tau_N^2)$, with fixed standard deviation $\tau_N = 0.1$. For those trials that report changes in HAQ score conditional on response (i.e. trials $j = 1, 2$), we have, for each of the four combinations of (treatment or placebo) and (response or no response),

$$\delta_j^{t,c;\text{resp,noresp}} \sim N[N_j + \partial_j^{t,c;\text{resp,noresp}}, (\tau_j^{t,c;\text{resp,noresp}})^2]$$

For those trials that do not report changes in HAQ score conditional on response (i.e. trial $j = 3$), we calculate the average predicted changes in HAQ score ∂_j^t, ∂_j^c for each treatment arm:

$$\partial_j^t = \pi_j^t \partial_j^{t,\text{resp}} + (1 - \pi_j^t)\partial_j^{t,\text{noresp}} \text{ and } \partial_j^c = \pi_j^c \partial_j^{c,\text{resp}} + (1 - \pi_j^c)\partial_j^{c,\text{noresp}}$$

The observed mean changes in HAQ (reported in %) are assumed to relate to these underlying changes in HAQ by

$$\delta_j^t * \sim N\left[100\frac{N_j + \partial_j^t}{H_j^c}, (\tau_j^t)^2\right] \text{ and}$$

$$\delta_j^c * \sim N\left[100\frac{N_j + \partial_j^c}{H_j^c}, (\tau_j^c)^2\right]$$

for each treatment arm, where the asterisk indicates that these quantities are reported as 'percentage change from initial HAQ value', and H_j^t and H_j^c denote these initial values, assumed known. Furthermore, in this Bayesian analysis, we use the data on the natural progression of the disease as an informative prior on ∂_d:

$$4\partial_d \sim N(\delta_{4d}, \tau_{4d}^2)$$

For the remaining unknown parameters we specify uninformative priors as follows:

$$\partial_i^{t,\text{resp}} \sim N(0, 10000^2),\ \partial_i^{t,\text{noresp}} \sim N(0, 10000^2),$$
$$\partial^{c,\text{resp}} \sim N(0, 10000^2)$$

Evidence synthesis results

The results of the evidence synthesis are shown in *Table 18*.

TABLE 18 *Results of the evidence synthesis*

Evidence synthesis	Parameter meaning	Posterior mean	Standard deviation
Π_I	Probability of response to infliximab	0.7705	0.0582
Π_E	Probability of response to etanercept	0.7705	0.0356
Π_C	Probability of response to placebo	0.2509	0.0317
$\partial_I^{t,\text{noresp}}$	Incremental HAQ change for infliximab non-responders	–0.2169	0.0901
$\partial_I^{t,\text{resp}}$	Incremental HAQ change for infliximab responders	–0.6667	0.0905
$\partial_E^{t,\text{noresp}}$	Incremental HAQ change for etanercept non-responders	–0.2414	0.0719
$\partial_E^{t,\text{resp}}$	Incremental HAQ change for etanercept responders	–0.7214	0.0551
$\partial^{c,\text{resp}}$	Incremental HAQ change for placebo responders	–0.2827	0.0553
∂_d	HAQ change by natural progression	0.0166	0.0073

The quantities of interest are the probabilities of response to either treatment (Π_i) and to placebo (Π_c), and also the underlying changes in HAQ score conditional on response and non-response to either treatment ($\partial_{I,E}^{t;\text{resp,noresp}}$), response to placebo ($\partial^{c,\text{resp}}$) or caused by the natural progression (∂_d). Because placebo is not a treatment option in the long-term model, the results of the evidence synthesis will be adjusted for the placebo effect in the appropriate equations of the long-term economic model. The model fit appears to be robust regarding the particular uninformative priors that are chosen.

The marginal posterior distributions for the parameters of interest are summarised in *Table 17*.

We used the full posterior distributions in the long-term model of cost-effectiveness, which preserves the information on distributional shape and parameter correlations that is lost in presenting the results in a summary table as above.

The probability of responding to infliximab treatment is estimated to be 0.7705 and for etanercept this probability is also estimated as 0.7705. The RR of infliximab versus etanercept of 1.0 (95% CI: 0.82 to 1.18) also highlights that, as far as response rates are concerned, the evidence synthesis suggests the two treatments are very similar. For reference, the response rate for placebo treatment is estimated to be 0.2509 and the evidence synthesis-generated RR of infliximab versus placebo is 3.1 (95% CI: 2.32 to 4.15), and that for etanercept versus placebo is 3.1 (95% CI: 2.40 to 4.09).

The evidence synthesis shows that responders to either treatment experience a statistically significant improvement in HAQ scores. Incremental to the natural progression baseline change in HAQ of 0.0166 (95% CI: 0.002 to 0.031), responders to etanercept treatment experience an additional change in HAQ of –0.72 (95% CI: –0.83 to –0.61), and responders to infliximab treatment of –0.67 (95% CI: –0.84 to –0.49). Both of these HAQ changes are significantly different from the incremental HAQ change experienced by placebo responders, of –0.28 (95% CI: –0.39 to –0.18), but do not differ substantially between the two active treatments. We also estimated the change in HAQ of non-responders to either treatment, because we are aware that PsARC does not fully capture treatment success.

In summary, both treatments are superior to the placebo treatment with regard to response rates and to changes in HAQ scores for responders, but the between-treatment difference is not significant with regard to either response rates or changes in HAQ for responders. These findings are relevant for review of the success or otherwise of treatment after the first 3 months. They do not provide an indication of the relative efficacy of treatments in the long term, evidence for which is lacking for both drugs.

Chapter 5
Economic review

Published economic evaluations

The search strategy for published economic evaluations yielded 117 potentially relevant studies. Of these, none fulfilled the inclusion criteria of being a full economic evaluation of etanercept or infliximab for the treatment of PsA.

Company submissions

Two cost-effectiveness models were received from manufacturers, one for etanercept (from Wyeth) and one for infliximab (from Schering-Plough).

Wyeth's cost-effectiveness model

Details of Wyeth's model are presented in Appendix 9, section 'Cost-effectiveness model (Wyeth) – data extraction' (p. 223) in terms of a data extraction table and Appendix 9, section 'Cost-effectiveness model submitted by Wyeth – quality assessment' (p. 225) presents a quality assessment.

Summary

Methods

The Wyeth model is heavily influenced by an earlier model developed for etanercept in RA.[42] It assesses the cost-effectiveness of etanercept in PsA as part of two alternative treatment sequences. It is assumed that patients would have failed DMARD treatment with MTX and SSZ before etanercept is considered. The etanercept sequence of therapies was, therefore, etanercept followed, in treatment failures, by DMARD therapy with CSA in combination with MTX or leflunomide. Once the latter therapy fails, patients are assumed to undergo 'palliative therapy'. The comparator sequence consists only of CSA in combination with MTX or leflunomide. When this therapy fails, patients move on to palliative therapy.

Alternative time horizons of 6 months, 2 years, 5 years and 10 years are explored in the model, although the focus is on 10 years. Health effects are assessed in terms of quality-adjusted life-years (QALYs) and, in the base-case analysis, the perspective is that of the NHS. The model takes the form of a patient-level simulation (discrete event simulation) and, in the base-case analysis, patients from Mease and colleagues'[128] trial are sampled. Key effectiveness data are taken from the same trial: response rate at 12 weeks in terms of PsARC and change in HAQ during the 12-week period. It is assumed that patients who experience a PsARC response at 12 weeks continue on etanercept; non-responders move to CSA in combination with MTX or leflunomide. The change in HAQ is estimated, based on the trial data, using an ordinary least-squares (OLS) regression as a function of baseline covariates and treatment allocation. This facilitates an assessment of variability in HAQ response between patients, which is then factored into the model by sampling from the baseline characteristics. It is assumed that there is no HAQ progression in patients responding to etanercept. Longer term (i.e. post-12-week) failure rates for etanercept are taken from a Swedish observational study in RA patients.

For the comparator therapies (CSA in combination with MTX or leflunomide), initial treatment response (in terms of PsARC) at 12 weeks is assumed to be the same as for the placebo arm of Mease and colleagues' trial.[128] The same assumption is made with respect to change in HAQ in responding patients on the comparator therapies. Unlike etanercept, it is assumed patients who respond to comparator therapies progress in terms of HAQ based on observational data. Longer term failure (treatment withdrawal) rates for comparator therapies are based on estimates in the literature relating to PsA and RA patients. Patients failing active therapy with etanercept or the comparator DMARDs are assumed to move to palliative therapy where patients experience progression of HAQ equivalent to natural history. An estimate for this natural history progression rate is taken from a sample of 24 PsA patients in Leeds.

A key structural assumption in the model is what happens to patients, in terms of HAQ, once they fail on treatment. The Wyeth model implements two alternative assumptions: (1) that HAQ deteriorates by the same magnitude to their initial improvement (i.e. rebound equal to gain) and (2) that HAQ returns to the the value it had when the patient started therapy. In the case of treatment with etanercept where patients are assumed not to

progress in terms of HAQ when responding to treatment, these two scenarios amount to the same thing. This is not the case with DMARD therapy, however.

HAQ score is the basis for ascribing costs (other than those relating to the drugs being evaluated) and utility in the model. This is implemented using OLS regression, which estimates mean cost and mean utility for a given level of HAQ. The cost regression is based on earlier work by Kobelt and colleagues on RA.[43] The utility regression is based on an unpublished analysis in a sample of PsA patients in Leeds who completed the EuroQoL-5D (EQ-5D) instrument.

Results

The base-case results are presented in *Table 19*. Three sets of results are presented for four alternative time horizons. Results are not reported relative to a specific comparator (i.e. CSA plus MTX or leflunomide), only against a composite comparator. The results show that the cost per QALY gained for etanercept declines as the time horizon increases, ranging from £66,580 for a 6-month time horizon to £28,189 for a 10-year time horizon.

A range of uncertainty analysis was undertaken. A probabilistic sensitivity analysis indicated that the probability of etanercept being more cost-effective than the 'comparator' was 0.58 (with a 10-year time horizon and with base-case assumptions). A number of one-way sensitivity analyses were also presented generating incremental cost-effectiveness ratios (ICERs) ranging from £35,216 per QALY (using a lower rate for HAQ progression) to £17,195 per QALY (incorporating indirect (productivity) costs).

Limitations of the Wyeth model

There are various aspects of the model that might be criticised. The major limitations are considered below.

- *Comparators*. Given the licence for etanercept, it seems inappropriate to compare its cost-effectiveness against any DMARDs as its use is limited to situations when those drugs have failed. The Wyeth model sets up a comparison against CSA plus MTX or leflunomide, but assumes the efficacy of these treatments is no greater than that seen in placebo in the etanercept trials. This assumption can probably be explained by the absence of data on PsARC response and HAQ for most DMARD therapies. If such a lack of efficacy were the case, it is hard to see why such therapies would be used given their acquisition cost.
- *HAQ progression while responding*. The Wyeth model assumes that there is no progression in HAQ while a patient is responding to etanercept. The evidence for this is limited, but contrasts with the assumption of progression while patients are responding to DMARDs. This is explored using one-way sensitivity analysis and the results are found to be sensitive to the assumption. A fuller scenario analysis about these assumptions is warranted.
- *Rebound assumptions*. An important structural assumption in the model is what happens to a patient's HAQ score when they fail therapy. As described above, the Wyeth model assesses two scenarios: rebound equal to gain, and rebound

TABLE 19 *Base-case results from the Wyeth model*

	Alternative time horizon							
	6 months		1 year		5 years		10 years	
	Etanercept	Comparator	Etanercept	Comparator	Etanercept	Comparator	Etanercept	Comparator
Total costs (£)	4,897	1,901	8,974	3,675	33,103	15,813	51,122	28,010
Incremental cost (£)	2,996		5,299		17,290		23,112	
QALY	0.29	0.24	0.63	0.52	2.71	2.24	4.49	3.67
Incremental QALY	0.04		0.10		0.46		0.82	
Incremental cost per QALY (£)	66,589		52,076		37,398		28,189	

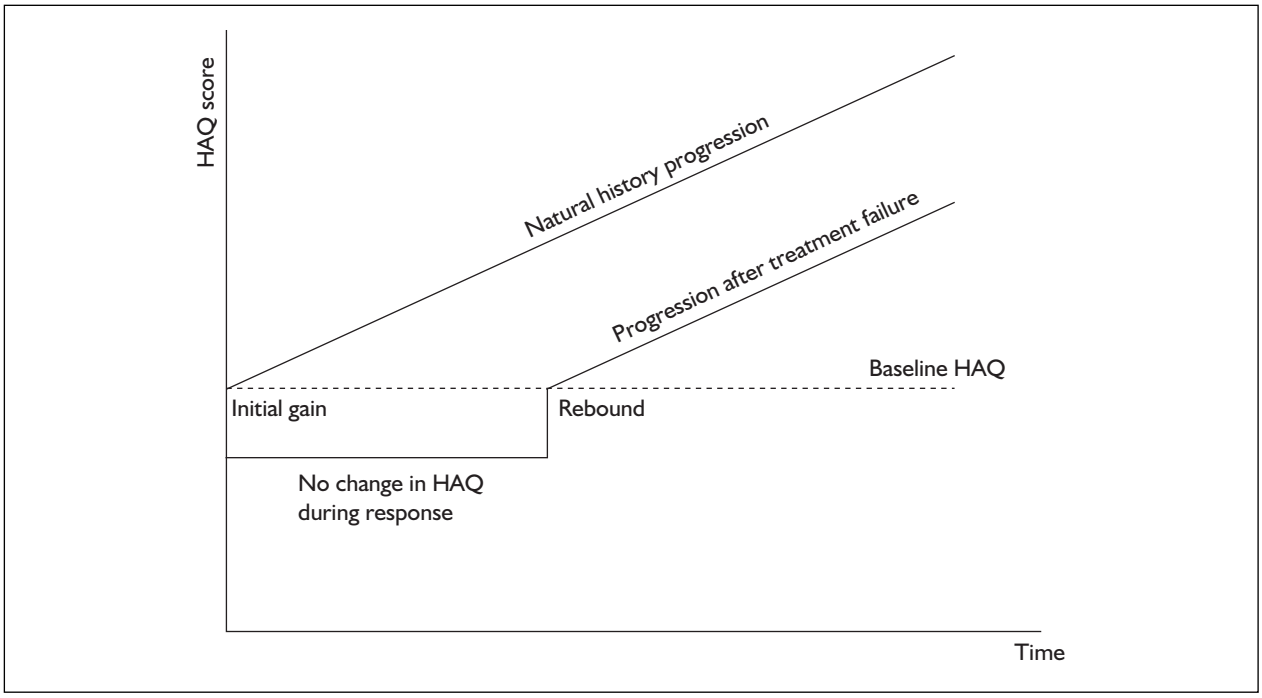


FIGURE 1 *Illustration of the base-case rebound scenario for etanercept in the Wyeth model: rebound equal to gain*

back to baseline. The base-case assumption is rebound equal to gain which is illustrated in *Figure 1*. The top line shows the underlying natural history progression of HAQ over time (a higher HAQ score indicates worse disability). Successful therapy will reduce HAQ (improve disability). Once therapy fails, patients are assumed to rebound by an amount equal to their gain. The scenario that is not considered in the Wyeth model is rebound back to natural history, which is illustrated in *Figure 2*. That is, when a patient fails therapy, their HAQ returns to what it would have been had they not been treated.

- *The costs failing therapy*. Assumptions made in the Wyeth model would seem to overestimate the cost implications of failing therapy. The first is that, once a patient fails etanercept or DMARDs (CSA plus MTX or leflunomide), they are assumed to go on to 'palliative care', which is taken as having costs over and above those estimated by regression according to Kobelt and colleagues.[43] However, the Kobelt regression already includes a full range of costs for all HAQ states, so adding the costs for palliation may be considered to be double counting. Furthermore, given higher failure costs with the non-etanercept treatment sequence, this is likely to underestimate etanercept's ICER. A further issue of double counting may exist because the Kobelt regression includes all costs (including drugs), so adding in the acquisition cost of etanercept and the DMARDs means that these are effectively included twice.

Schering-Plough's cost-effectiveness model

The Schering-Plough submission is not completely described, the cost-effectiveness model is presented partly in note form and many specifics of the modelling are not detailed. The authors explicitly state that the model is preliminary. As fully as possible, the details of the model are presented in Appendix 9, section 'Cost-effectiveness model (Schering-Plough) – data extraction' (p. 227) in terms of a data extraction table, and a quality assessment is shown in Appendix 9, section 'Cost-effectiveness model (Schering-Plough) – quality assessment' (p. 228).

Summary

The Schering-Plough model takes a different approach to assessing the cost-effectiveness of infliximab to that taken by Wyeth with etanercept; it is also different to most of the main cost-effectiveness models of biological therapies in RA.[41–43,129] Instead of using HAQ as the basis for defining disease progression and hence disability, utility and non-drug costs, the number of active joints is used. This measure is also used to model patients' response to treatment: patients are assumed to remain on infliximab until and unless they experience three consecutive cycles (where each cycle is 16 weeks) in the worst health state

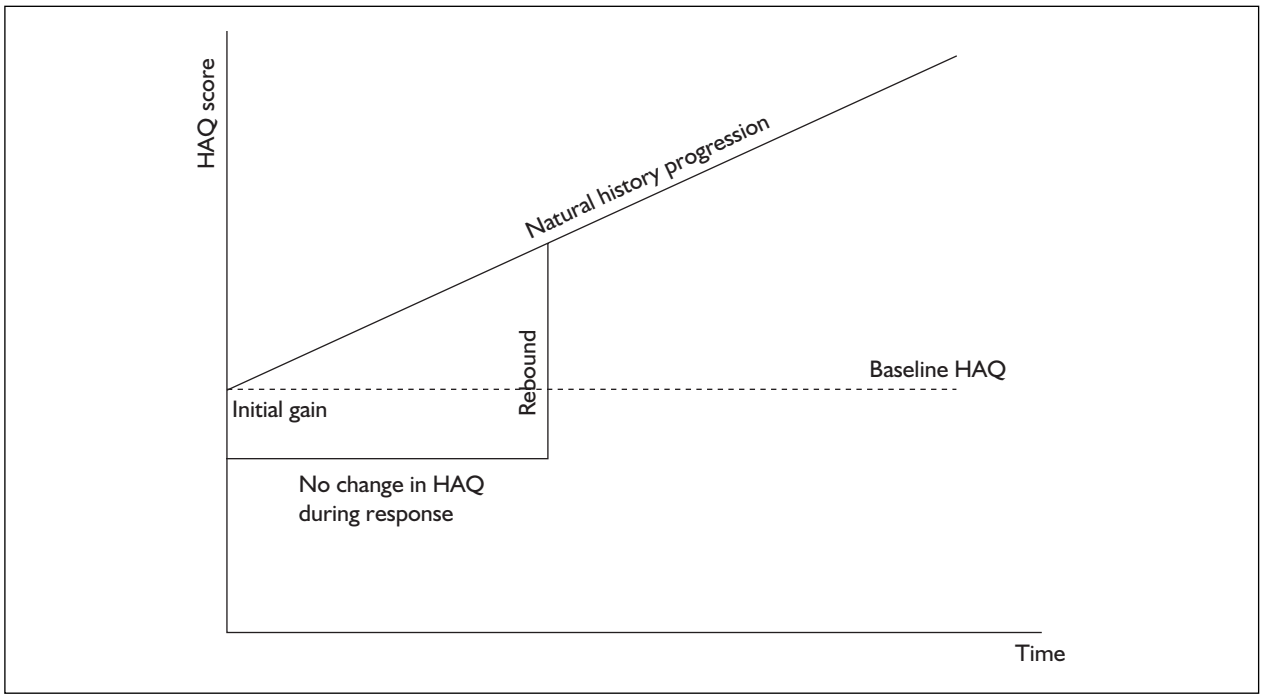


FIGURE 2 *Illustration of a third rebound scenario for etanercept not considered in the Wyeth model: rebound to natural history progression*

(10 or more active joints). This is a strong assumption given that in clinical practice anti-TNF treatment will be withdrawn if patients fail to achieve the PsARC response within 3 months of treatment.[35] This contrasts with the approach in the Wyeth model of using PsARC response as a basis for assessing response. The comparison in the model is infliximab and 'standard supportive therapy'.

Two (apparently related) Markov models were undertaken: the Active Joint Model and the Chronic Active Joint model. The former relates to the short-term effect of the disease (flares of active joints), whereas the latter includes this short-term effect and how flares contribute to long-term progression in terms of development of chronic deformed joints. The key effectiveness parameters in the models were taken from the IMPACT trial[61] and from the Toronto Psoriatic Arthritis Research Programme – an observational study. The detail of how this was undertaken is not clear from the submission although, in general terms, it seems that the observational study was used to provide estimates of baseline transitions between the states and to give a basis for extrapolation beyond the trial, and the IMPACT trial was used to estimate the relative treatment effect of infliximab versus standard supportive therapy. Utility estimates for the health states were taken from the Toronto observational study, as were the estimates of resource use. Utility impact in terms of EQ-5D (but costs also) relates to PsA only, rather than to effects on psoriasis. The model was analysed as a patient-level simulation. Probabilistic sensitivity analysis was undertaken, but the methods used were not reported.

Tables 20 and *21* show the base-case results of the models. *Table 20* details the results of the Active Joint Model for a 5-year time horizon. This suggests an incremental cost per QALY gained for infliximab of £36,786. Sensitivity analysis is reported on the variation of the ICER with changes in the time horizon. Two-, 10- and 30-year time horizons give ICERs of £58,612, £33,282 and £31,071, respectively.

Table 21 shows the results of the Chronic Active Joint Model based on a 30-year time horizon. The ICER for this scenario is similar to the first (£33,877). Sensitivity analysis is reported on the variation of the ICER with changes in the time horizon. Five-, 10- and 45-year time horizons give ICERs of £41,105, £37,396 and £35,327, respectively.

Limitations of the Schering-Plough model

Based on the description offered in the Schering-Plough submission, there are a number of weaknesses with the analysis and several important issues relating to the model are unclear:

TABLE 20 *Base-case results for the Active Joint version of the Schering-Plough model with a 5-year time horizon*

	Costs (£)	QALYs	Incremental cost per QALY gained (£)
Supportive care	6,970	1.41	
Infliximab	61,019	2.88	36,768

TABLE 21 *Base-case results for the Chronic Active Joint version of the Schering-Plough model with a 30-year time horizon*

	Costs (£)	QALYs	Incremental cost per QALY gained (£)
Supportive care	25,444	5.88	
Infliximab	235,483	12.08	33,877

- The details of how the Markov models are populated and the treatment effect of infliximab implemented are not clear.
- In particular, no information is supplied on what happens to patients, in terms of health state, utility and costs, if they fail on infliximab.
- Treatment response is not based on a clinical measure but on an apparently arbitrary feature of the model. This does not reflect either how decisions are likely to be taken in clinical practice about when to take patients off infliximab or any empirical estimates of treatment withdrawals in practice.
- The cost analysis within the model (except the drug costs) is based on resource use estimates from Canada rather than from the NHS.
- Very limited sensitivity analysis is reported. The methods of probabilistic sensitivity analysis are not detailed.

As main conclusions, the model does not include any of the two main instruments which have been used for measuring clinical response in PsA: the PsARC and the ACR. It does not consider the inclusion of patient disability measures, such as the HAQ. Although the number of active joints has been shown to be a good predictor for short-term outcomes, other outcome measures should have been considered in order to capture the effect of disability in the long term and its effects on QoL. Results need to be explored further in the light of different rebound scenarios as the model does not make explicit what happens after patients withdraw from infliximab. Finally, it is not clear whether the results are applicable to a UK setting given that direct costs are based on resource use estimates from Canada rather than from the NHS.

Chapter 6
Economic modelling

Introduction

Chapter 5 indicates that there are only two economic analyses available to support NHS decision-making regarding the cost-effectiveness of etanercept and infliximab for PsA: the economic models submitted by Wyeth and Schering-Plough, respectively. These models do not provide an adequate framework for decisions about cost-effectiveness. In the case of the Wyeth model, there is a range of assumptions and structural features which may be considered inappropriate. The Schering-Plough model has only been partially described, and it takes a modelling approach which is completely different to that used by other analysts for the economic evaluation of biological therapies in PsA (i.e. the Wyeth submission) and RA.[41–43,129] However, the main limiting factor with the two manufacturers' models is that they do not provide a means of comparing the two biological therapies **with each other based on all available trial evidence**.

For this reason, it has been necessary to develop a *de novo* model (hereafter referred to as the 'York Model'). Although it shares some of the assumptions and parameter estimates of the two manufacturers' models (particularly that submitted by Wyeth), it has a different structure and, unlike the manufacturers' models, is based on all the available trial data for each biological therapy. Specifically, the model incorporates the short-term efficacy data generated by the evidence synthesis described in the section 'Evidence synthesis' (p. 30).

Methods

Overview

The aim of the York Model is to assess the cost-effectiveness of three treatment options in patients with PsA who have failed on DMARDs: etanercept, infliximab and palliative care. The model uses short-term trial data (based on the evidence synthesis [see the section 'Evidence synthesis' (p. 30)] to model the response of patients to biological therapy at 12 weeks based on PsARC measured in the trials. Disability from PsA is based on HAQ scores that are worsening over time (a natural history progression), but response to biological therapy can retard this progression. HRQoL, in terms of utility, is based on HAQ score, as are all PsA costs except for the cost of the biological therapies themselves (acquisition, administration and monitoring). Health effects are expressed in terms of QALYs. Four alternative time horizons are modelled: 1, 5, 10 and 40 years (i.e. lifetime).

The added value of anti-TNF treatment on the skin component of the disease is not incorporated into the York Model (this is also the case with the two manufacturers' models). There are two main reasons that justify this decision: first, there exists no validated composite outcome measure that can take into account the impact of treatment on both skin disease and arthritis; second, although the degree of correlation between skin disease severity and joint severity is still an object of debate,[130,131] the fact that patients with active PsA have generally mild skin disease is generally recognised among clinical experts.[132] The British Society for Rheumatology (BSR) recommends combined care of joint and skin pathologies whenever possible but, in practice, the arthritis condition tends to take priority given its progressive nature.

Comparators

The cost-effectiveness comparison in the York Model is etanercept, infliximab and supportive care. In other words, it is based on the view that the anti-TNFs would be considered once available DMARD therapies have been tried and have failed. This choice of comparators is justified for several reasons. First, the product licences for etanercept and infliximab, granted in 2003 and 2004 respectively (*Table 22*), imply that all available DMARDs used in PsA should be tried before patients are given etanercept or infliximab.

As for their use in RA, however, the licences for the anti-TNFs in PsA may be interpreted as requiring a minimum number of DMARDs to be tried before patients progress to the new therapies. This number is not stated in the current SPCs for infliximab and etanercept. The latest BSR guidelines for the use of anti-TNF drugs for PsA[35] state that at least two DMARDs individually or in combination should have been tried. A much

TABLE 22 *Anti-TNF therapeutic indications for psoriatic arthritis*

Treatment	Indications
Etanercept	Treatment of active and progressive PsA in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate
Infliximab	In combination with MTX, is indicated for the treatment of active and progressive PsA in patients who have responded inadequately to disease-modifying antirheumatic drugs

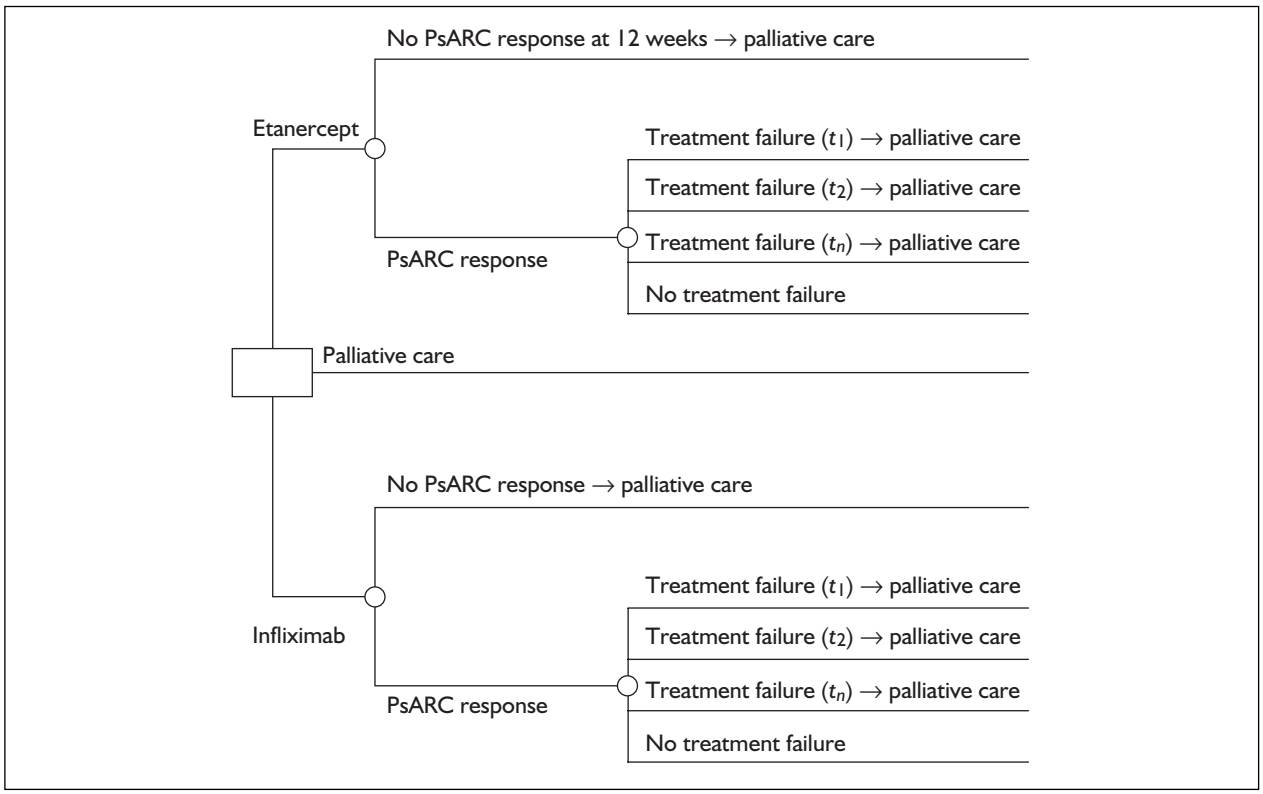


FIGURE 3 *A simplified version of the structure of the York Model. Note: patients are at risk of all-cause mortality at every time period in the model, but mortality assumed is the same between treatments.*

smaller number of DMARDs are routinely used in PsA than in RA, typically SSZ, MTX and CSA, none of which is currently licensed for use in active PsA in the UK, which is a further reason for not including them as comparators in the York Model. Leflunomide is now licensed for PsA but this is a new class of therapy which, it is understood, will be subject to a separate appraisal by NICE.

The decision regarding the choice of comparators is also justified on more practical grounds. In order to compare infliximab and etanercept with DMARDs such as SSZ, MTX and CSA, trial data on response in terms of PsARC and change in disability based on HAQ are required. As shown in the section 'DMARDs for the treatment of psoriatic arthritis' (p. 23), these data are not available.

Model structure

The York Model is a cohort model and takes the form of a modified decision tree. A simplified version of the structure is shown in *Figure 3*.

For the two biological therapies, initial response is determined on the basis of short-term PsARC response. This is justified as the BSR guidelines[35] state that patients who fail to achieve a PsARC response within 3 months of treatment with anti-TNFs should been withdrawn from therapy because of lack of efficacy. For those who respond, there is then an on-going risk of withdrawal of treatment at any time point in the model. Initial or later treatment failures are assumed to move on to palliative care, with biological therapies being the 'end of the line' in terms of active interventions. After the withdrawal of biologics,

patients would continue to be given some kind of treatment, but the type and cost are impossible to determine and very much clinician dependent. In any case, all the potential treatments a clinician can use at this stage (joint injections, intramuscular gold, etc.) are relatively inexpensive.

Underlying the structure shown in *Figure 3* is a natural history progression rate in terms of HAQ, that is, a worsening of disability in the face of no active intervention. Patients who do not receive etanercept or infliximab (i.e. those receiving palliative care from the outset) and those that fail with biological therapy at the initial point (taken as 12 weeks) are assumed to experience a deterioration in HAQ in line with the natural history progression.

Those patients who respond to biological therapy will experience an initial gain in HAQ which is based on the trial data for infliximab and etanercept and the results of the evidence synthesis. In addition to this initial improvement in HAQ, these patients are also assumed to experience a slower progression rate in HAQ as long as they are responding. Patients who fail on either biological therapy after the initial (12-week) period will experience some form of rebound in terms of HAQ, but trial data are too short-term to be able to characterise this accurately. The model, therefore, considers two rebound scenarios:

1. *Rebound equal to gain*. When patients fail therapy (after initially responding), their HAQ deteriorates by the same amount by which it improves when they responded to therapy (see *Figure 1* for illustration).
2. *Rebound back to natural history*. When patients fail therapy, their HAQ returns to the level and subsequent trajectory it would have been had they not initially responded to therapy (see *Figure 2* for illustration).

Given the absence of evidence on rebound, both scenarios (rebound equal to gain and rebound back to natural history) are presented as the 'best-case' and 'worst-case' scenarios possible. In other words, the reality regarding rebound is likely to be somewhere between these two scenarios, which should, therefore, be seen as the limits.

Patients are at risk of all-cause mortality at every time point in the model, but there is no **differential** mortality risk between the therapies being evaluated. Apart from the cost of the biological therapies themselves (acquisition, administration and monitoring), all other costs of PsA are assumed to vary according to HAQ score. Similarly, HRQoL (in terms of utility) is implemented as a function of HAQ score.

Parameter estimates

The parameter estimates used in the York Model, together with their sources, are detailed in *Table 23*.

Patients' characteristics at baseline

The results of the analysis are conditional on three specific features of the patient cohort under treatment. The baseline (starting) HAQ determines a patient's starting point in terms of disability from where they deteriorate over time and this has an effect on costs and QALYs. For the base-case analysis, a baseline HAQ of 1.16 is assumed based on the average in the three Phase III trials of the biologic therapies: the Mease (2000),[60] Mease (2004)[36] and IMPACT[61] trials. Starting age will affect the all-cause mortality rate in the model. In the base-case an age of 46 years is assumed, again based on the mean from the three Phase III trials. The patient's weight determines the dosing and hence the cost of infliximab. The mean weight in the IMPACT study[61] of infliximab is used as an estimate of this baseline parameter.

An important contextual factor is that the average number of DMARDs previously failed by the trial patients differs between the infliximab and the two etanercept trials. In both the Mease (2000)[60] and Mease (2004)[36] trials, eligible patients were aged 18–70 years, had active PsA (i.e. with at least three swollen joints and three tender or painful joints at screening) and a previous inadequate response to NSAID therapy. Patients were permitted to have received previous DMARD therapy, but this was not an inclusion criterion for trial entry. With respect to infliximab, however, only subjects with active PsA who had failed at least one DMARD were included in the IMPACT study.[61] As a result, one out of four patients was DMARD-naïve in the Mease (2004) trial (etanercept) compared with none in the infliximab trial (IMPACT). Furthermore, whereas the proportion of patients who had previously failed two or more DMARDs was about 50% in the infliximab trial, only one out of five patients had failed two previous DMARDs in the Mease (2004) trial. Although results are not reported in the same format for the Mease (2000) trial, given that the inclusion criteria for patients are exactly the same, it can be expected to have had similar baseline characteristics to the Mease (2004) trial (see *Table 2* for further details).

TABLE 23 *List of parameter estimates used in the York Model*

Parameter	Mean value	Standard error	Distribution	Description	Source
Baseline patient characteristic					
Baseline HAQ	1.16	–	Fixed	Average in the three Phase III trials of the biologic therapies	Mease, 2000;[60] Mease, 2004;[36] and IMPACT trial[61]
Age (years)	47	–	Fixed	Average in the three Phase III trials of the biologic therapies	Mease, 2000;[60] Mease. 2004;[36] and IMPACT trial[61]
Weight (kg)	82	–	Fixed	Only infliximab dosing is dependent on weight, 80 kg used to estimate dosage (as in Schering-Plough submission)	IMPACT trial[61]
Initial PsARC response probabilities[a]					
Infliximab	0.7705	0.0582	Direct from posterior of evidence synthesis	Posterior mean (SE) reported here, results after adjustment for placebo effect used in the model	See the section 'Evidence synthesis', p. 30. See Appendix 10
Etanercept	0.7705	0.0356	Direct from posterior of evidence synthesis	Posterior mean (SE) reported here, results after adjustment for placebo effect used in the model	See the section 'Evidence synthesis', p. 30. See Appendix 10
Placebo	0.2509	0.0317	Direct from posterior of evidence synthesis	Posterior mean (SE) reported	See the section 'Evidence synthesis', p. 30. See Appendix 10
Initial HAQ change given a treatment response[a]					
Infliximab	–0.6667	0.0905	Direct from posterior of evidence synthesis	Posterior mean (SE) reported here, results after adjustment for placebo effect used in the model	See the section 'Evidence synthesis', p. 30. See Appendix 10
Etanercept	–0.7214	0.0551	Direct from posterior of evidence synthesis	Posterior mean (SE) reported here, results after adjustment for placebo effect used in the model	See the section 'Evidence synthesis', p. 30. See Appendix 10
Placebo	–0.2827	0.0553	Direct from posterior of evidence synthesis	Posterior mean (SE) reported here, results after adjustment for placebo effect used in the model	See the section 'Evidence synthesis', p. 30. See Appendix 10
Initial HAQ change given no treatment response[a]					
Infliximab	–0.2169	0.0901	Direct from posterior of evidence synthesis	Posterior mean (SE) reported here, results after adjustment for placebo effect used in the model	See the section 'Evidence synthesis', p. 30. See Appendix 10
Etanercept	–0.2414	0.0719	Direct from posterior of evidence synthesis	Posterior mean (SE) reported here, results after adjustment for placebo effect used in the model	See the section 'Evidence synthesis', p. 30. See Appendix 10
Annual withdrawal probability					
Infliximab	0.113	–	β ($a = 43$, $b = 236$)	Based on estimates from 3 to 20 months as initial withdrawal at 3 months already accounted for in the probability of PsARC response. Average estimate for both drugs	Geborek *et al.*, 2002[76]
Etanercept	0.113	–	β ($a = 43$, $b = 236$)	Based on estimates from 3 to 20 months as initial withdrawal at 3 months already accounted for in the probability of PsARC response. Average estimate for both drugs	Geborek *et al.*, 2002[76]
Long-term HAQ progression					
Responders to infliximab	0	0	–	Assumption that biologics can halt HAQ progression while responding to treatment	

continued

TABLE 23 *List of parameter estimates used in the York Model (cont'd)*

Parameter	Mean value	Standard error	Distribution	Description	Source
Responders to etanercept	0	0	–	Assumption that biologics can halt HAQ progression while responding to treatment	
Natural history progression with no active therapy (at 3 months)	0.0166	0.0073	Direct from posterior of evidence synthesis	Based on a sample of 24 PsA patients from observational cohort of PsA patients in Leeds (NESPAR study, detailed in Wyeth submission). Posterior mean (SE) reported here, results after adjustment for placebo effect used in the model	See the section 'Evidence synthesis', p. 30. See Appendix 10
Mortality					
SMR – women	1.60	–	Inverse β (a = 16.30, b = 26.00)		Wong *et al.*, 1997[21]
SMR – men	1.66	–	Inverse β (a = 16.30, b = 27.00)		Wong *et al.*, 1997[21]
Utilities as a function of HAQ					
Intercept	0.8177	0.0347	Normal	Leeds study. Linear regression results as reported in Wyeth submission	
Slope	–0.3000	0.0297	Normal	Leeds study. Linear regression results as reported in Wyeth submission	
Total therapeutic cost, 1st 3 months (drug acquisition + administration + monitoring), 2004 UK£					
Infliximab	5,936	–	Fixed	Based on base-case assumption of 4 vials per infusion	See *Table 24* and Appendix 12 on total therapeutic costs
Etanercept	2,519	–	Fixed		See *Table 24* and Appendix 12 on total therapeutic costs
Subsequent annual therapeutic cost (drug acquisition + administration + monitoring), 2004 UK£					
Infliximab	12,597	–	Fixed	Based on base-case assumption of 4 vials per infusion	See *Table 24* and Appendix 12 on total therapeutic costs
Etanercept	9,500	–	Fixed		See *Table 24* and Appendix 12 on total therapeutic costs
Direct costs as a function of HAQ[b] (£)					
Intercept	1004.78	353.68	Normal	Mean annual costs from 1999. Estimates updated to 2004 based on the HCHS inflation rate. 15% of direct costs taken out in order to exclude costs of therapeutic medication for PsA	Linear regression based on Kobelt *et al.*, 2002[29]
Slope	303.93	196.60	Normal	Mean annual costs from 1999. Estimates updated to 2004 based on the HCHS inflation rate. 15% of direct costs taken out in order to exclude costs of therapeutic medication for PsA	Linear regression based on Kobelt *et al.*, 2002[29]
Annual discount rate (%)					
On costs	6		Fixed		NICE guidance[133]
On QALYs	1.5		Fixed		NICE guidance[133]

[a] 12 weeks following initiation of treatment, according to BSR guidelines recommendations on withdrawal for lack of efficacy reasons.
[b] 2004 UK £.
SMR, standard mortality ratio.

Short-term effectiveness parameters

As explained above, two short-term effectiveness parameters are taken from the Phase III trials for infliximab and etanercept: response probabilities and change in HAQ conditional on response status. The company submissions and trial reports do not provide information in a format that is directly suitable for cost-effectiveness modelling. Specifically, the short-term change in HAQ score (compared with baseline) is not reported separately for responders and non-responders (based on PsARC). These data were specifically requested from Wyeth and Schering-Plough and were made available for two of the three Phase III trials [Mease (2004) and IMPACT]. The evidence synthesis [see the section 'Evidence Synthesis' (p. 30)] has been developed in such a way as to include the additional data provided by the companies and the aggregated data for the Mease (2000) trial.

The evidence synthesis [see the section 'Evidence Synthesis' (p, 30)] estimates treatment effects, using trial data, for etanercept, infliximab and placebo. Given that 'placebo' is not a specific intervention within the economic model, the treatment effects have been adjusted to 'net out' the placebo effect of each treatment. The methods used for this purpose are shown in Appendix 10.

Longer term treatment withdrawal

If initial therapy is successful, patients are assumed to remain on that treatment until they are withdrawn. The estimate of annual withdrawal rate is based on the probability of long-term failure (treatment withdrawal) from 3 to 20 months as reported in Geborek and colleagues.[76] The rationale for this decision is that withdrawal for lack of efficacy is higher during the first 3 months, and this initial withdrawal has already been accounted for in the model using the probability of no PsARC response during the initial treatment period. Withdrawal rates between 3 and 20 months for etanercept and infliximab were almost identical, so the average between them was used.

Annual HAQ progression

In order to identify studies that reported estimates of long-term HAQ progression for PsA patients, a focused, pragmatic search was carried out in OVID MEDLINE for relevant cohort studies. A specific search for publications based on the Toronto Psoriatic Arthritis Program was also undertaken as the Schering-Plough submission suggested that such data may be available from that source. In addition, citation searching of selected published studies identified as reporting results from UK cohort studies on PsA was undertaken.[134–136] The Social Science Citation Index and Science Citation Index (1981–2004) were searched. Relevant publications by key UK authors who have recently undertaken cohort studies on PsA were also searched. See Appendix 11 for further details on these searches. HAQ progression estimates from the literature are also presented in Appendix 11.

In the absence of any better source of data, estimates of patients' HAQ progression while responding to biologics was based on the open-label studies provided in the manufacturers' submissions. Based on the results of these studies, there is no differential deterioration between the two anti-TNF treatments, and the HAQ progression is halted in patients who continue to receive etanercept or infliximab for 48 and 34 weeks, respectively, after the break of randomisation. It has therefore been assumed that the annual mean HAQ change in patients responding to biological therapy is 0. This assumption has been checked against expert clinical opinion and is subject to sensitivity analysis.

In the absence of a better source of data, estimates of HAQ natural history progression are taken from a sample of 24 patients with PsA in Leeds (cohort study not published; results detailed in the Wyeth submission).

Mortality

Patients are at risk of all-cause mortality at every time point in the model, although the therapies under evaluation are assumed not to confer a differential mortality effect. Mortality rates are based on standard UK age- and sex-specific mortality rates.[137] Based on Wong and colleagues,[21] a standardised mortality rate of 1.60 in women and 1.66 in men is used to reflect the higher risk of mortality in individuals with PsA.

Utilities

HRQL (in terms of utilities) is implemented in the model as a function of patients' HAQ score. This is taken directly from the Wyeth submission in the form of a linear regression with EQ-5D[138] being the dependent variable and HAQ the independent variable. There is a modest amount of evidence available on the impact of psoriasis on HRQoL in terms of utility. However, no information has been identified which considers how this effect interacts with the HRQoL effect of arthritis. Hence no

attempt has been made here to incorporate the effect of the biological therapies on HRQoL through their effect on psoriasis.

Adverse events

No additional cost or utility implications of adverse drug events are introduced into the model. The implications of adverse events are assumed to be reflected in the short-term efficacy parameters and the longer term withdrawal rates in that short- and long-term treatment withdrawal will partly reflect patients' ability to tolerate therapy.

Drug acquisition costs

A summary of the drug costs used in the model is presented in *Table 24*, with full details of calculations in Appendix 12. The estimate of etanercept dosage is based on the summary of product characteristics recommended dose regimen (25-mg injections administered twice weekly as a subcutaneous injection), the same as used in the clinical reports. The initial 3-month acquisition cost of etanercept is £2,145.12 and the annual cost thereafter is £9,295.52.

The estimate of infliximab dosage is based on the dose selected for the IMPACT trial, 5 mg/kg in the absence of methotrexate. [**Confidential information removed**]. Infliximab is supplied in individually boxed single-use vials, each of which contains 100 mg. A dose of 5 mg/kg is given as an intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. It is infused according to body weight. The mean weight of the subjects included in the IMPACT trial was approximately 82 kg. The economic model presented by the Schering-Plough model applied a body weight of 80 kg, which gives an exact number of four vials of 100-mg per infusion per patient.

Although HAQ change estimates at 14 weeks (as reported in the IMPACT trial) are used in the model, an assumption is used of 12 weeks as the initial trial period for consistency between the two anti-TNF therapies. In practical terms, this implies a difference between three treatments at 12 weeks and four treatments at 14 weeks.

Infliximab should be administered every 8 weeks after initial doses (at baseline and 2 and 6 weeks).[139] However, in the treatment of RA, it has been reported that the frequency of infliximab infusion (every 5 or 6 weeks) and/or the dose has to increase after initial response in order to sustain efficacy.[140,141] The combined administration of a low dose of methotrexate is an alternative strategy to maintain efficacy.[142] Despite this observation, the number of subsequent annual treatments after the initial trial period was taken to be 6.5 (52 weeks/8), and 6.5 outpatient visits for administration of the drug were also added. Wastage is not an issue in current clinical practice, because the most common choice for a given patient is between three and four vials. Four vials of 100 mg per treatment were used for the base-case analysis, with the scenario of three vials presented as sensitivity analysis. The initial 3-month acquisition cost of infliximab is £5035 and the annual cost thereafter is £10,912.

Drug administration costs

According to the SPC, etanercept treatment should be initiated and supervised by a specialist physician experienced in the treatment of PsA, so the cost of an initial outpatient attendance is assumed. After the first educational visit for self-injection, the cost of monthly visits to a nurse has been included in order to check progress according to current routine clinical practice. Monitoring visits take place every 3 months after the patient is stable, with alternate visits between nurse and consultant.

For infliximab, the infusion is administered using a pump over a period of 2 hours. When the infusion is complete, the patient stays in the rheumatology department for 1–2 hours following treatment.[143] After the initial outpatient attendance, the cost of infliximab administration is estimated as a half day-case based on clinical opinion. In order to avoid double counting, clinician and nurse times for regular clinical examinations and tests are assumed to be covered in the cost of visits for administration.

Drug monitoring costs

The BSR guidelines for anti-TNFα therapy in PsA[35] were followed in order to determine the type and frequency of recommended monitoring tests. The BSR guidelines recommend that patients prescribed a TNFα blocker without a DMARD should have blood monitoring. In particular, full blood count, urea and electrolytes (U&E), ESR and liver function tests (LFTs) at baseline, 3 months, 6 months and thereafter at 6-monthly intervals are required (see Appendix 12).

The BSR guidelines also recommend repeat blood tests for anti-nuclear antibodies (ANA) and DNA binding if patients develop 'lupus-like' symptoms, and TB screening after risk assessment. However,

TABLE 24 *Summary of costs used for infliximab and etanercept (2004 UK £) – full details are provided in Appendix 12*

	Initial trial period (3 months)			Annual cost (after initial 3 months)			Total costs	
Treatment and dosage	**Acquisition drug cost**	**Administration cost**	**Monitoring costs**	**Acquisition drug cost**	**Administration cost**	**Monitoring costs**	**Initial trial period**	**Subsequent annual costs**
Etanercept 25 mg	2,145.12	246.00	127.91	9,295.52	0.00	205.08	2,519.03	9,500.60
Infliximab 5 mg/kg, 4 vials (base-case)	5,035.44	772.50	127.91	10,910.12	1,673.75	13.08	5,935.85	12,596.95
Infliximab 5 mg/kg, 3 vials	3,776.58	772.50	127.91	8,182.59	1,673.75	13.08	4,676.99	9,869.42

TABLE 25 *Direct costs used in the OLS regression based on Kobelt and colleagues (2002)[29] updated to 2004[a] prices (UK£)*

HAQ states	HAQ midpoint	UK direct costs
0–0.6	0.3	1384
>0.6–1.1	0.85	3553
>1.1–1.6	1.35	2357
>1.6–2.1	1.85	3480
>2.1–2.6	2.35	3834
>2.6	2.8	3040

[a] US$ converted to UK£ using the published conversion of $1.00 = £0.67 referenced in the original source. UK costs updated using 2004 HCHS inflation rate.

the proportion of patients at risk of TB or developing antibodies cannot be accurately predicted, so we have included costs for eligibility tests as a one-off, in addition to an outpatient visit to administer them before treatment initiation.

Other costs

A range of costs will be incurred in managing patients with PsA in addition to the cost of the biological therapies, and these can be assumed to positively relate to disability. Total mean annual direct costs according to HAQ level have been reported by Kobelt and colleagues,[29] for a sample of patients with RA, and these are shown in *Table 25*. The cost year is not reported but, based on their referenced Early RA Study (ERAS) study,[144] it is assumed that costs correspond to 1999 and these have been updated using the 2004 Hospital and Community Health Services (HCHS) inflation index. However, these data also include the cost of RA medications (which are calculated separately here). The proportion of costs represented by RA medication is not explicitly reported by Kobelt and colleagues,[29] or in contemporaneous publications based on the ERAS study. In order to exclude the cost of drugs used by RA patients (and hence avoid double counting), we have subtracted 15% of direct costs as an approximation based on general UK estimates.[28]

One potential limitation of the Kobelt and colleagues[29] study for the purposes of populating the York Model is that the number of patients with very severe disability (HAQ score >2.6) was rather limited. However, according to the ERAS study, at 5 years follow-up orthopaedic surgery was required for 16.2% of the patients and major joint replacement was required in 8% of RA patients.[144] For this reason, we consider that adding palliative care costs to the direct costs related to HAQ severity (as done in the Wyeth model) will have the effect of double counting the cost for severe patients. A further reason not to add palliative and direct costs is that the type and cost of this kind of last-resort treatment is impossible to determine and very much consultant dependent.

Analysis

The expected costs and QALYs of the three management strategies under evaluation are estimated over the four alternative time horizons: 1, 5, 10 and 40 years (i.e. lifetime). Standard decision rules are used[145] and incremental costs per QALY gained calculated as appropriate.

Probabilistic sensitivity analysis (PSA) is used to assess the implications of parameter uncertainty (the imprecision with which input parameters are estimated). This is based on second-order Monte Carlo simulation[146] using the probability distributions detailed in *Table 23*. The results of the PSA are presented using cost-effectiveness acceptability curves (CEACs), which show the probability that each of the alternatives is the most cost-effective, conditional on the threshold value of cost-effectiveness for an additional QALY.[147,148]

A number of scenarios are presented to assess the implications of structural uncertainty in the model. These include running the model for the four alternative time horizons, for males and females and for alternative rebound assumptions.

Results

Expected costs and QALYs

The base-case results of the model are presented in *Tables 26* and *27* under alternative assumptions about what happens to patients' HAQ score when they come off treatment (i.e. alternative rebound scenarios).

The first scenario assumes rebound equal to gain, that is, that a patient's HAQ score deteriorates by exactly the same amount as it improved on the initial success of the treatment. The results for this scenario are shown in *Table 26* for the four time horizons and separately for males and females. Infliximab is consistently dominated by etanercept because of its higher acquisition and administration costs and without superior effectiveness. Differences between males and females are very small. The incremental cost per QALY gained of etanercept compared with palliative care ranges from £14,818 (females, 40-year time horizon) to £49,374 (males, 1-year time horizon).

The alternative rebound scenario is that when they come off therapy, patients' HAQ scores return to what they would have been had they not initially responded (i.e. rebound to the natural history progression). These results are shown in *Table 27*. Compared with the first scenario, the costs of infliximab and etanercept are higher and the QALYs lower. Infliximab remains dominated for all time horizons and for males and females. The ICERs of etanercept compared with palliative care are higher than for the first scenario, ranging from £25,443 (females, 40-year time horizon) to £49,441 (males, 1-year time horizon).

TABLE 26 *Base-case[a] cost-effectiveness results under the rebound scenario of rebound equal to gain*

Treatment	Mean costs (£)	Mean QALYs	ICER (£)	Probability cost-effective for threshold of £20,000	£30,000	£40,000
Time horizon 1 year – males						
Infliximab	13,840	0.590	D	0.000	0.000	0.000
Etanercept	8,756	0.603	49,374	0.000	0.000	0.043
Palliative care	1,311	0.452	NA	1.000	1.000	0.957
Time horizon 1 year – females						
Infliximab	13,846	0.592	D	0.000	0.000	0.000
Etanercept	8,763	0.605	49,212	0.000	0.000	0.041
Palliative care	1,318	0.453	NA	1.000	1.000	0.959
Time horizon 5 years – males						
Infliximab	42,216	2.636	D	0.000	0.000	0.000
Etanercept	31,179	2.684	35,258	0.000	0.140	0.761
Palliative care	6,029	1.970	NA	1.000	0.860	0.239
Time horizon 5 years – females						
Infliximab	42,245	2.655	D	0.000	0.000	0.000
Etanercept	31,197	2.702	35,111	0.000	0.134	0.763
Palliative care	6,060	1.987	NA	1.000	0.866	0.237
Time horizon 10 years – males						
Infliximab	60,334	4.533	D	0.000	0.000	0.001
Etanercept	45,897	4.604	26,205	0.072	0.719	0.956
Palliative care	10,677	3.260	NA	0.928	0.281	0.043
Time horizon 10 years – females						
Infliximab	60,496	4.595	D	0.000	0.000	0.001
Etanercept	45,965	4.664	25,882	0.091	0.703	0.960
Palliative care	10,783	3.305	NA	0.909	0.297	0.039
Time horizon 40 years – males						
Infliximab	77,643	6.330	D	0.000	0.007	0.027
Etanercept	60,533	6.415	16,801	0.738	0.928	0.954
Palliative care	17,386	3.847	NA	0.262	0.065	0.019
Time horizon 40 years – females						
Infliximab	79,803	6.920	D	0.000	0.016	0.054
Etanercept	62,600	7.006	14,818	0.840	0.949	0.931
Palliative care	19,611	4.105	NA	0.160	0.035	0.015

D, dominated; ICER, incremental cost-effectiveness ratio (i.e. incremental cost per QALY gained); NA, not applicable.
[a] Base-case assumptions: annual discount rates, 6% on costs, 1.5% on QALYs; 4 vials infliximab; mean HAQ progression while responding to biologics, 0.0.

Probabilistic sensitivity analysis

Tables 26 and *27* show some summary results of the probabilistic sensitivity analysis. The tables show the probability of each of the three options being the most cost-effective for three alternative threshold cost-effectiveness values. A fuller representation of this analysis is shown in *Figures 4–7*, which show CEACs for males only and for the time horizons of 10 and 40 years, under the two rebound scenarios. It can be seen that these probabilities show that (based on the assumptions made and evidence available) etanercept and palliative care have the highest probabilities of being cost-effective. At lower levels of the threshold willingness to pay (WTP), palliative care has the higher probability of being cost-effective. As the threshold increases, so does the probability that etanercept is optimal.

Cost breakdown

One implication of changing the time horizon for the analysis is that the proportion of total costs made up of the costs of the biological therapies compared to other direct costs which are a function of HAQ score [see the section 'Parameter estimates' (p. 43)] changes. This is shown in *Figure 8* for males under the assumption of rebound equal to gain. For etanercept, the

TABLE 27 *Base-case[a] cost-effectiveness results under the rebound scenario of rebound equal to natural history*

Treatment	Mean costs (£)	Mean QALYs	ICER (£)	Probability cost-effective for threshold of		
				£20,000	£30,000	£40,000
Time horizon 1 year – males						
Infliximab	13,846	0.589	D	0.000	0.000	0.000
Etanercept	8,762	0.602	49,441	0.000	0.000	0.040
Palliative care	1,317	0.451	NA	1.000	1.000	0.960
Time horizon 1 year – females						
Infliximab	13,848	0.592	D	0.000	0.000	0.000
Etanercept	8,765	0.604	49,284	0.000	0.000	0.051
Palliative care	1,319	0.453	NA	1.000	1.000	0.949
Time horizon 5 years – males						
Infliximab	42,214	2.606	D	0.000	0.000	0.000
Etanercept	31,174	2.653	36,973	0.000	0.060	0.667
Palliative care	6,020	1.973	NA	1.000	0.940	0.333
Time horizon 5 years – females						
Infliximab	42,267	2.616	D	0.000	0.000	0.000
Etanercept	31,253	2.665	36,647	0.000	0.074	0.669
Palliative care	6,076	1.978	NA	1.000	0.926	0.331
Time horizon 10 years – males						
Infliximab	60,561	4.354	D	0.000	0.000	0.001
Etanercept	46,017	4.422	30,400	0.006	0.423	0.906
Palliative care	10,712	3.261	NA	0.994	0.577	0.093
Time horizon 10 years – females						
Infliximab	60,595	4.405	D	0.000	0.000	0.001
Etanercept	46,098	4.476	29,957	0.006	0.461	0.916
Palliative care	10,754	3.296	NA	0.994	0.539	0.083
Time horizon 40 years– males						
Infliximab	78,346	5.342	D	0.000	0.007	0.027
Etanercept	61,053	5.417	27,681	0.038	0.600	0.879
Palliative care	17,503	3.844	NA	0.962	0.393	0.094
Time horizon 40 years – females						
Infliximab	80,223	5.725	D	0.000	0.016	0.055
Etanercept	62,921	5.802	25,443	0.119	0.708	0.887
Palliative care	19,544	4.097	NA	0.881	0.276	0.058

D, dominated; ICER, incremental cost-effectiveness ratio (i.e. incremental cost per QALY gained); NA, not applicable.
[a] Base-case assumptions: annual discount rates, 6% on costs, 1.5% on QALYs; 4 vials infliximab; mean HAQ progression while responding to biologics, 0.0.

cumulative cost of the drug as a proportion of cumulative total costs falls from 87% for a 1-year time horizon to 74% at a 40-year time horizon. For infliximab, these proportions are 92 and 80%, respectively. These proportions are practically the same under the assumption of rebound equal to natural history.

Alternative assumptions

A range of assumptions are made in the model. The sensitivity of the results of the analysis to variation in these assumptions is assessed using scenario analysis, the results of which are presented in *Tables 28* (assuming rebound equal to gain) and *29* (assuming rebound equal to natural history). Results of an additional sensitivity analysis to examine an alternative specification of the prior distribution in the evidence synthesis used to reflect between-trial variation in the placebo response rate are also presented in *Tables 30–32*.

The first scenario analysis looks at the implications of changing the base-case assumption that an infusion of infliximab requires four vials of the drug by using an alternative assumption of three vials. Under both rebound assumptions, infliximab remains dominated by etanercept.

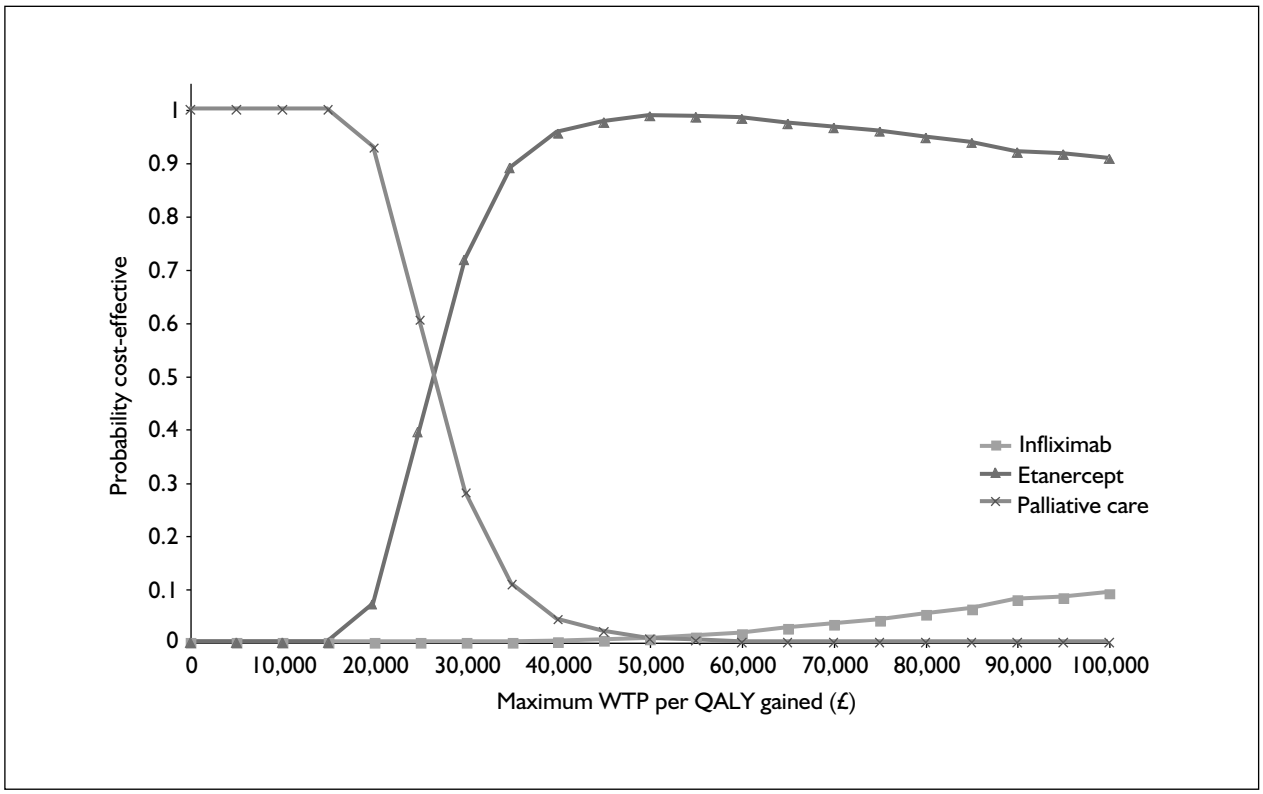


FIGURE 4 *CEACs: males, 10-year time horizon, rebound equal to gain*

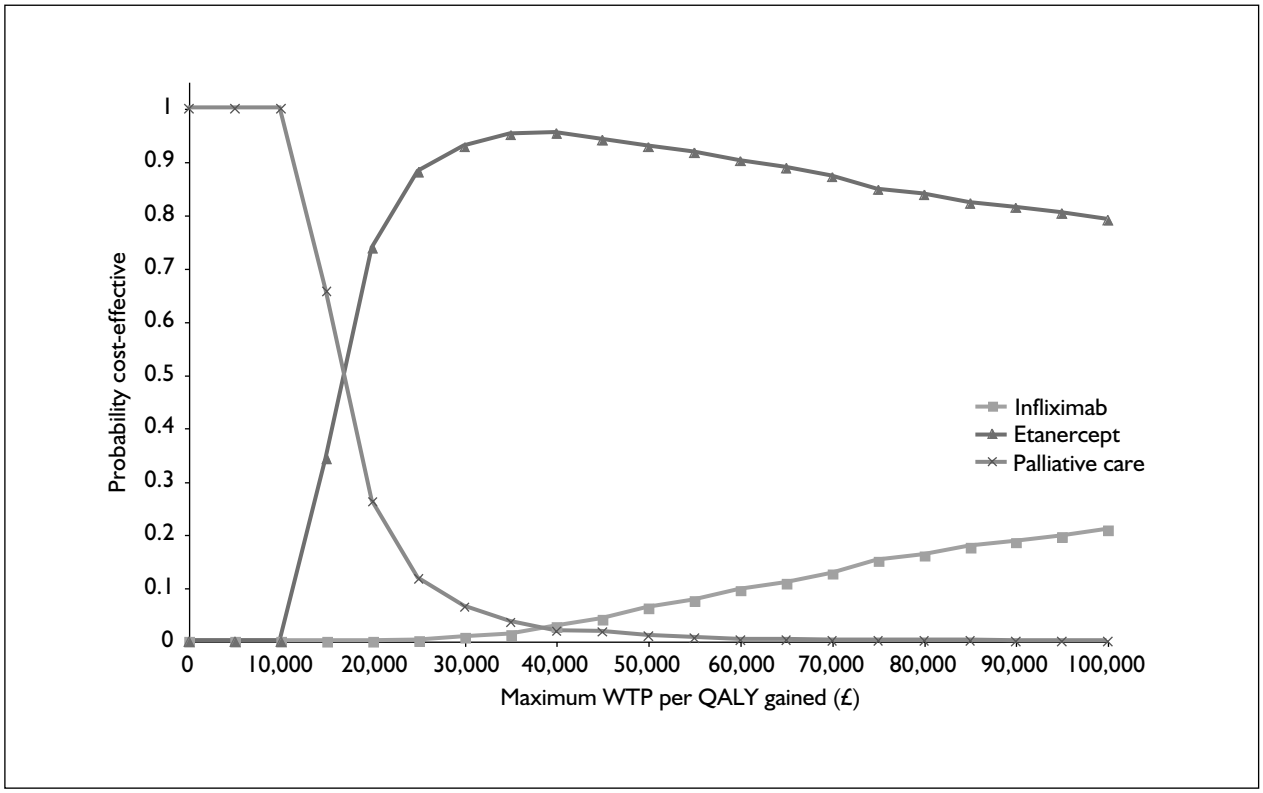


FIGURE 5 *CEACs: males, 40-year time horizon, rebound equal to gain*

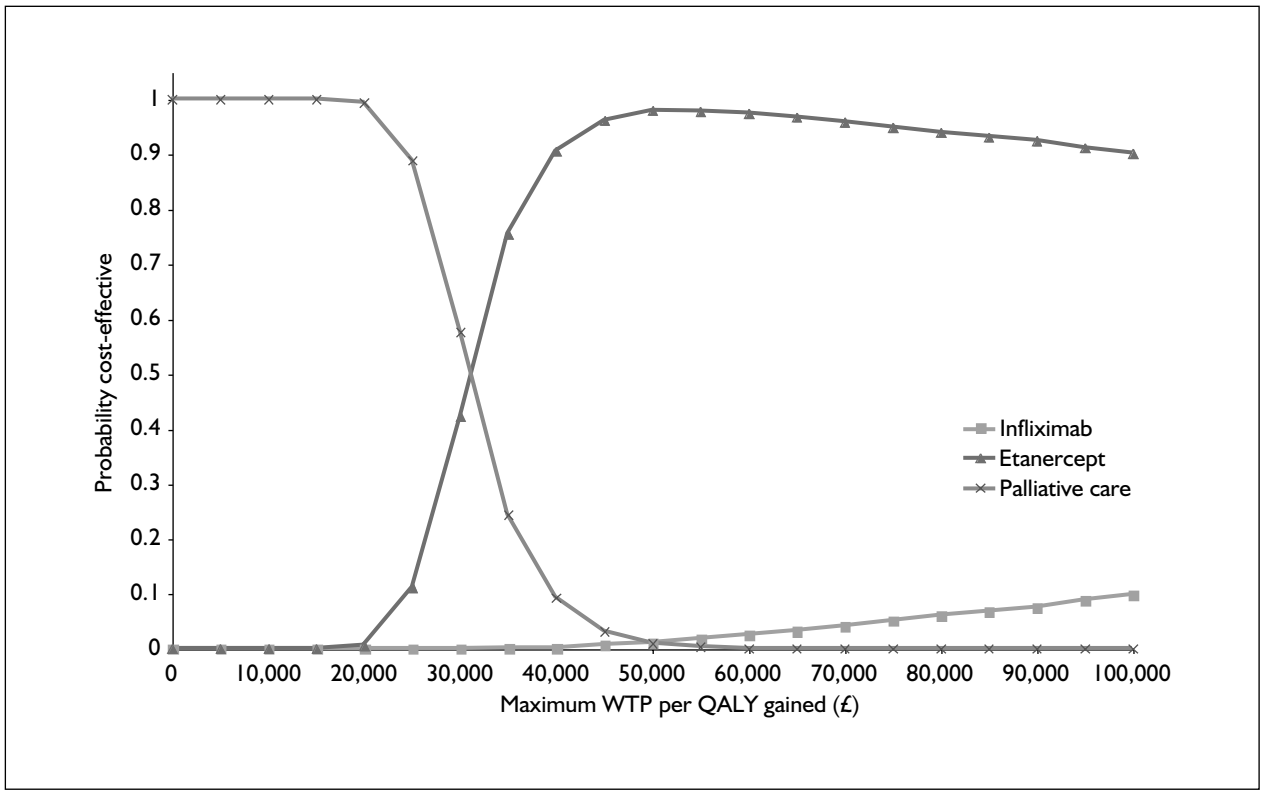


FIGURE 6 *CEACs: males, 10-year time horizon, rebound equal to natural history*

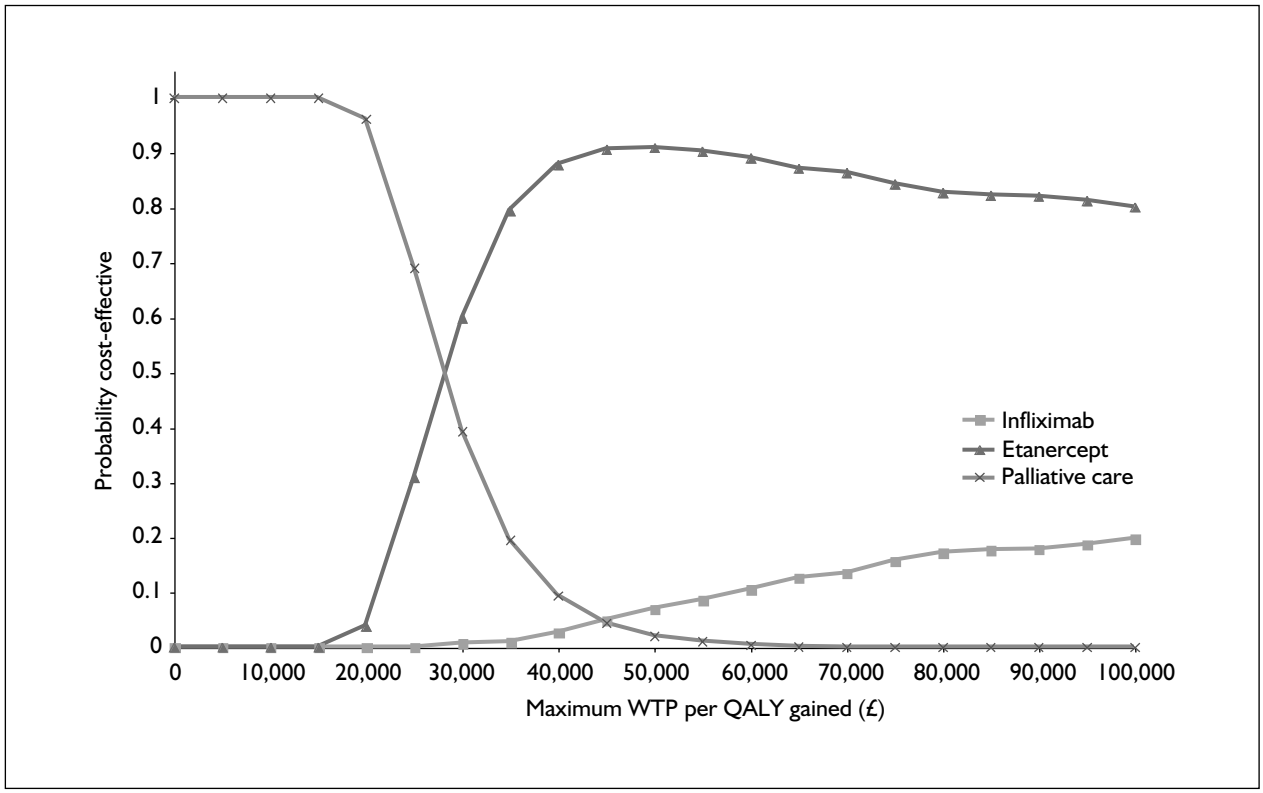


FIGURE 7 *CEACs: males, 40-year time horizon, rebound equal to natural history*

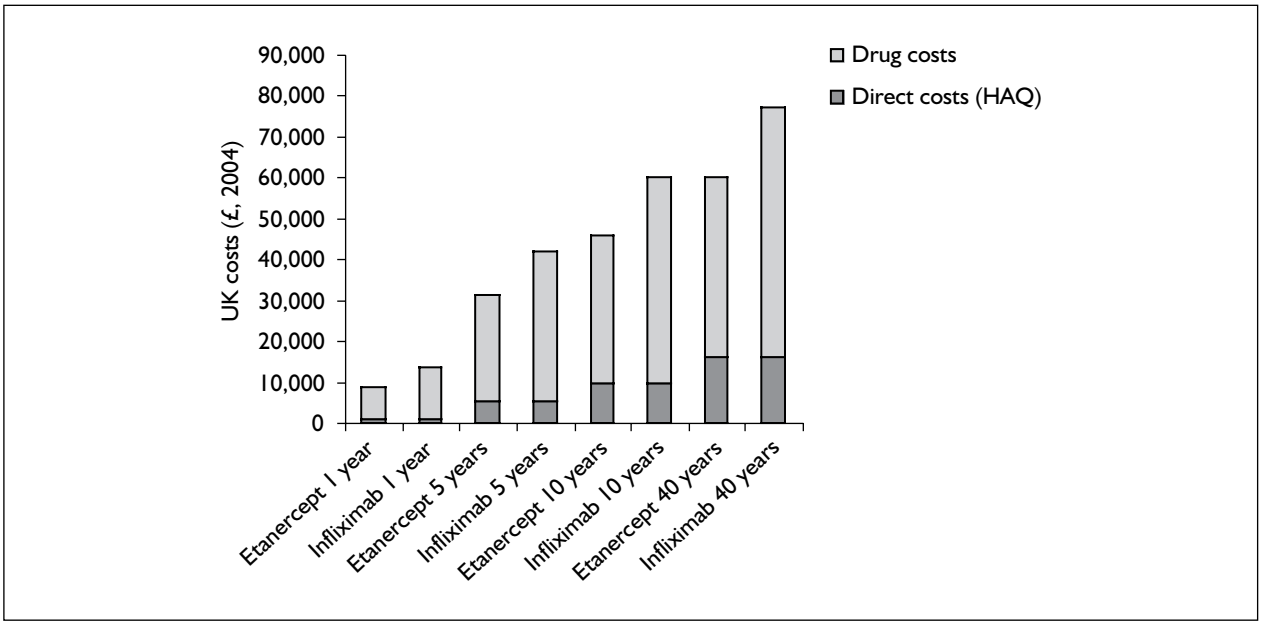


FIGURE 8 *Proportion of drug costs to other costs for etanercept and infliximab for different time horizons (males, rebound equal to gain)*

TABLE 28 *Results of a scenario analysis to assess the sensitivity of model results to alternative assumptions: all scenarios relate to males, a 10-year time horizon and the assumption of rebound equal to gain*

				Probability cost-effective for threshold of		
Treatment	**Mean costs (£)**	**Mean QALYs**	**ICER (£)**	**£20,000**	**£30,000**	**£40,000**
Alternative assumption: 3 vials of infliximab per infusion (base-case: 4 vials)						
Infliximab	49,383	4.529	D	0.004	0.065	0.124
Etanercept	45,911	4.602	26,228	0.062	0.634	0.838
Palliative care	10,690	3.259	NA	0.934	0.301	0.038
Alternative assumption: HAQ of responders to etanercept and infliximab progresses at same rate as natural history after initial HAQ improvement (base-case: no progression whilst responding)						
Infliximab	60,711	4.009	D	0.000	0.000	0.000
Etanercept	46,247	4.080	43,814	0.000	0.000	0.222
Palliative care	10,613	3.266	NA	1.000	1.000	0.778
Alternative assumption: annual discount rate 3.5% on both costs and QALYs (base-case: 6% on costs, 1.5% on QALYs)						
Infliximab	65,969	4.148	D	0.000	0.000	0.000
Etanercept	50,417	4.214	31,501	0.007	0.375	0.835
Palliative care	11,931	2.992	NA	0.993	0.625	0.165

D, dominated; ICER, incremental cost-effectiveness ratio (i.e. incremental cost per QALY gained); NA, not applicable.

The second analysis considers the base-case assumption that, when patients respond to etanercept or infliximab, they experience an initial gain in HAQ but then their HAQ does not change until the therapy is withdrawn. An alternative assumption is assessed whereby patients progress at the same rate as the natural history progression. This is equivalent to assuming that the anti-TNFs generate an initial improvement in symptoms but do not change disease progression. *Tables 28* and *29* indicate that this alternative assumption results in appreciably lower QALYs for the two biological therapies, and hence a higher ICER for etanercept.

A third scenario assesses the implications of using different annual discount rates. In the base-case analysis annual rates of 6 and 1.5% on costs and QALY, respectively, are used, following current

TABLE 29 *Results of a scenario analysis to assess the sensitivity of model results to alternative assumptions: all scenarios relate to males, a 10-year time horizon and the assumption of rebound equal to natural history*

				Probability cost-effective for threshold of		
Treatment	**Mean costs (£)**	**Mean QALYs**	**ICER (£)**	**£20,000**	**£30,000**	**£40,000**
Alternative assumption: 3 vials of infliximab per infusion (base-case: 4 vials)						
Infliximab	49,503	4.353	D	0.000	0.046	0.137
Etanercept	45,979	4.423	30,400	0.001	0.402	0.784
Palliative care	10,666	3.261	NA	0.999	0.552	0.079
Alternative assumption: HAQ of responders to etanercept and infliximab progresses at same rate as natural history after initial HAQ improvement (base-case: no progression whilst responding)						
Infliximab	60,740	3.990	D	0.000	0.000	0.000
Etanercept	46,240	4.059	44,594	0.000	0.000	0.195
Palliative care	10,624	3.261	NA	1.000	1.000	0.805
Alternative assumption: annual discount rate 3.5% on both costs and QALYs (base-case: 6% on costs, 1.5% on QALYs)						
Infliximab	66,166	3.996	D	0.000	0.000	0.001
Etanercept	50,585	4.061	36,312	0.000	0.140	0.685
Palliative care	11,937	2.997	NA	1.000	0.860	0.314

D, dominated; ICER, incremental cost-effectiveness ratio (i.e. incremental cost per QALY gained); NA, not applicable.

TABLE 30 *Mean posterior distributions of PsARC response rates*

	New PsARC response rate	**Base-case PsARC response rates[a]**	**Absolute change**
Response rate infliximab	0.8397	0.7705	0.0692
Response rate etanercept	0.7283	0.7705	–0.0422
Response rate placebo	0.2518	0.2509	–0.0009

[a] As reported in assessment report *Table 15*.

NICE guidelines. As an alternative analysis, annual discount rates of 3.5% on both costs and QALYs are used. These alternative rates result in higher costs and lower QALYs for all options and a slightly higher ICER for etanercept.

Last, we decided to explore the assumptions used in our evidence synthesis. It should be emphasised that, because of the small numbers of studies and patients in those trials, the results of the evidence synthesis could potentially be sensitive to alternative assumptions (although the ultimate measure of cost-effectiveness may not be sensitive).

To model the between-trials variability in the evidence synthesis, we used a random study effect, fixed treatment effects model. Our objective was to specify uninformative (vague) prior distributions for all parameters. However, with a limited number of trials ($n = 3$), several authors have noted that the choice of model for the study effects can potentially influence the posterior distribution.[149] Therefore, we conducted an additional sensitivity analysis using an alternative specification for the study effects. The revised analysis models the distribution of log-odds for the placebo arms of the studies as a normal distribution[59] as opposed to modelling the distribution of absolute probabilities as a β distribution. Appendix 13 shows the changes made for this sensitivity analysis in terms of WinBUGS code.

A random treatment effect was not modelled owing to the small number of trials (one trial for infliximab and two for etanercept). The treatment effects for response were modelled as fixed-effects additive to the placebo probability of response on the log-odds scale. This assumption of the evidence synthesis remains the same in the revised analysis.

Table 30 presents the mean posterior response rates for infliximab, etanercept and placebo. Compared with previous results, results using this

TABLE 31 *Cost-effectiveness results based on the new evidence synthesis results – rebound equal to gain scenario*

Treatment	Mean costs (£)	Mean QALYs	ICER (£)	Probability cost-effective for threshold of £20,000	£30,000	£40,000
Time horizon 10 years – males						
Infliximab	64,274	4.636	165,363[a]	0.000	0.001	0.009
Etanercept	44,111	4.514	26,361[b]	0.070	0.693	0.931
Palliative care	10,718	3.248	NA	0.930	0.306	0.060
Time horizon 40 years – males						
Infliximab	82,414	6.558	84,473[a]	0.000	0.041	0.159
Etanercept	58,178	6.271	16,891[b]	0.741	0.889	0.809
Palliative care	17,355	3.854	NA	0.259	0.070	0.032

[a] ICER calculated as infliximab versus etanercept.
[b] ICER calculated as etanercept versus palliative care.

TABLE 32 *Cost-effectiveness results based on the new evidence synthesis results – rebound equal to natural history scenario*

Treatment	Mean costs (£)	Mean QALYs	ICER (£)	Probability cost-effective for threshold of £20,000	£30,000	£40,000
Time horizon 10 years – males						
Infliximab	64,418	4.455	205,345[a]	0.000	0.000	0.005
Etanercept	44,169	4.356	30,628[b]	0.005	0.446	0.878
Palliative care	10,679	3.263	NA	0.995	0.554	0.117
Time horizon 40 years – males						
Infliximab	83,085	5.485	168,753[a]	0.001	0.006	0.041
Etanercept	58,813	5.341	27,805[b]	0.043	0.587	0.854
Palliative care	17,475	3.855	NA	0.956	0.407	0.105

[a] ICER calculated as infliximab versus etanercept.
[b] ICER calculated as etanercept versus palliative care.

alternative uninformative prior report give a slightly better response rate for infliximab (0.839662 versus 0.771478; absolute change, 0.06818) and a slightly worse response rate for etanercept (0.728291 versus 0.770618; absolute change, –0.04233) in terms of absolute change. These results appear more consistent with the RRs based on the trial efficacy data.

An alternative specification of the synthesis using an unconstrained baseline was also explored,[59] but the results were very similar to those of the sensitivity analysis presented here.

Table 31 presents the results of the cost-effectiveness analysis based on the sensitivity analysis for the evidence synthesis. These results are shown for time horizons of 10 years and lifetime (40 years) for both rebound scenarios.

Compared with the base-case analysis (see *Tables 26* and *27*), infliximab is no longer dominated in any time horizon – either 10 years or lifetime – or under any rebound scenarios. However, the ICER for infliximab is high: under the most 'optimistic' scenario (40-year time horizon, rebound equal to gain) the incremental cost per QALY gained with infliximab compared with etanercept is £84,473 (£168,753 per QALY assuming rebound back to natural history). The probabilities that each treatment is more cost-effective than the others conditional on different maximum WTP for an additional QALY have not substantively changed compared with the base-case. Etanercept has the highest probability of being cost-effective for a threshold of £30,000–40,000 per QALY. The ICERs of 10 years' and lifetime treatment with etanercept remain practically the same, ranging from £16,891 to £30,628 per additional QALY.

In short, the sensitivity analysis for the evidence synthesis has generated some nominal changes in the differences in response rates between infliximab and etanercept, although the interpretation of the cost-effectiveness results is unlikely to differ from that in the base-case. Although infliximab is no longer dominated by etanercept in the sensitivity analysis, it has a very high ICER that ranges between £165,363 and £205,345 per QALY assuming a 10-year time horizon and between £84,473 and £168,753 per QALY for a 40-year time horizon.

Interpretation and comparison with manufacturer models

The results of the York Model suggest that both etanercept and infliximab will increase patients' expected quality-adjusted survival duration, but also the costs incurred by the health service. Regardless of rebound scenario, sex or time horizon, infliximab is consistently dominated by etanercept. This is because infliximab has higher acquisition and administration costs, and the evidence synthesis (consistent with the trial data) indicates that it has a slight gain in HAQ for both patients who respond and those who do not respond to therapy. The incremental cost per QALY gained of etanercept compared with palliative care varies depending on the rebound scenario and time horizon. Under base-case assumptions, the more 'optimistic' assumption about rebound (rebound equal to gain) results in ICERs between £14,818 (females, 40-year time horizon) and £49,374 (males, 1-year time horizon). The less optimistic rebound scenario (rebound back to natural history) generates ICERs of between £25,443 (females, 40-year time horizon) and £49,441 (males, 1-year time horizon).

How do the results of the York Model compare with those of the manufacturers? *Table 33* summarises the differences between the models and estimates the extent to which these differences drive differences in the results. The Schering-Plough model is difficult to compare with the York Model directly as it has used a different modelling framework. It is clear, however, that its estimates of the cost impact of infliximab differ markedly to those from the York Model. Over a 5-year time horizon, Schering-Plough estimate the cost impact of infliximab to be £61,019 (the Active Joint Model) compared with £42,216 (rebound equal to gain) and £42,214 (rebound equal to natural history) in males in the York Model. This is despite the fact that the estimates in the control/palliative care group are very similar [£6,970 over 5 years in the Schering-Plough model and £6029 (in males) over the same period in the York Model]. The estimates of QALYs also differ. The QALY estimates in the York Model (males) for control/palliative care are higher than those in the Schering-Plough model over 5 years (1.970 versus 1.47) but lower for infliximab (2.636 versus 2.88). The net result of this is that Schering-Plough estimate the ICER of infliximab to vary between £31,071 (based on a 30-year time horizon) and £58,612 (based on a 2-year horizon). However, the Schering-Plough model did not directly compare infliximab with etanercept. This comparison was undertaken in the York Model, which consistently found that infliximab is dominated by etanercept. For comparison, the ICER of infliximab versus palliative care in the base-case version of the York Model (i.e. removing etanercept from the comparison) ranges from £21,382 (females, rebound equal to gain, 40-year time horizon) to £90,790 (males, rebound to natural history, 1-year time horizon).

The Wyeth analysis uses a similar modelling framework to the York Model, sharing a number of assumptions and parameter estimates. In particular, a patient's HAQ over time is the driver behind costs (except the cost of study drugs) and QALYs. As described in the section 'Company submissions' (p. 35), the York Model has adopted some important alternative assumptions to the Wyeth model:

- The comparators are infliximab and palliative care rather than CSA plus MTX or leflunomide. This has the effect of reducing the cost of the comparators and increasing the **incremental** cost of etanercept compared with the Wyeth model.
- It was felt that the Wyeth model was double counting some of the longer term costs by including all costs (including the cost of biological therapies) from the Kobelt regression analysis and adding the cost of palliative therapy. These have been removed in the York Model.
- Given the need to model the cost-effectiveness of both biological therapies based on all evidence, the evidence synthesis was undertaken an incorporated into the York Model. This is a different approach to the Wyeth model, which had access to individual patient data and did not model infliximab.
- The difference in annual discount rates used in the two models result in some differences. The Wyeth model adopted a 3.5% annual discount

TABLE 33 *Comparison of the modelling approach and main assumptions used in the Schering-Plough, Wyeth and York models*

Area	York Model	Wyeth model	Schering-Plough model	Degree to which drives differences in results
Modelling approach and main characteristics				
Modelling approach	Modified decision tree	Individual patient-level simulation	Markov model	Low
Perspective used	UK NHS	UK NHS	UK NHS	Models similar
Timeframe	Results presented at 1, 5, 10 (base-case) and 40 years (lifetime)	Results presented at 6 months and 1, 5 and 10 years	Active Joint Model: 2, 5 (base case) 10 and 30 years. Chronic Active Joint model: 5, 10, 30 (base case) and 45 years	Models similar
Outcome measure	PsARC and HAQ score	PsARC and HAQ score	Number of active and deformed joints	Uncertain
Main assumptions present in the models				
Comparators	Biologics are presented as a last-option therapy. Etanercept is compared with infliximab and with palliative care. Based on their SPCs, the anti-TNFs would be considered once available DMARD therapies have been tried and have failed	The model compares two sequences of treatments for PsA for patients that have already failed two DMARDs. CSA and leflunomide are presented as two mutually exclusive valid comparators, although *de facto* results are only reported for CSA. Choice of comparators based on BSR guidelines for use of anti-TNFs in PsA	It seems the comparator is 'standard supportive therapy', defined as mainly physiotherapy and NSAIDs	Medium
Cost and effectiveness of comparators	Response of patients to biological therapy and treatment effectiveness at 12 weeks based on trial data. After the withdrawal of biologics, patients would continue to be given some kind of treatment (i.e. palliative), but the type and cost are impossible to determine, relatively inexpensive and very much clinician dependent, so no cost is added above direct costs related to HAQ scores. Palliative therapy is assumed to have no treatment effect. No differential mortality risk between the therapies evaluated	Although neither CSA nor leflunomide was the comparator arm in the Mease trials, it is assumed that the placebo effect is equal to the effectiveness of CSA/leflunomide – both HAQ and PsARC response – based on very limited evidence. No differential mortality risk between the therapies evaluated. Acquisition costs of CSA and leflunomide are added to the comparator sequence. Palliative care is taken as having costs over and above those estimated by Kobelt *et al.* regression	It seems that the IMPACT trial was used to estimate the relative treatment effect of infliximab versus 'standard supportive therapy', when the IMPACT trial compares infliximab vs placebo. In other words, it is assumed that the placebo effect is equal to the effectiveness of 'standard supportive therapy'. No differential mortality risk between the therapies evaluated. Drug acquisition costs of the comparator not stated	Medium

continued

TABLE 33 *Comparison of the modelling approach and main assumptions used in the Schering-Plough, Wyeth and York models (cont'd)*

Area	York Model	Wyeth model	Schering-Plough model	Degree to which drives differences in results
Disease progression	A patient with PsA will experience a deterioration in terms of HAQ progression without adequate treatment. Spontaneous remission is not modelled	A patient with PsA will experience a deterioration in terms of HAQ progression without adequate treatment. Spontaneous remission is not modelled	Progression modelled as transition probabilities between joint health states	High degree
Long-term use of anti-TNF therapy	Given the limited experience in the administration of anti-TNF drugs for PsA, the model extrapolates their efficacy up to 10 years; 40 years (lifetime) is presented as a limit	Extrapolation up to 10 years	In the chronic model, infliximab administered up to 30 years in the absence of withdrawal for lack of efficacy	High degree
HAQ progression while responding to treatment	Biologics can halt HAQ progression while responding to treatment (based on evidence provided by open-label studies). Assumption explored in sensitivity analysis	HAQ progression is halted while responding to etanercept. In comparison, the annual HAQ progression rate used for DMARDs is 0.02818 (Sokoll study)	NA	High degree
Withdrawal from treatment	The PsARC response determines withdrawal from treatment at 3 months. After this period the decision to withdraw from treatment is based on the probability of long-term failure from 3 to 20 months and modelled as a constant rate per annum	The PsARC response determines withdrawal from treatment at 3 months. After this period the decision to withdraw from treatment is based on the probability of 12 months failure as reported in and modelled as a constant rate per annum	Response rates are not incorporated in the model, as treatment is assumed to be continuous unless during the individual patient simulation 3 consecutive cycles (of 16 weeks) were experienced at the highest active joint count ($\geq$10). Annual withdrawal rates based on adverse effects or lack of efficacy are also disregarded	Medium
Rebound after withdrawal from biologics	Given the lack of evidence, two scenarios are presented (rebound equal to gain and rebound back to natural history) as limits and potentially possible, according to expert opinion	Rebound equal to gain presented as base-case scenario (i.e. HAQ deteriorates by the same magnitude to their initial improvement)	Not explicitly modelled. No details provided	High
Correction for placebo effect	Given the magnitude of the placebo effect observed in PsA trials, the placebo effect (HAQ change) was 'netted out' in both the treatment effect of both etanercept and infliximab by PsARC responder status	As reflected in the HAQ equations at 4 and 12 weeks, the placebo effect is averaged among the etanercept and the placebo arms	Not explicitly modelled. No details provided	Low

continued

TABLE 33 *Comparison of the modelling approach and main assumptions used in the Schering-Plough, Wyeth and York models (cont'd)*

Area	York Model	Wyeth model	Schering-Plough model	Degree to which drives differences in results
Severe adverse events	Disutilities and cost implications of potential adverse events of etanercept and infliximab are not included	Disutilities and cost implications of potential adverse events of etanercept are not included	Disutilities and cost implications of potential adverse events of infliximab are not included	Models similar
Skin component	The added value of anti-TNF treatment on the skin component of the disease is not incorporated	The added value of anti-TNF treatment on the skin component of the disease is not incorporated	The added value of anti-TNF treatment on the skin component of the disease is not incorporated	Models similar
Direct costs	UK direct costs are estimated as a linear function of HAQ (i.e. OLS regression based on evidence provided by a study on RA costs)	UK direct costs are estimated as a linear function of HAQ (i.e. OLS regression based on evidence provided by a study on RA costs)	Direct healthcare resources, based on the Toronto observational study, excluded medication in order not to double count acquisition drugs, were converted to 16-week cycles and stratified by joint health states. Canadian health resource utilisation assigned UK-based costs	Medium
Infliximab dosage	Conservative assumption that the frequency of infliximab infusions is maintained as 8 per week after initial response in order to sustain efficacy. No need to increase the dose or combined administration with MTX either	NA	Conservative assumption that the frequency of infliximab infusions is maintained as 8 per week after initial response in order to sustain efficacy	Medium

NA, not applicable.

rate on costs and benefits, which is the NICE guideline from the 11th wave. The base-case of the York Model uses 6% on costs and 1.5% on QALY, which is NICE's current guidance.
- The rebound scenario of rebound back to natural history was not considered in the Wyeth model.

The differences between the York and the Wyeth models do not result in all changes going in the same direction. For the 10-year analysis, for example, in the comparison of Wyeth's base-case estimates with the York Model (males, 10-year time horizon, rebound equal to gain), the York Model has higher incremental cost (£35,230 versus £23,112) but higher incremental QALYs (1.344 versus 0.82). The net effect of these differences is a slightly lower ICER with the York Model than with Wyeth's: £26,176 versus £28,189. However, under the York scenario of rebound equal to natural history, the York Model generates a slightly higher ICER (£30,400 versus £28,189).

Chapter 7
Discussion

General points

The literature searches conducted for this review were comprehensive and we were also able to include data made available in the company submissions and clinical trial reports provided by Wyeth and Schering-Plough. We are confident that all relevant studies have been included in our review of adverse events and that we identified all RCTs regarding the efficacy of other treatments for PsA. RCTs represent the best design of clinical study by which to evaluate the efficacy of an intervention. This is particularly true for trials in PsA, for which it has been demonstrated that the placebo response is consistently and significantly high, rendering the results of uncontrolled trials unreliable.[47]

A potential limitation of our review could stem from the difficulties in assessing the activity of PsA and its response to therapy. As discussed at some length in the background to this report, there are a number of outcome measures that are used, none of which has been clearly identified as optimal for PsA. In this report, we have attempted to include as much good-quality clinical trial data as possible while utilising the best available outcome measures. This has meant that, in the clinical evaluation, we have made use of a number of efficacy outcome measures as reported in the various clinical trials, namely PsARC, ACR 20, 50 and 70, HAQ and PASI. In addition, we have reported measures used in older trials: TJC; SJC, pain, PtGA, PhGA and biochemical markers of disease activity (ESR). These measures are not ideal but are the best available, especially when data for joint and skin are both used. More objective measures of joint disease such as radiological assessments are not necessarily reflective of the patient's perspective on their health and, furthermore, such data are very sparse in PsA.

In order to utilise the efficacy evaluation data in the economic model, it was necessary to select a single outcome measure. The main reason for the choice of HAQ as our main outcome variable was the fact that it makes it technically feasible to evaluate the impact of retarding and/or halting the progression of the disease, in terms of both cost-effectiveness and QoL. Ideally, the economic evaluation would have captured the added benefits to both skin and joints. However, there exists no validated composite outcome measure that can take into account the impact of treatment on both skin disease and arthritis. None of the company submissions incorporated the skin component.

To put the limitations of HAQ into perspective, although PsA affects both joints and skin, the arthritis is frequently the most significant aspect of the disease.[132] This is certainly true for the populations in the majority of the RCTs conducted to date. The trials of SSZ and CSA did not assess psoriasis and, even in the recent trials, only around 60% of etanercept patients and around 40% of infliximab patients were evaluable for psoriasis. One exception is the fairly recent trial of leflunomide in which all patients had to have at least 3% BSA psoriasis, and mean PASI at baseline was around 9.[46]

Clinical evaluation

There is only a limited amount of RCT-based efficacy data for both etanercept and infliximab. For etanercept there are only two RCTs totalling 265 patients, with only 131 treated with etanercept. For infliximab there is only a single RCT of 104 patients, 52 treated with infliximab. However, all three were good-quality trials and provide a clear indication of response to treatment at 12 weeks with continued efficacy at 24 weeks for etanercept and at 14–16 weeks for infliximab. The majority of patients in the trials had received at least one DMARD previously for PsA and some had received two or more. None of the trial populations were specifically those for whom etanercept and infliximab are licensed, i.e. none specified failure to respond to all DMARDs (or at least two DMARDs) as an enrolment criterion.

In the populations studied, there is evidence from double-blind placebo-controlled trials of a good level of efficacy for etanercept in the treatment of PsA, with beneficial effects on arthritis and psoriasis and functional status assessed by the HAQ score. Follow-up of patients (including some uncontrolled data) indicates that treatment benefit is maintained for at least 50 weeks; however, these data may not

be reliable. Importantly, there are radiographic data from controlled trials of etanercept in PsA that demonstrate a beneficial effect on disease progression at 24 weeks. Normally 24 weeks is considered too short a period over which to detect radiological changes; a significant effect at this stage of treatment suggests that onset of action of etanercept is rapid. Data from uncontrolled follow-up indicate that this effect on disease progression may continue for at least 1 year. Controlled long-term data are needed to confirm that effects are maintained. A 2-year controlled trial of etanercept versus best care, probably MTX or possibly leflunomide, is warranted.

There is only one RCT of infliximab totalling 104 patients, of whom only 52 were treated with infliximab. This good-quality trial gives a clear indication of response to treatment in the short term but there are no RCT data on continued efficacy at 24 weeks and no radiographic data. Hence, there is no good-quality evidence that infliximab delays the progression of PsA. Uncontrolled studies of infliximab have not been considered in this report because of the low level of evidence that such data represent.

The level of efficacy demonstrated for both etanercept and infliximab in the first 3 months of treatment (approximately) is similar, with both achieving ACR 20 in 65% of patients and ACR 50 in around 50% of patients. The evidence synthesis found that the probability of a response with the two drugs was similar and there was no substantial difference in their effects on improving HAQ.

All trials of etanercept and infliximab in PsA included a significant proportion of patients who took concomitant MTX. Analysis of these subgroups found no indication of a lack of effect of either drug when administered without MTX or, conversely, of any synergistic effect when combined with MTX. However, the effects of MTX need proper investigation, particularly in combination with infliximab, since its licence in RA (although not PsA) requires its concomitant use in order to limit the development of antibodies to infliximab and their associated tachyphylaxis with continued use of the drug.

Despite their demonstrable efficacy in short-term treatment, it is important to remember that PsA is a chronic disease and long-term evidence is lacking for both drugs.

Adverse effects data for etanercept are derived primarily from trials in RA and from clinical experience. In summary, 24 weeks of treatment with etanercept 25 mg twice weekly is associated with a high rate of adverse events, but only injection site reactions are clearly linked to etanercept. The significance of uncommon serious adverse events is not discernible from the published reports of clinical trials. The situation is similar for infliximab, with few data derived from patients with PsA. Overall, the drug appears to be well tolerated, with some concern over infusion reactions, and uncommon but serious infections, particularly TB. The possible risk of lymphomas, SLE and MS requires caution and further monitoring and investigation.

Although the product licences for both etanercept and infliximab are for their use only in patients who have failed to respond to, or are unable to take, DMARDs, we felt it was important to compare, as far as possible, the evidence base for the new drugs with that for the older more established drugs. From our review, it can be seen that existing therapies for PsA are used without any real supporting evidence. Therefore, although the evidence base for neither etanercept nor infliximab can be said to be strong, compared with other treatments used in PsA the evidence supporting their use is, we believe, convincing in terms of quality of data and size of treatment effect.

Economic evaluation

There is a dearth of published economic evaluations in the field of PsA, and no published studies were found looking at the cost-effectiveness of etanercept and infliximab for this indication. The company submissions from Wyeth and Schering-Plough both included previously unpublished cost-effectiveness models. Each compared their specific therapy with one or more comparators, that is neither model compared the two biological therapies. The Wyeth model was heavily influenced by an earlier model developed for etanercept in RA.[42] Some of the assumptions in the Wyeth model may be considered inappropriate. These include the choice of DMARD comparators. The use of such therapies as comparators at all is open to doubt (see below), but when these comparators are given acquisition costs but no additional efficacy over placebo, this can certainly be criticised. Other potentially weak assumptions in the Wyeth model are the double counting of some of the costs (i.e. palliative care and RA medication) and a failure to consider a scenario of HAQ rebound back to natural history.

The Schering-Plough model used a markedly different approach to cost-effectiveness modelling than Wyeth using the number of active and deformed joints as their main driver of costs and QALYs. Although the choice of HAQ as the measure of disability which drives both QoL and costs is consistent with both the Wyeth model and many cost-effectiveness models of biological therapies in RA,[41–43,129] the use of radiological measures of disease progression may be preferable if the main aim of the modelling is to capture all aspects of disease activity (i.e. deformity or damage resulting from the disease process, especially in late PsA). Currently, however, radiological data are not available with which to structure a cost-effectiveness model comparing all relevant therapies. The Schering-Plough submission presents a preliminary model and provides limited detail of many of the methods used, so a full critical appraisal of the analysis has been difficult.

It was necessary to develop the York Model, given the need to address some of the limitations in the manufacturers' models, in particular their failure to compare both anti-TNF therapies and palliative care simultaneously. The York Model is closer to the Wyeth model in that costs and QALYs are largely driven by changes in HAQ, and it shares a number of parameter estimates. However, a notable difference is that it is a cohort model (rather than a patient-level simulation) and includes a comparison of etanercept and infliximab, in addition to palliative care. In order to provide estimates of cost-effectiveness for these three treatment options, the evidence synthesis was required to undertake an indirect comparison of etanercept and infliximab in terms of PsARC response and change in HAQ from baseline. It also needed estimates of HAQ change from baseline conditional on whether or not a patient responded in terms of PsARC. Although these data were made available by the manufacturers for the Mease (2004) trial[36] (etanercept) and the IMPACT study[61] (infliximab), they were unavailable for the Mease (2000) trials.[60] The evidence synthesis used the aggregate data from the Mease (2000) trial[60] (i.e. overall change in HAQ not conditional on PsARC response) and combined it with the data supplied by the manufacturers.

The York Model indicates that infliximab is consistently dominated by etanercept. In spite of our conservative assumption regarding frequency of infusions (every 8 weeks as stated in the SPC), infliximab's drug costs are consistently higher (partly because it has to be administered in hospital) and its effectiveness is not superior. Administration costs for infliximab were the object of a sensitivity analysis. In the base-case analysis, half a day in a rheumatology department for infliximab infusion is assumed, as suggested by clinical experts. This was costed using fully allocated costs based on NHS reference costs for 2004. As an alternative assumption, a sensitivity analysis was undertaken using the administration costs from the Birmingham Rheumatoid Arthritis Model (BRAM) study,[129] £124 per infliximab infusion (source of unit cost not reported). Although, as expected, mean costs with infliximab are reduced, infliximab is still dominated under all circumstances, even when using three vials per infusion and for a 40-year time horizon.

Etanercept is consistently found to cost more than palliative care but to generate additional QALYs. Its incremental cost per QALY gained varies, most markedly according to the rebound assumption and time horizon; patient sex has a very minor effect.

Another important assumption that influences the ICER for etanercept relates to progression in HAQ score while patients are responding to therapy. In the base-case analysis of the York Model (and the Wyeth submission), it was assumed that there was zero progression in HAQ in responding patients. An alternative scenario was considered whereby, after the initial improvement at 3 months, HAQ was assumed to progress at the same rate as natural history; this is equivalent to assuming that biological therapy generates a symptomatic gain but does not influence disease progression. This alternative assumption raises the ICER of etanercept to £44,636 (males, 10-year time horizon). This alternative assumption would only really make clinical sense if the rebound assumption of back to natural history progression were considered plausible. It would not be logically consistent with an assumption of rebound equal to gain.

Lack of long-term efficacy and safety data is the main limitation of any economic evaluation of PsA. A number of parameters in our model are based on very limited evidence. This applies, in particular, to the long-term withdrawal rate (based on a 2-year non-randomised observational study in RA, assuming a constant rate of withdrawal and no difference between the two biological therapies), the natural history HAQ progression (based on an unpublished cohort study of 24 PsA patients reported in the Wyeth submission), and the HAQ progression in patients responding to

therapy (assumed to be zero based on evidence from the open-label continuation studies after etanercept and infliximab).

There are three other important issues which need to be kept in mind when interpreting the results of the York Model. The first is the choice of comparators. The model considers the cost-effectiveness of etanercept and infliximab compared with each other and with palliative care. This is equivalent to assuming that the biological therapies would be used 'end of line' once DMARD therapies have been tried and failed. As explained in the section 'Comparators' (p. 41), there are three reasons why DMARD therapies were not used as comparators to the biological therapies in the model. The first is that a strict interpretation of the licences of etanercept and infliximab would suggest that **all DMARDs** should be used prior to the biological therapies.

The second reason is that, even if the strict interpretation of the licences is not used, it is not clear how many DMARDs should have been tried and failed before the biological therapies are used. BSR guidelines suggest that at least two DMARDs should have been tried.[35] However, only three are routinely used in PsA (SSZ, MTX and CSA) and none of these is licensed for the disease. The third reason is a pragmatic one, namely there are no data available on the traditional DMARDs – SSZ, MTX or CSA – regarding response rates in terms of PsARC and efficacy in terms of change in HAQ from baseline. Some of those data exist for leflunomide but, as a recently licensed therapy, its place in care is also uncertain.

The second issue relates to the lack of long-term data on the use of anti-TNF drugs. Potential severe adverse events have not been incorporated in our model and this should be considered when its results are interpreted. Both manufacturers' models also share this limitation. Further, we have extrapolated clinical trial data up to 40 years (base-case scenario) as a reasonable assumption based on expert advice, but the reality is that there is limited experience on the administration of biologic drugs for PsA and RA patients, so the number of years that a patient can safely use biologics is uncertain.

The third issue is the fact that the York Model was not able to incorporate the possible QoL impact of the biological therapies on the skin component of the disease. This assumption also had to be made in the two manufacturers' models. It results from the lack of any data on the **combined QoL effect** (in terms of utility) of improvement in disability associated with patients' arthritis and in their psoriasis. It should be noted, however, that patients with active PsA generally have mild skin disease.[132]

The generalisability of the findings of this clinical and economic review is limited for two main reasons. First, the efficacy data used in the clinical evaluation, evidence synthesis and the economic model were very sparse, being derived from three trials with a total of 369 patients; only 134 patients were treated with etanercept and only 52 were treated with infliximab. Second, these trial populations were not precisely representative of those for whom etanercept and infliximab are licensed: neither population was made up exclusively of patients who had failed to respond to at least two DMARDS.

Recommendations for research

All of the following are equally important.

- Long-term controlled trials are required to confirm that symptomatic benefits for joint and skin disease and improvements in function are maintained. Data on long-term HAQ progression while responding to biologics are required.
- Long-term controlled trials on the effects on joint disease progression are also required.
- Further research on the combined effects on QoL of the therapeutic impact on both arthritis and psoriasis is required, including in terms of a generic preference based (utility) instrument.
- A 2-year controlled trial of etanercept versus best care (probably MTX or leflunomide) is warranted; such a trial should gather comparative data on HAQ and radiographic progression with leflunomide.
- RCTs investigating the effects of combination with MTX with reference to any synergistic effect and the possibility of tachyphylaxis are warranted.
- Long-term monitoring studies of adverse events and regular reviews of the significance of serious adverse events are essential. Research should establish whether long-term patterns of adverse events are similar to those in RA. The setting up of a Biologics Registry for the treatment of PsA is advisable.
- Long-term information on withdrawal rates from biologics for lack of efficacy and adverse events is important.
- Research to establish whether intermittent biologic therapy is a reasonable option for the treatment of PsA would be of value.

Chapter 8
Conclusions

- The limited data available indicate that etanercept is efficacious in the treatment of PsA with beneficial effects on both joint and psoriasis symptoms and on functional status. Short-term data indicate that etanercept can delay joint disease progression. Further long-term data are required to confirm and consolidate the evidence base for etanercept.
- The limited data available indicate that infliximab is efficacious in the treatment of PsA with beneficial effects on both joint and psoriasis symptoms and on function. There are no controlled data as yet to indicate that infliximab can delay joint disease progression. Further data are required to confirm the findings of the currently available trials and to demonstrate that response is maintained and that disease progression is delayed in the long term.
- Treatment for 12 weeks with both etanercept and infliximab demonstrated a significant degree of efficacy, with no statistically significant difference between them.
- For both etanercept and infliximab, adverse events are common with mild injection/infusion reactions being the main treatment-related effect. Concerns exist over uncommon serious and long-term adverse effects and, in the authors' opinion, further monitoring of the safety profiles of both drugs is required.
- The York Model indicates that etanercept is more cost-effective than infliximab as it has a lower cost with little difference in outcomes. The incremental cost per QALY gained of etanercept compared with palliative care (i.e. to no active therapy) ranges from £14,818 (females, 40-year time horizon) to £49,374 (males, 1-year time horizon) under the assumption of rebound equal to gain. It ranges from £25,443 (females, 40-year time horizon) to £49,441 (males, 1-year time horizon) under the assumption of rebound equal to natural history progression. The cost-effectiveness of etanercept is also sensitive to assumptions made about the extent of disease progression when patients are responding to therapy. The number of years a patient can remain safely on biologics is uncertain, so these results should be considered with caution.

Acknowledgements

We thank the expert advisory panel for their useful advice and constructive comments on the report. We also wish to thank Professor Tony Ades of the MRC Health Services Research Collaboration at the University of Bristol for his help and advice on the mixed treatment comparison model applied in the evidence synthesis.

Contribution of authors

Nerys Woolacott (Research Fellow) was the lead reviewer responsible for writing the protocol, all aspects of the clinical evaluation and coordinating the final report. Yolanda Bravo Vergel (Research Fellow) was responsible for the systematic review of economic evaluations, implementation of the economic model and re-analysis of the company submissions and contributed to the protocol and report writing. Neil Hawkins (Research Fellow) contributed to the evidence synthesis and development of the economic model and contributed to the protocol and report writing. Anita Kainth (Research Fellow) was a reviewer involved in the clinical evaluation section and was involved in the study selection, data extraction and validity assessment. Zarnie Khadjesari (Research Fellow) was a reviewer involved in the clinical evaluation section and was involved in the study selection, data extraction, validity assessment and writing the final report. Kate Misso (Information Officer) devised the search strategy and carried out the literature searches. Kate Light (Information Officer) wrote the search methodology sections of the report. Christian Asseburg (Research Fellow) developed and implemented the evidence synthesis. Stephen Palmer (Senior Research Fellow) contributed to the development of the economic model. Karl Claxton (Senior Lecturer) contributed to the development of the economic model. Ian Bruce (Senior Lecturer and Consultant Rheumatologist) provided input at all stages, contributed to the protocol, commented on various drafts of the report and contributed to the discussion section of the report. Mark Sculpher (Professor of Health Economics) provided input at all stages, commented on various drafts of the report and had overall responsibility for the economic evaluation sections of the report. Rob Riemsma (Senior Research Fellow) provided input at all stages, commented on various drafts of the report and had overall responsibility for project coordination.

This report was commissioned by the NHS R&D HTA Programme. The views expressed in this report are those of the authors and not necessarily those of the NHS R&D Programme. Any errors are the responsibility of the authors.

References

1. Patel S, Veale D, FitzGerald VO, McHugh NJ. Psoriatic arthritis – emerging concepts. *Rheumatology* 2001;**40**:243–6.
2. Kay LJ, Parry-James JE, Walker DJ. The prevalence and impact of psoriasis and psoriatic arthritis in the primary care population in North East England. *Arthritis Rheum* 1999;**42** Suppl:s299.
3. Harrison BJ, Silman AJ, Barrett EM, Scott DGI, Symmons DPM. Presence of psoriasis does not influence the presentation or short-term outcome of patients with early inflammatory polyarthritis. *J Rheumatol* 1997;**24**:1744–9.
4. Ruderman EM. Evaluation and management of psoriatic arthritis: the role of biologic therapy. *J Am Acad Dermatol* 2003;**49** (Suppl 2):s125–32.
5. Galadari H, Fuchs B, Lebwohl M. Newly available treatments for psoriatic arthritis and their impact on skin psoriasis. *Int J Dermatol* 2003;**42**:231–7.
6. Gladman DD. Effectiveness of psoriatic arthritis therapies. *Semin Arthritis Rheum* 2003;**33**:29–37.
7. Pipitone N, Kingsley GH, Manzo A, Scott DL, Pitzalis C. Current concepts and new developments in the treatment of psoriatic arthritis. *Rheumatology* 2003;**42**:1138–48.
8. Krueger GG. Clinical features of psoriatic arthritis. *Am J Manage Care* 2002;**8**(6 Suppl):s160–70.
9. Kane D, Stafford L, Bresniham B, FitzGerard O. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. *Rheumatology* 2003;**42**:1460–8.
10. Husted JA, Gladman DD, Long JA, Farewell VT. A modified version of the Health Assessment Questionnaire (HAQ) for psoriatic arthritis. *Clin Exp Rheumatol* 1995;**13**:439–43.
11. Gladman DD, Hing EN, Schentag CT, Cook RJ. Remission in psoriatic arthritis. *J Rheumatol* 2001; **28**:1045–8.
12. Gottlieb AB. Psoriatic arthritis: a guide for dermatology nurses. *Dermatol Nurs* 2003;**15**:107–19.
13. McHugh NJ, Balachrishnan C, Jones SM. Progression of peripheral joint disease in psoriatic arthritis: a 5-yr prospective study. *Rheumatology* 2003;**42**:778–83.
14. Gladman DD, Stafford-Brady F, Chang CH, Lewandowski K, Russell ML. Longitudinal study of clinical and radiological progression in psoriatic arthritis. *J Rheumatol* 1990;**17**:809–12.
15. Gladman DD, Farewell VT, Nadeau C. Clinical indicators of progression in psoriatic arthritis: multivariate relative risk model. *J Rheumatol* 1995;**22**:675–9.
16. Queiro-Silva R, Torre-Alonso JC, Tinture-Eguren T, Lopez-Lagunas I. A polyarticular onset predicts erosive and deforming disease in psoriatic arthritis. *Ann Rheum Dis* 2003;**62**:68–70.
17. Moll JM, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum* 1973;**3**:55–78.
18. Mease P, Goffe BS. Diagnosis and treatment of psoriatic arthritis. *J Am Acad Dermatol* 2005; **52**:1–19.
19. Husted JA, Gladman DD, Farewell VT, Cook RJ. Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. *Arthritis Care Res* 2001; **45**:151–8.
20. Curran S, Winchester R, Costello P, Peterson K, Bresnihan B, FitzGerald O. Methotrexate therapy reduces polyclonal T cell infiltration in the psoriatic arthritis synovium, revealing expanded CD4 and CD8 T-cell clones. *Arthritis Rheum* 1999; **42**:S372.
21. Wong K, Gladman DD, Husted J, Long JA, Farewell VT. Mortality studies in psoriatic arthritis: results from a single outpatient clinic. I. Causes and risk of death. *Arthritis Rheum* 1997;**40**:1868–72.
22. Gladman DD, Farewell VT, Wong K, Husted J. Mortality studies in psoriatic arthritis: results from a single outpatient center. II. Prognostic indicators for death. *Arthritis Rheum* 1998;**41**:1103–10.
23. Javitz HS, Ward MM, Farber E, Nail L, Vallow SG. The direct cost of care for psoriasis and psoriatic arthritis in the United States. *J Am Acad Dermatol* 2002;**46**:850–60.
24. Kvien TK. Epidemiology and burden of illness of rheumatoid arthritis. *Pharmacoeconomics* 2004; **22** (2 Suppl):1–12.
25. Jonsson B, Kaarela K, Koblet G. *Economic consequences of the progression of rheumatoid arthritis: a Markov model.* Stockholm: Stockholm School of Economics; 1997.
26. Kobelt G, Eberhardt K, Jonsson L, Jonsson B. Economic consequences of the progression of rheumatoid arthritis in Sweden. *Arthritis Rheum* 1999;**42**:347–56.

27. Jonsson B, Rehnberg C, Borgquist L, Larsson SE. Locomotion status and costs in destructive rheumatoid arthritis. A comprehensive study of 82 patients from a population of 13,000. *Acta Orthop Scand* 1992;**63**:207–12.

28. McIntosh E. Clinical audit: the cost of rheumatoid arthritis. *Br J Rheumatol* 1996;**35**:781–90.

29. Kobelt G, Jonsson L, Lindgren P, Young A, Eberhardt K. Modelling the progression of rheumatoid arthritis: a two-country model to estimate costs and consequences of rheumatoid arthritis. *Arthritis Rheum* 2002;**46**:2310–19.

30. Goldsmith CH, Smythe HA, Helewa A. Interpretation and power of a pooled index. *J Rheumatol* 1993;**20**:575–8.

31. Clegg DO, Reda DJ, Mejias E, Cannon GW, Weisman MH, Taylor T, *et al.* Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. *Arthritis Rheum* 1996; **39**:2013–20.

32. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, *et al.* American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;**38**:727–35.

33. Felson DT, Anderson JJ, Lange ML, Wells G, LaValley MP. Should improvement in rheumatoid arthritis clinical trials be defined as fifty percent or seventy percent improvement in core set measures, rather than twenty percent? *Arthritis Rheum* 1998; **41**:1564–70.

34. Gladman DD, Helliwell P, Mease PJ, Nash P, Ritchlin C, Taylor W. Assessment of patients with psoriatic arthritis – a review of currently available measures. *Arthritis Rheum* 2004;**50**:24–35.

35. McHugh N, Chandler D, Griffiths CE, Helliwell P, Lewis J, McInnes I, *et al.* BSR guideline for anti-TNFa therapy in psoriatic arthritis [webpage on the Internet]. London: British Society for Rheumatology; 2004. URL: http://www.msecportal.org/portal/editorial/PublicPages/bsr/536883013/FinalPsoriaticArthritisGuideline.pdf. Accessed 14 December 2004.

36. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, *et al.* Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004; **50**:2264–72.

37. Wassenberg S, Fischer-Kahle V, Herborn G, Rau R. A method to score radiographic change in psoriatic arthritis. *Z Rheumatol* 2001;**60**:156–66.

38. Gladman DD, Helliwell P, Mease PJ, Nash P, Ritchlin C, Taylor W. Assessment of patients with psoriatic arthritis: a review of currently available measures. *Arthritis Rheum* 2004;**50**:24–35.

39. Taccari E, Spadaro A, Rinaldi T, Riccieri V, Sensi F. Comparison of the Health Assessment Questionnaire and Arthritis Impact Measurement Scale in patients with psoriatic arthritis. *Revue du Rhumatisme (English Edition)* 1998;**65**:751–8.

40. Blackmore MG, Gladman DD, Husted J, Long JA, Farewell VT. Measuring health status in psoriatic arthritis: the Health Assessment Questionnaire and its modification. *J Rheumatol* 1995;**22**:886–93.

41. Wong JB, Singh G, Kavanaugh A. Estimating the cost-effectiveness of 54 weeks of infliximab for rheumatoid arthritis. *Am J Med* 2002;**113**:400–8.

42. Brennan A, Bansback N, Reynolds A, Conway P. Modelling the cost-effectiveness of etanercept in adults with rheumatoid arthritis in the UK. *Rheumatology* 2004;**43**:62–72.

43. Kobelt G, Jonsson L, Young A, Eberhardt K. The cost-effectiveness of infliximab (Remicade) in the treatment of rheumatoid arthritis in Sweden and the United Kingdom based on the ATTRACT study. *Rheumatology* 2003;**42**:326–35.

44. Marguerie L, Flipo RM, Grardel B, Beaurain D, Duquesnoy B, Delcambre B. Use of disease-modifying antirheumatic drugs in patients with psoriatic arthritis. *Joint Bone Spine* 2002;**69**:275–81.

45. Alldred A, Emery P. Leflunomide: a novel DMARD for the treatment of rheumatoid arthritis. *Expert Opin Pharmacother* 2001;**2**:125–37.

46. Kaltwasser JP, Nash P, Gladman D, Rosen CF, Behrens F, Jones P, *et al.* Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum* 2004;**50**:1939–50.

47. Jones G, Crotty M, Brooks P. Interventions for treating psoriatic arthritis: Art. No.: CD000212. DOI: 10.1002/14651858.CD000212. In *The Cochrane database of systematic reviews. 2000: Issue 2.* Chichester: Wiley; 2000.

48. Department of Health. Hospital episode statistics England: financial year 2003–04 [web page on the Internet]. London: Department of Health; 2003. URL: http://www.dh.gov.uk/assetRoot/04/09/70/91/04097091.xls. Accessed 12 December 2004.

49. British Medical Association BM. *British national formulary, No. 48 [CD-ROM]*. London: British Medical Association; 2005.

50. Department of Health. Prescription cost analysis, England 2003: prescription items dispensed in the community in England and listed alphabetically within chemical entity by therapeutic class [web page on the Internet]. London: Department of Health; 2004.URL: http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsStatistics/PublicationsStatisticsArticle/fs/en?CONTENT_ID=4081720&chk=kVOup3. Accessed 17 December 2004.

51. Gorter S, van der Heijde D, van der Linden S, Houben H, Rethans JJ, Scherpbier A, *et al.* Psoriatic arthritis: performance of rheumatologists in daily practice. *Ann Rheum Dis* 2002;**61**:219–24.

52. Pariser DM. Management of moderate to severe plaque psoriasis with biologic therapy. *Manage Care* 2003;**12**:36–44.

53. Gniadecki R, Zachariae C, Calverley M. Trends and developments in the pharmacological treatment of psoriasis. *Acta Derm Venereol* 2002; **82**:401–10.

54. Prinz JC. The role of T cells in psoriasis. *J Eur Acad Dermatol Venereol* 2003;**17**:257–70.

55. Drummond M, O'Brien B, Stoddart G, Torrance G. *Methods for the economic evaluation of health care programmes*. 2nd ed. Oxford: Oxford Medical Publications; 1997.

56. NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness. CRD's guidance for carrying out or commissioning reviews.* 2nd ed. York: NHS Centre for Reviews and Dissemination; 2001.

57. Whitehead A. *Meta-analysis of controlled clinical trials.* Chichester: Wiley; 2002.

58. Higgins JPT, Whitehead J. Borrowing strength from external trials in meta-analysis. *Stat Med* 1996;**15**:2733–49.

59. Ades AE. A chain of evidence with mixed comparisons: models for multi-parameter evidence synthesis and consistency of evidence. *Stat Med* 2003;**22**:2295–3016.

60. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet* 2000;**356**:385–90.

61. Antoni C, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester G, Schneider U, *et al.* Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). *Arthritis Rheum* 2005;**52**:1227–36.

62. Schering-Plough Ltd. *Remicade in the treatment of psoriatic arthritis in the United Kingdom: a submission to the National Institute for Clinical Excellence [Industry submission].* Kenilworth, NJ: Schering-Plough; 2004.

63. Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, *et al.* Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis* 2005; **64**:1150–7.

64. Khanna D, McMahon M, Furst DE. Safety of tumour necrosis factor-a antagonists. *Drug Saf* 2004;**27**:307–24.

65. Kavanaugh A, Keystone EC. The safety of biologic agents in early rheumatoid arthritis. *Clin Exp Rheumatol* 2003;**21** (5 Suppl 31):S203–8.

66. Weisman MH. What are the risks of biologic therapy in rheumatoid arthritis? An update on safety. *J Rheumatol Suppl* 2002;**65**:33–8.

67. Ellerin T, Rubin RH, Weinblatt ME. Infections and anti-tumor necrosis factor a therapy. *Arthritis Rheum* 2003;**48**:3013–22.

68. Gardam MA, Keystone EC, Menzies R, Manners S, Skamene E, Long R, *et al.* Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *Lancet Infect Dis* 2003;**3**:148–55.

69. Antoni C, Braun J. Side effects of anti-TNF therapy: current knowledge. *Clin Exp Rheumatol* 2002;**20** (6 Suppl 28):S152–7.

70. Keystone EC. Advances in targeted therapy: safety of biological agents. *Ann Rheum Dis* 2003; **62** Suppl 2:34–36.

71. Culy CR, Keating GM. Etanercept: an updated review of its use in rheumatoid arthritis, psoriatic arthritis and juvenile rheumatoid arthritis. *Drugs* 2002;**62**:2493–537.

72. Bresnihan B, Cunnane G. Infection complications associated with the use of biologic agents. *Rheum Dis Clin North Am* 2003;**29**:185–202.

73. Goffe B, Cather JC. Etanercept: an overview. *J Am Acad Dermatol* 2003;**49** (2A Suppl):S105–11.

74. Davis JC, van der Heijde D, Braun J, Dougados M, Cush J, Clegg DO, *et al.* Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003;**48**:3230–6.

75. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, *et al.* Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double blind randomised controlled trial. *Lancet* 2004; **363**:675–81.

76. Geborek P, Crnkic M, Petersson IF, Saxne T, South Swedish Arthritis Treatment Group. Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. *Ann Rheum Dis* 2002;**61**:793–8.

77. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, *et al.* Etanercept therapy in rheumatoid arthritis: a randomized, controlled trial. *Ann Intern Med* 1999;**130**:478–86.

78. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, *et al.*

A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;**343**:1586–93.

79. Willis RF, Pedersen R. A long-term, open-label trial of the safety and efficacy of etanercept (25 mg twice weekly) in patients with rheumatoid arthritis (interim analysis). *J Rheumatol* 2001;**28** Suppl 63: W104.

80. Phillips K, Husni ME, Karlson EW, Coblyn JS. Experience with etanercept in an academic medical center: are infection rates increased? *Arthritis Rheum* 2002;**47**:17–21.

81. Elewski B, Boh E, Papp K, Rafal E, Griffiths G, Zitnik R, Nakanishi A. Efficacy and safety of etanercept in patients with psoriasis: results of a global phase 3 study. *J Am Acad Dermatol* 2004;**30**:159.

82. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, *et al.* Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003;**349**:2014–22.

83. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, *et al.* A randomized trial of etanercept as monotherapy for psoriasis. *Arch Dermatol* 2003;**139**:1627–32.

84. British Medical Association. *British national formulary, No. 46*. London: British Medical Association; 2003.

85. Sweetman S. *Martindale: the complete drug reference [CD-ROM]*. London: Pharmaceutical Press; 2002.

86. United States Pharmacopeial Convention. *USPDI, vol. 1: drug information for the health care professional*. Rockville, MD: United States Pharmacopeial Convention; 2004.

87. Keating GM, Perry CM. Infliximab: an updated review of its use in Crohn's disease and rheumatoid arthritis. *BioDrugs* 2002;**16**:111–48.

88. Wagner CL, Schantz A, Barnathan E, Olson A, Mascelli MA, Ford J, *et al.* Consequences of immunogenicity to the therapeutic monoclonal antibodies ReoPro and Remicade. *Dev Biol (Basel)* 2003;**112**:37–53.

89. Sandborn WJ, Hanauer SB. Infliximab in the treatment of Crohn's disease: a user's guide for clinicians. *Am J Gastroenterol* 2002;**97**:2962–72.

90. Hanauer SB. Review article: safety of infliximab in clinical trials. *Aliment Pharmacol Ther* 1999; **13** Suppl 4:16–22.

91. Kamm MA. Safety issues relating to biological therapies, with special reference to infliximab therapy. *Res Clin Forums* 2002;**24**:79–86.

92. Centocor. Advisory Committee briefing document for safety with Remicade. Rockville, MD: US Food and Drug Administration; 2001. URL: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3779b2_03_centocor.pdf. Accessed 7 October 2004.

93. Health and Human Services, Food and Drug Administration Center for Biologics Evaluation and Research: Arthritis Advisory Committee. Safety update on TNF-a antagonists; infliximab and etanercept. Rockville, MD: US Food and Drug Administration; 2001. URL: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3779b2.htm. Accessed 7 October 2004.

94. Baeten D, Kruithof E, van den Bosch F, van den Bossche N, Herssens A, Mielants H, *et al.* Systematic safety follow up in a cohort of 107 patients with spondyloarthropathy treated with infliximab: a new perspective on the role of host defence in the pathogenesis of the disease? *Ann Rheum Dis* 2003;**62**:829–34.

95. Sample C, Bailey RJ, Todoruk D, Sadowski D, Gramlich L, Milan M, *et al.* Clinical experience with infliximab for Crohn's disease: the first 100 patients in Edmonton, Alberta. *Can J Gastroenterol* 2002;**16**:165–70.

96. Farrell RJ, Shah SA, Lodhavia PJ, Alsahli M, Falchuk KR, Michetti P, *et al.* Clinical experience with infliximab therapy in 100 patients with Crohn's disease. *Am J Gastroenterol* 2000;**95**:3490–7.

97. Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L, *et al.* The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol* 2003; **98**:1315–24.

98. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, *et al.* Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet* 1999; **354**:1932–9.

99. Cohen RD, Tsang JF, Hanauer SB. Infliximab in Crohn's disease: first anniversary clinical experience. *Am J Gastroenterol* 2000;**95**:3469–77.

100. Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, *et al.* Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;**350**:876–85.

101. Hommes DW, Parlevliet W, Sterringa GJ, Hermans M, Bartelsman J, van Deventer SJH. Infliximab therapy in patients with Crohn's disease; experience with 132 patients. *Ned Tijdschr Geneeskd* 2002;**146**:1187–91.

102. Baert F, Noman M, Vermeire S, Van Assche G, D'Haens G, Carbonez A, *et al.* Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003; **348**:601–8.

103. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, *et al.* Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**:1541–9.

104. Colombel JF, Loftus Jr EV, Tremaine WJ, Egan LJ, Harmsen WS, Schleck CD, *et al.* The safety profile of infliximab in patients with Crohn's disease: the Mayo Clinic experience in 500 patients. *Gastroenterology* 2004;**126** (1 Suppl 1):19–31.

105. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, *et al.* Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998; **41**:1552–63.

106. Gottlieb A, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, *et al.* Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2004;**51**:534–42.

107. Fraser AD, van Kuryk A, Westhovens R, Karim Z, Gerards A, Landewe RBM, *et al.* A randomised, double-blind, placebo controlled multi-centre trial of combination therapy with methotrexate plus cyclosporin vs methotrexate plus placebo in patients with active psoriatic arthritis (PsA). *Arthritis Rheum* 2003;**48**:344.

108. Salvarani C, Macchioni P, Olivieri I, Marchesoni A, Cutolo M, Ferraccioli G, *et al.* A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis. *J Rheumatol* 2001;**28**:2274–82.

109. Spadaro A, Riccieri V, Sili-Scavalli A, Sensi F, Taccari E, Zoppini A. Comparison of cyclosporin A and methotrexate in the treatment of psoriatic arthritis: a one-year prospective study. *Clin Exp Rheumatol* 1995;**13**:589–93.

110. Gupta AK, Grober JS, Hamilton TA, Ellis CN, Siegel MT, Voorhees JJ, *et al.* Sulfasalazine therapy for psoriatic arthritis: a double blind, placebo controlled trial. *J Rheumatol* 1995;**22**:894–8.

111. Willkens RF, Williams HJ, Ward JR, Egger MJ, Reading JC, Clements PJ, *et al.* Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. *Arthritis Rheum* 1984;**27**:376–81.

112. Clegg DO, Reda DJ, Abdellatif M. Comparison of sulfasalazine and placebo for the treatment of axial and peripheral articular manifestations of the seronegative spondylarthropathies: a Department of Veterans Affairs cooperative study. *Arthritis Rheum* 1999;**42**:2325–9.

113. Dougados M, van der Linden S, Leirisalo-Repo M, Huitfeldt B, Juhlin R, Veys E, *et al.* Sulfasalazine in the treatment of spondylarthropathy. A randomized, multicenter, double-blind, placebo-controlled study. *Arthritis Rheum* 1995;**38**:618–27.

114. Fraser SM, Hopkins R, Hunter JA, Neumann V, Capell HA, Bird HA. Sulphasalazine in the management of psoriatic arthritis. *Br J Rheumatol* 1993;**32**:923–5.

115. Combe B, Goupille P, Kuntz JL, Tebib J, Liote F, Bregeon C. Sulphasalazine in psoriatic arthritis: a randomized, multicentre, placebo-controlled study. *Br J Rheumatol* 1996;**35**:664–8.

116. Farr M, Kitas GD, Waterhouse L, Jubb R, Felix-Davies D, Bacon PA. Sulphasalazine in psoriatic arthritis: a double-blind placebo-controlled study. *Br J Rheumatol* 1990;**29**:46–9.

117. Palit J, Hill J, Capell HA, Carey J, Daunt SO, Cawley MI, *et al.* A multicentre double-blind comparison of auranofin, intramuscular gold thiomalate and placebo in patients with psoriatic arthritis. *Br J Rheumatol* 1990;**29**:280–3.

118. Carette S, Calin A, McCafferty JP, Wallin BA. A double-blind placebo-controlled study of auranofin in patients with psoriatic arthritis. *Arthritis Rheum* 1989;**32**:158–65.

119. Levy J, Paulus H, Barnett E, Sokoloff M, Bangert R, Pearson C. A double-blind controlled evaluation of azathioprine treatment in rheumatoid arthritis and psoriatic arthritis. *Arthritis Rheum* 1972;**15**:116–7.

120. Salvarani C, Macchioni PL, Marchesoni A, Cutolo M, Ferraccioli GF, Cantini F, *et al.* Comparison of cyclosporine and sulfasalazine and symptomatic therapy for the treatment of psoriatic arthritis. *Arthritis Rheum* 1999;**42**:s378.

121. Dukes M, Aronson J. *Meyler's side effects of drugs: an encyclopedia of adverse reactions and interactions*. 14th ed. Amsterdam: Elsevier; 2000.

122. BMJ. Clinical evidence [database on the Internet]. London: BMJ; 2004. URL: http://www.clinicalevidence.com/ceweb/conditions/index.jsp. Accessed November 2004.

123. Al-Heresh AM, Proctor J, Jones SM, Dixey J, Cox B, Welsh K, *et al.* Tumour necrosis factor-alpha polymorphism and the HLA-Cw*0602 allele in psoriatic arthritis. *Rheumatology* 2002;**41**:525–30.

124. Wolf R, Ruocco V. Triggered psoriasis. *Adv Exp Med Biol* 1999;**455**:221–5.

125. Whiting-O'Keefe QE, Fye KH, Sack KD. Methotrexate and histologic hepatic abnormalities: a meta-analysis. *Am J Med* 1991;**90**:711–16.

126. Roenigk HH, Auerbach R, Maibach H, Weinstein G, Lebwohl M. Methotrexate in psoriasis: consensus conference. *J Am Acad Dermatol* 1998;**38**:478–85.

127. Centocor. *A multicenter placebo-controlled, double-blind, randomised study of anti-TNF chimeric monoclonal*

antibody (cA2, infliximab) in patients with active psoriatic arthritis (IMPACT): protocol no. P02114 [industry submission]. Malvern, PA: Centocor; 2003.

128. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, *et al.* Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004;**50**:2264–72.

129. Barton P, Jobanputra P, Wilson J, Bryan S, Burls A. The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis. *Health Technol Assess* 2004; **8**(11).

130. Jones SM, Armas JB, Cohen MG, Lovell CR, Evison G, McHugh NJ. Psoriatic arthritis: outcome of disease subsets and relationship of joint disease to nail and skin disease. *Br J Rheumatol* 1994; **33**:834–9.

131. Elkayam O, Ophir J, Yaron M, Caspi D. Psoriatic arthritis: interrelationships between skin and joint manifestations related to onset, course and distribution. *Clin Rheumatol* 2000;**19**:301–5.

132. Cohen MR, Reda DJ, Clegg DO. Baseline relationships between psoriasis and psoriatic arthritis: analysis of 221 patients with active psoriatic arthritis. *J Rheumatol* 1999;**26**:1752–6.

133. National Institute for Clinical Excellence. *Technical guidance for manufacturers and sponsors on making a submission to a technology appraisal.* London: National Institute for Clinical Excellence; 2001.

134. Sokoll KB, Helliwell PS. Comparison of disability and quality of life in rheumatoid and psoriatic arthritis. *J Rheumatol* 2001;**28**:1842–6.

135. Kane D, Stafford L, Bresnihan B, FitzGerald O. A classification study of clinical subsets in an inception cohort of early psoriatic peripheral arthritis – 'DIP or not DIP revisited'. *Rheumatology* 2003;**42**:1469–76.

136. Kay L, Walker D. Therapy for psoriatic arthritis: sometimes a conflict for psoriasis. *Br J Rheumatol* 1998;**37**:234–5.

137. Government Actuary´s Department. Interim life tables 2001–2003. London: Government Actuary's Department. URL: http://www.gad.gov.uk/life_tables/interim_life_tables.htm. Accessed December 2004.

138. Kind P. The EuroQoL instrument: an index of health-related quality of life. In Spilker B, editor. *Quality of life and pharmacoeconomics in clinical trials.* 2nd ed. New York: Lippincott-Raven; 1996. pp. 191–201.

139. Schering-Plough Ltd. Remicade [infliximab: summary of product characteristics] [web page on the Internet]. London: Electronic Medicines Compendium; 2005. URL: http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=3236. Accessed 15 December 2001.

140. Ostuni P, Botsios C, Sfriso P, Semerano L, Grava C, Todesco S. Clinical efficacy of infliximab combined with low-dose methotrexate in active refractory [web page on the Internet]. European League Against Rheumatism: Annual European Congress of Rheumatology, EULAR 2002. URL: http://mcic3.textor.com/cgi-bin/mc/printabs.pl?APP=eular2002SCIE-abstract&TEMPLATE=&keyf=0746&showHide=show. Accessed 25 January 2005.

141. Sidiropoulos P, Kakavouli G, Bertsias G, Mamoulaki M, Siakka P, Kouroumali H, *et al.* Long-term follow-up in patients with rheumatoid arthritis (RA) on anti-TNF therapy: response rates and dose adjustment after initial response [web page on the Internet]. European League Against Rheumatism: Annual European Congress of Rheumatology, EULAR 2003. URL: http://mcic3.textor.com/cgi-bin/mc/printabs.pl?APP=eular2003SCIE-abstract&TEMPLATE=&keyf=1995&showHide=show&client=. Accessed 25 January 2005.

142. Dumoulin C, Richez C, Lignot S, Dehais J, T. S. Time-limited response to infliximab: what is the meaning and how to manage? [web page on the Internet]. European League Against Rheumatism: Annual European Congress of Rheumatology, EULAR 2003. URL: http://mcic3.textor.com/cgi-bin/mc/printabs.pl?APP=eular2003SCIE-abstract&TEMPLATE=&keyf=1970&showHide=show&client=. Accessed 25 January 2005.

143. Royal College of Nursing Rheumatology Biologics Working Party, Arthritis and Musculoskeletal Alliance, Royal College of Nursing Paediatric Rheumatology Specialist Nurses Group. Assessing, managing and monitoring biologic therapies for inflammatory arthritis: guidance for rheumatology practitioners. An advisory document. London: Royal College of Nursing; 2003. URL: http://www.rcn.org.uk/publications/pdf/inflammatory-arthritis.pdf. Accessed 14 December 2003.

144. Young A, Dixey J, Cox N, Davies P, Devlin J, Emery P, *et al.* How does functional disability in early rheumatoid arthritis (RA) affect patients and their lives? Results of 5 years of follow-up in 732 patients from the Early RA Study (ERAS). *Rheumatology* 2000;**39**:603–11.

145. Johannesson M, Weinstein S. On the decision rules of cost-effectiveness analysis. *J Health Econ* 1993; **12**:459–67.

146. Briggs AH, Price M, Ades AE. Probabilistic assessment of a transition matrix for Markov modelling: an application of Bayesian methods using the Dirichlet distribution. *Med Decis Making* 2001;**23**:341–50.

147. van Hout BA, Al MJ, Gordon GS, Rutten FFH. Costs, effects and c/e-ratios alongside a clinical trial. *Health Econ* 1994;**3**:309–19.

148. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;**10**:779–89.

149. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;**23**:3105–24.

150. Wyeth-Ayerst Research. *Double-blind, randomized, placebo-controlled study of etanercept (recombinant human tumor necrosis factor receptor [p75] fusion protein; ENBREL) in the treatment of psoriatic arthritis (PsA) and psoriasis, with open-label extension: final report. Protocol no.: 016.0612*. Philadelphia, PA: Wyeth-Ayerst Research; 2001.

151. Wyeth-Ayerst Research. *Double-blind, randomized, placebo-controlled phase 3 study of etanercept (ENBREL) in the treatment of psoriatic arthritis (PsA) and psoriasis: final report: protocol no.: 016.0030 [industry submission]*. Philadelphia, PA: Wyeth-Ayerst Research; 2001.

152. Ory P, Sharp JT, Salonen D, Rubenstein J, Mease PJ, Kivitiz A, *et al.* Etanercept (ENBREL (R)) inhibits radiographic progression in patients with psoriatic arthritis. *Arthritis Rheum* 2002;**46**:S196.

153. Krueger G, Lebwohl M, Gottlieb AB, Mease PJ, Burge G. Etanercept improves psoriasis in patients with psoriatic arthritis: results of a phase 3 multicenter clinical trial. *Ann Dermatol Venereol* 2002;**129** (Suppl 1 Pt 1):1989.

154. Wyeth Research. *Double-blind, randomized, placebo-controlled phase 3 study of etanercept (ENBREL) in the treatment of psoriatic arthritis (PsA) and psoriasis: radiographic results: protocol no.: 016.0030 [industry submission]*. Philadelphia, PA: Wyeth Research; 2003.

155. Antoni C, Kavanaugh A, Kirkham B, Burmester G, Weisman M, Keystone E, *et al.* The infliximab multinational psoriatic arthritis controlled trial (IMPACT). *Arthritis Rheum* 2002;**46**:S381.

156. Antoni C, Kavanaugh A, Kirkham B, Burmester G, Manger B, Schneider U, *et al.* The one year results of the infliximab multinational psoriatic arthritis controlled trial (IMPACT). *Arthritis Rheum* 2003; **48**:604.

157. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, *et al.* Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002; **46**:1443–50.

158. Bathon JM, Genovese MC. The Early Rheumatoid Arthritis (ERA) trial comparing the efficacy and safety of etanercept and methotrexate. *Clin Exp Rheumatol* 2003;**21** (5 Suppl 31):S195–7.

159. Wyeth Research. *Phase 3 study of the safety and efficacy of Enbrel in psoriasis: final 12-week report: protocol no.: 20021642 [industry submission]*. Philadelphia, PA: Wyeth Research; 2003.

160. Wyeth Research. *Phase 3 study of the safety and efficacy of Enbrel in psoriasis: open-label final report: protocol no.: 20021642 [industry submission]*. Philadelphia, PA: Wyeth Research; 2003.

161. Gordon K, Karman N, Frankel E. Efficacy of etanercept in an integrated multi-study database of patients with psoriasis. *62nd Annual Meeting of American Academy of Dermatology*, 6–11 February 2004. Washington DC. p. 8.

162. Gottieb AB, Goffe B, Veith J. Safety of etanercept in an integrated multi-study database of patients with psoriasis. *62nd Annual Meeting American Academy of Dermatology*, 6–11 February 2004. Washington DC. p. 616.

163. Wyeth Pharmaceuticals. *Enbrel and psoriasis: an appraisal submission for the National Institute for Clinical Excellence [industry submission]*. Philadelphia, PA: Wyeth Pharmaceuticals; 2004.

164. Wyeth Research. *Double-blind, placebo-controlled, phase 2 study of Etanercept (ENBREL®) in the treatment of psoriasis: final report: protocol no.: 016.0032 [industry submission]*. Philadelphia, PA: Wyeth Research; 2003.

165. Gaspari A, Gottlieb AB, Kang S, Gordon K, Feng S. Enbrel improves the clinical and pathologic features of psoriasis. *J Invest Dermatol* 2002;**119**:236.

166. Gottlieb AB, Gordon K, Wang A, Zitnik R. Withdrawal from etanercept after successful clinical response in psoriasis patients: disease characteristics and the durability of treatment response. *J Am Acad Dermatol* 2004;**50**(3) (Suppl 1):146.

167. Wyeth Research. *Multicenter dose-ranging study of the safety and efficacy of Enbrol in psoriasis: protocol no. 0881A6 [industry submission]*. Philadelphia, PA: Wyeth Research; 2003.

168. Krenger GC, Lebwohl M, Wang A, Zitnik R. Continuance on etanercept after early incomplete response in patients with psoriasis [industry submission]. *62nd Annual Meeting of American Academy of Dermatology*, 6–11 February, Washington DC; 2004.

169. Wyeth Pharmaceuticals. *Marketing authorisation for enbrel: expert report on the clinical documentation [industry submission]*. Philadelphia, PA: Wyeth Pharmaceuticals; 2001.

170. Wajdula J, Pedersen R, Sanda M. A long-term, open-label trial of the safety and efficacy of etanercept (25 mg twice weekly) in patients with rheumatoid arthritis (interim analysis). *Arthritis Rheum* 2000;**43** (9 Suppl):974.

171. Cohen RD. Efficacy and safety of repeated infliximab infusions for Crohn's disease: 1-year clinical experience. *Inflamm Bowel Dis* 2001; **7** Suppl 1:S17–22.

172. Gottlieb A, Hamilton TK, Caro I, Chastain R, Rundle AC, Gordon KB. Efficacy and safety outcomes of extended efalizumab therapy in patients with moderate to severe chronic plaque psoriasis: an update [web page on the Internet]. New York: American Academy of Dermatology; 2004. URL: http://www.xoma.com/pdf/GNU-04-0335%20SmmrAAD%20Gottleib%20Final.pdf. Accessed 24 August 2004.

173. Rutgeerts P, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, *et al.* Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004;**126**:402–13.

174. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, *et al.* Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000;**343**:1594–602.

175. Wyeth Pharmaceuticals. Enbrel [etanercept: summary of product characteristics] [web page on the Internet]. Electronic Medicines Compendium; 2004. URL: http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=3343. Accessed 15 December 2001.

176. Arthritis Advisory Committee. Etanercept (ENBREL) and congestive heart failure. Rockville, MD: US Food and Drug Administration; 2003. URL: http://www.fda.gov/ohrms/dockets/ac/03/briefing/3930B1_01_D-Immunex.Briefing.pdf. Accessed 7 October 2004.

177. Aletaha D, Smolen JS. The rheumatoid arthritis patient in the clinic: comparing more than 1,300 consecutive DMARD courses. *Rheumatology* 2002; **41**:1367–74.

178. Crnkic M, Petersson IF, Saxne T, Geborek P. Infiximab, etanercept and leflunomide in rheumatoid arthritis. Clinical experience in southern Sweden. *Rheumatology* 2001;**40** (Suppl): 82.

179. Mease PJ, Ruderman EM, Kivitz A, Burch FX, Siegel EL, Cohen SB, *et al.* Continued efficacy and safety of etanercept (ENBRELR) in patients with psoriatic arthritis and psoriasis. *American College of Rheumatology Annual Meeting* 2003; Abstract 343.

180. Antoni C, Dechant C, Lorenz P-M, Wendler J, Ogilvie A, Lueftl M, *et al.* Open-label study of infliximab treatment for psoriatic arthritis: clinical and magnetic resonance imaging measurements of reduction of inflammation. *Arthritis Care Res* 2002;**47**:506–12.

181. Feletar M, Brockbank JE, Schentag CT, *et al*. Treatment of refractory psoriatic arthritis with influximab: a 12 month observational study of 16 patients. *Ann Rheum Dis* 2004;**63**:156–61.

182. Mease PJ, Ruderman EM, Ritchlin C, Ory P, Tsuji W. Etanercept in psoriatic arthritis: sustained improvement in joint and skin disease and inhibition of radiographic progression at 2 years [conference abstract]. In *Annual European Congress of Rheumatology, 2004*; Berlin: European League Against Rheumatism; 2004. p. OP0136. URL: http://www.eular.org/. Accessed 30 May 2006.

183. Settas L, Sfetsios T, Theodoridou A, Triantafyllidou E, Mamali C. Infliximab (Remicade) in the treatment of psoriatic arthritis and psoriasis: results of a one year open clinical study. *Rev Clin Pharmacol Pharmacokinet Int Ed* 2004;**18**(Pt1):1–67.

Appendix 1

Literature searches

Clinical effectiveness evidence

Searching for the clinical effectiveness component of this review was addressed by several separate searches to identify:

- reports of RCTs of etanercept or infliximab in PsA
- reports of RCTs of comparator treatments in PsA
- reports of RCTs and reports of adverse events for infliximab
- reports of adverse events of comparator treatments.

Separate search strategies were devised for each topic. Full details of the databases searched and search strategies used are provided below.

Search A: RCTs of etanercept or infliximab in PsA

MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/): 1966–2004 April week 5

This search retrieved 28 references.

1. randomized controlled trial.pt.
2. exp randomized controlled trials/
3. random allocation/
4. double blind method/
5. single blind method/
6. clinical trial.pt.
7. exp clinical trials/
8. controlled clinical trials/
9. clin$ trial$.ti,ab.
10. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).ti,ab.
11. placebo$.ti,ab.
12. placebos/
13. random$.ti,ab.
14. exp evaluation studies/
15. follow up studies/
16. exp research design/
17. prospective studies/
18. (control$ or prospectiv$ or volunteer$).ti,ab.
19. or/1-18
20. animals/
21. human/
22. 20 not (20 and 21)
23. 19 not 22
24. Arthritis, Psoriatic/
25. (psoria$ adj2 (arthrit$ or arthropath$)).mp.
26. or/24-25
27. (etanercept or enbrel).mp.
28. (infliximab or remicade).mp.
29. or/27-28
30. 23 and 26 and 29

EMBASE (OVID Online – http://www.ovid.com/): 1980–2004 week 19

This search retrieved 48 references.

1. randomized controlled trial/
2. randomization/
3. double blind procedure/ or single blind procedure/
4. exp clinical trial/
5. controlled study/
6. clin$ trial$.ti,ab.
7. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).ti,ab.
8. placebo$.ti,ab.
9. Placebo/
10. random$.ti,ab.
11. evaluation/
12. follow up/
13. exp methodology/
14. prospective study/
15. (control$ or prospectiv$ or volunteer$).ti,ab.
16. or/1-15
17. (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
18. exp ANIMAL/
19. Animal Experiment/
20. Nonhuman/
21. Human/
22. Human Experiment/
23. or/17-20
24. 21 or 22
25. 23 not (23 and 24)
26. 16 not 25
27. Psoriatic Arthritis/
28. (psoria$ adj2 (arthrit$ or arthropath$)).mp.
29. 27 or 28
30. Etanercept/
31. (etanercept or enbrel).mp.
32. Infliximab/
33. (infliximab or remicade).mp.
34. or/30-33
35. 26 and 29 and 34

National Research Register (NRR) (CD-ROM): 2004 Issue 1
This search retrieved two references.

#1 ARTHRITIS-PSORIATIC single term (MeSH)
#2 (PSORIA* next ARTHRIT*)
#3 (PSORIA* next ARTHROPATH*)
#4 ((#1 or #2) or #3)
#5 (ETANERCEPT or ENBREL)
#6 (INFLIXIMAB or REMICADE)
#7 (#5 or #6)
#8 (#4 and #7)

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm): 2004 Issue 2
This search retrieved two references.

#1 (psoria* next arthrit*)
#2 (psoria* next arthropath*)
#3 ARTHRITIS PSORIATIC single term (MeSH)
#4 (#1 or #2 or #3)
#5 (etanercept or enbrel)
#6 (infliximab or remicade)
#7 (#5 or #6)
#8 (#4 and #7)

ISI Science and Technology Proceedings (Web of Knowledge): 1990–2004 (15 May update)
Social Science Citation Index and Science Citation Index (Web of Science – http://wos.mimas.ac.uk/): 1981–2004 (16 May update)
The same strategy was used in both instances. The search of ISI Science and Technology Proceedings retrieved one reference and that of Social Science Citation Index and Science Citation Index retrieved 48 references.

1. TS=(((study or studies) SAME design*))
2. TS=(((singl* or doubl* or trebl* or tripl*) SAME (blind* or mask*)))
3. TS=(((clinic* same trial*) or placebo* or random* or (control* or prospectiv* or volunteer*)))
4. #1 or #2 or #3
5. TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*)
6. #4 not #5
7. TS=((PSORIA* same ARTHRIT*) or (PSORIA* same ARTHROPATH*))
8. TS=(ETANERCEPT or ENBREL or INFLIXIMAB or REMICADE)
9. #6 and #7 and #8

All databases were searched from inception date.

Search B: RCTs of comparator treatments in PsA

MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/): 1966–2004/May week 2
This search retrieved 247 references.

1 randomized controlled trial.pt.
2 exp Randomized Controlled Trials/
3 random allocation/
4 double blind method/
5 single blind method/
6 clinical trial.pt.
7 exp clinical trials/
8 controlled clinical trials/
9 clin$ trial$.ti,ab.
10 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).ti,ab.
11 placebo$.ti,ab.
12 placebos/
13 random$.ti,ab.
14 exp evaluation studies/
15 follow up studies/
16 exp research design/
17 prospective studies/
18 (control$ or prospectiv$ or volunteer$).ti,ab.
19 or/1-18
20 animal/
21 human/
22 20 not (20 and 21)
23 19 not 22
24 Arthritis, Psoriatic/
25 (psoria$ adj2 (arthrit$ or arthropath$)).mp.
26 or/24-25
27 sulphasalazine.mp.
28 Sulfasalazine.mp.
29 SULFASALAZINE/
30 Methotrexate.mp.
31 Methotrexate/
32 mtx.mp.
33 Ciclosporin$.mp.
34 Cyclosporin$.mp.
35 Cyclosporine.mp.
36 neoral.mp.
37 Csa.mp.
38 Cya.mp.
39 Cyc-a.mp.
40 Sandimmum.mp.
41 exp CYCLOSPORINS/
42 Auranofin.mp.
43 AURANOFIN/
44 Intramuscular$ gold.mp.
45 Intra muscular$ gold.mp.
46 Intra-muscular$ gold.mp.
47 Imi gold.mp.
48 (inject$ adj2 gold).mp.

49 Im gold.mp.
50 Gold preparation$.mp.
51 Gold salt$.mp.
52 (Peroral$ adj2 gold).mp.
53 (Parenterally adj2 gold).mp.
54 (Intramuscular$ administration$ adj2 gold).mp.
55 (Intra muscular$ administration$ adj2 gold).mp.
56 (Intra-muscular$ administration$ adj2 gold).mp.
57 INJECTIONS INTRAMUSCULAR/
58 GOLD/
59 57 and 58
60 Azathioprine.mp.
61 AZATHIOPRINE/
62 aza.mp.
63 Penicillamine.mp.
64 PENICILLAMINE/
65 d-Penicillamine.mp.
66 d Penicillamine.mp.
67 "Enkephalin, D-Penicillamine (2,5)-"/
68 dpa.mp.
69 Leflunomide.mp.
70 Hydroxychloroquine.mp.
71 HYDROXYCHLOROQUINE/
72 Hcq.mp.
73 hxchl.mp.
74 Salazopyrin.mp.
75 (Salicylazosulphapyridine or Salicylazosulfapyridine).mp.
76 sasp.mp.
77 placebo$.mp.
78 PLACEBOS/
79 or/27-56,59-78
80 23 and 26 and 79

EMBASE (OVID Online – http://www.ovid.com/): 1980–2004 week 22

This search retrieved 258 references.

1. randomized controlled trial/
2. randomization/
3. double blind procedure/ or single blind procedure/
4. exp clinical trial/
5. controlled study/
6. clin$ trial$.ti,ab.
7. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).ti,ab.
8. placebo$.ti,ab.
9. Placebo/
10. random$.ti,ab.
11. evaluation/
12. follow up/
13. exp methodology/
14. prospective study/
15. (control$ or prospectiv$ or volunteer$).ti,ab.
16. or/1-15
17. (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
18. exp ANIMAL/
19. Animal Experiment/
20. Nonhuman/
21. Human/
22. Human Experiment/
23. or/17-20
24. 21 or 22
25. 23 not (23 and 24)
26. 16 not 25
27. Psoriatic Arthritis/
28. (psoria$ adj2 (arthrit$ or arthropath$)).mp.
29. 27 or 28
30. Salazosulfapyridine/
31. Methotrexate/
32. cyclosporin/ or cyclosporin a/ or cyclosporin a derivative/
33. Auranofin/
34. Gold/im
35. gold/
36. intramuscular drug administration/
37. 35 and 36
38. azathioprine/ or azathioprine derivative/
39. Penicillamine/
40. Leflunomide/
41. hydroxychloroquine/ or hydroxychloroquine sulfate/
42. Placebo/
43. salicylazosulphapyridine.mp.
44. salicylazosulfapyridine.mp.
45. (sulphasalzine or sulfasalzine or salazopyrin or sasp).mp.
46. (methotrexate or mtx).mp.
47. (cyclosporin$ or ciclosporin$ or neoral or csa or cya or cyc-a).mp.
48. sandimmun$.mp.
49. auranofin.mp.
50. intramuscular$ gold.mp.
51. intra muscular$ gold.mp.
52. imi gold.mp.
53. (inject$ adj2 gold).mp.
54. im gold.mp.
55. (gold preparation$ or gold salt$).mp.
56. (peroral$ adj2 gold).mp.
57. (parenteral$ adj2 gold).mp.
58. (intramuscular$ administ$ adj2 gold).mp.
59. (intra muscular$ administ$ adj2 gold).mp.
60. azathioprine.mp.
61. aza.mp.
62. (penicillamine or d-penicillamine).mp.
63. dpa.mp.
64. hydroxychloroquine.mp.

65. hcq.mp.
66. hxchl.mp.
67. placebo$.mp.
68. or/30-34,37-67
69. 26 and 29 and 68
70. limit 69 to yr=1999–2004

National Research Register (NRR) (CD-ROM): 2004 Issue 1
This search retrieved 14 references.

1. (RANDOM* next (CONTROLLED next TRIAL*))
2. RCT*
3. RANDOMIZED-CONTROLLED-TRIALS single term (MeSH)
4. RANDOM-ALLOCATION single term (MeSH)
5. DOUBLE-BLIND-METHOD single term (MeSH)
6. SINGLE-BLIND-METHOD single term (MeSH)
7. (CLIN* next TRIAL*)
8. CLINICAL-TRIALS* single term (MeSH)
9. CONTROLLED-CLINICAL-TRIALS single term (MeSH)
10. (SINGL* near BLIND*)
11. (SINGL* near MASK*)
12. (DOUBL* near BLIND*)
13. (DOUBL* near MASK*)
14. (TREBL* near BLIND*)
15. (TREBL* near MASK*)
16. (TRIPL* near BLIND*)
17. (TRIPL* near MASK*)
18. PLACEBO*
19. PLACEBOS single term (MeSH)
20. RANDOM*
21. EVALUATION-STUDIES single term (MeSH)
22. FOLLOW-UP-STUDIES single term (MeSH)
23. RESEARCH-DESIGN explode all trees (MeSH)
24. PROSPECTIVE-STUDIES single term (MeSH)
25. ((CONTROL* or PROSPECTIV*) or VOLUNTEER*)
26. ((((((((((((((((((((((((#1 or #2) or #3) or #4) or #5) or #6) or #7) or #8) or #9) or #10) or #11) or #12) or #13) or #14) or #15) or #16) or #17) or #18) or #19) or #20) or #21) or #22) or #23) or #24) or #25)
27. ARTHRITIS-PSORIATIC single term (MeSH)
28. (PSORIA* near ARTHRIT*)
29. (PSORIA* near ARTHROPATH*)
30. ((#27 or #28) or #29)
31. SULPHASALAZINE
32. SULFASALAZINE
33. SULFASALAZINE single term (MeSH)
34. METHOTREXATE
35. METHOTREXATE single term (MeSH)
36. MTX
37. CICLOSPORIN*
38. CYCLOSPORIN*
39. NEORAL
40. CSA
41. CYA
42. CYC
43. SANDIMMUM
44. CYCLOSPORINS explode all trees (MeSH)
45. AURANOFIN
46. AURANOFIN single term (MeSH)
47. (INTRAMUSCULAR* near GOLD)
48. (INTRA next (MUSCULAR* next GOLD))
49. (IMI next GOLD)
50. (INJECT* near GOLD)
51. (IM next GOLD)
52. (GOLD next PREPARATION*)
53. (GOLD next SALT*)
54. (PERORAL* near GOLD)
55. (PARENTERALLY near GOLD)
56. INJECTIONS-INTRAMUSCULAR single term (MeSH)
57. GOLD single term (MeSH)
58. (#56 and #57)
59. AZATHIOPRINE
60. AZATHIOPRINE single term (MeSH)
61. AZA
62. PENICILLAMINE
63. PENICILLAMINE single term (MeSH)
64. ((DPA or LEFLUNOMIDE) or HYDROXYCHLOROQUINE)
65. HYDROXYCHLOROQUINE single term (MeSH)
66. ((((HCQ or HXCHL) or SALAZOPYRIN) or SALICYLAZOSLPHAPYRIDINE) or SASP)
67. PLACEBO*
68. PLACEBOS single term (MeSH)
69. (((((((((#31 or #32) or #33) or #34) or #35) or #36) or #37) or #38) or #39) or #40)
70. (((((((((#41 or #42) or #43) or #44) or #45) or #46) or #47) or #48) or #49) or #50)
71. ((((((#51 or #52) or #53) or #54) or #55) or #58) or #60)
72. (((((((#61 or #62) or #63) or #64) or #65) or #66) or #67) or #68)
73. (((#69 or #70) or #71) or #72)
74. ((#26 and #30) and #73)

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm): 2004 Issue 2
This search retrieved 50 references.

#1 (random* next controlled next trial*) or rct*

#2 RANDOMIZED CONTROLLED TRIALS
#3 RANDOM ALLOCATION
#4 DOUBLE-BLIND METHOD
#5 SINGLE-BLIND METHOD
#6 (clin* next trial*)
#7 CLINICAL TRIALS
#8 CONTROLLED CLINICAL TRIALS
#9 (singl* near blind*)
#10 (singl* near mask*)
#11 (doubl* near blind*)
#12 (doubl* near mask*)
#13 (trebl* near blind*)
#14 (trebl* near mask*)
#15 (tripl* near blind*)
#16 (tripl* near mask*)
#17 placebo*
#18 PLACEBOS
#19 random*
#20 EVALUATION STUDIES
#21 FOLLOW-UP STUDIES
#22 RESEARCH DESIGN
#23 PROSPECTIVE STUDIES
#24 (control* or prospectiv* or volunteer*)
#25 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or # or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 #24)
#26 ARTHRITIS PSORIATIC
#27 (psoria* near arthrit*)
#28 (psoria* near arthropath*)
#29 (#26 or #27 or #28)
#30 sulphasalazine
#31 sulfasalazine
#32 SULFASALAZINE
#33 methotrexate
#34 METHOTREXATE
#35 mtx
#36 ciclosporin*
#37 cyclosporin*
#38 neoral
#39 csa
#40 cya
#41 cyc
#42 sandimmum
#43 CYCLOSPORINS
#44 auranofin
#45 AURANOFIN
#46 (intramuscular* next gold)
#47 (intra next muscular* next gold)
#48 (imi next gold)
#49 (inject* near gold)
#50 (im next gold)
#51 (gold next preparation*)
#52 (gold next salt*)
#53 (peroral* near gold)
#54 (parenterally near gold)
#55 ((intramuscular* next administration*) near gold)
#56 ((intra next muscular* next administration*) near gold)
#57 INJECTIONS INTRAMUSCULAR
#58 GOLD
#59 (#57 and #58)
#60 azathioprine
#61 AZATHIOPRINE
#62 aza
#63 penicillamine
#64 PENICILLAMINE
#65 (d next penicillamine)
#66 ENKEPHALIN D-PENICILLAMINE (25)-
#67 dpa
#68 leflunomide
#69 hydroxychloroquine
#70 HYDROXYCHLOROQUINE
#71 hcq
#72 hxchl
#73 salazopyrin
#74 salicylazosulphapyridine or salicylazosulfapyridine
#75 sasp
#76 placebo*
#77 PLACEBOS
#78 (#30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77)
#79 (#25 and #29 and #78)

CenterWatch (Internet – http://www.centerwatch.com/): searched 4 May 2004

This search retrieved 32 references.

"psoriatic arthritis" OR "psoriatic arthopathy"

Current Controlled Trials (Internet – http://www.controlled-trials.com/): searched 4 May 2004

This search retrieved 29 references.

"psoriatic arthritis" OR "psoriatic arthopathy"

ClinicalTrials.gov (Internet – http://clinicaltrials.gov/): searched 4 May 2004

This search retrieved six references.

psoriatic arthritis OR psoriatic arthopathy

ISI Science and Technology Proceedings (Web of Knowledge): 1990–2004, searched 31 May 2004
Social Science Citation Index and Science Citation Index (Web of Science – http://wos.mimas.ac.uk/): 1981–2004, searched 31 May 2004
The same strategy was used in both instances. The search of ISI Science and Technology Proceedings retrieved six references and that of Social Science Citation Index and Science Citation Index retrieved 17 references.

1 TS=rct* or ramdon* control* trial*
2 TS=clin* trial*
3 TS=singl* same blind*
4 TS=singl* same mask*
5 TS=doubl* same blind*
6 TS=doubl* same mask*
7 TS=trebl* same blind*
8 TS=trebl* same mask*
9 TS=tripl* same blind*
10 TS=tripl* same mask*
11 TS=placebo*
12 TS=random*
13 TS=control* or prospectiv* or volunteer*
14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
15 TS=psoria* same arthrit*
16 TS=psoria* same arthropath*
17 #15 or #16 or #17
18 TS=sulphasalazine
19 TS=sulfasalazine
20 TS=methotrexate
21 TS=mtx
22 TS=ciclosporin*
23 TS=cyclosporin*
24 TS=neoral
25 TS=csa
26 TS=cya
27 TS=cyc
28 TS=sandimmum
29 TS=auranofin
30 TS=intramuscular* gold
31 TS=intra muscular* gold
32 TS=imi gold
33 TS=inject* same gold
34 TS=im gold
35 TS=gold preparation*
36 TS=gold salt*
37 TS=peroral* same gold
38 TS=parenterally same gold
39 TS=(intramuscular* administration*) same gold
40 TS=(intra muscular* administration*) same gold
41 TS=azathioprine
42 TS=aza
43 TS=penicillamine
44 TS=d penicillamine
45 TS=dpa
46 TS=leflunomide
47 TS=hydroxychloroquine
48 TS=hcq
49 TS=hxchl
50 TS=salazopyrin
51 TS=salicylazosulphapyridine
52 TS=salicylazosulfapyridine
53 TS=sasp
54 TS=placebo*
55 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54
56 (#14 and #17 and #55)

Search C: RCTs and reports of adverse events for infliximab

MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/): 1966–2004/April week 4
This search retrieved 442 references.

1. hypertension/ci or Infection/ci or Immunocompromised Host/ or Immunosuppressive Agents/ae
2. hypotension/ci
3. Cholecystitis/ci
4. GASTROINTESTINAL HEMORRHAGE/ci
5. DYSPNEA/ci
6. Demyelinating Diseases/ci
7. Seizures/ci
8. (hypertens$ or hyper tens$ or hypo tens$ or hypotens$).mp.
9. (oesophagitis or esophagitis or infection$ or immunocompromise$ or immuno compromise$ or immunosuppress$ or immuno suppress$).mp.
10. (cholecystitis or dyspn?ea).mp.
11. ((gastrointestinal or gastro intestinal) adj1 (haemorrhage$ or hemorrhage$)).mp.
12. (demyelinat$ adj1 (disorder$ or syndrome$ or disease$ or condition$)).mp.
13. seizure$.mp.
14. Chest Pain/ci
15. Urticaria/ci
16. Serum Sickness/ci
17. ANAPHYLAXIS/ci
18. DYSPEPSIA/ci
19. Diarrhea/ci
20. Constipation/ci
21. Hepatitis/

22. Diverticulitis/ci
23. Flushing/ci
24. Bradycardia/ci
25. Arrhythmia/ci
26. Sweating/ci
27. Syncope/ci
28. Ecchymosis/ci
29. Hematoma/ci
30. LUNG DISEASES, INTERSTITIAL/ci
31. Fibrosis/ci
32. Fatigue/ci
33. Anxiety/ci
34. Dizziness/ci
35. "Sleep Initiation and Maintenance Disorders"/ci
36. Confusion/ci
37. Amnesia/ci
38. Vaginitis/ci
39. Arthralgia/ci
40. Exanthema/ci
41. Alopecia/ci
42. Skin Pigmentation/de
43. (chest pain$ or urticaria or serum sickness or angiodema or anaphyla$ or hyspep$ or diarrhoea$ or diarrhea$).mp.
44. (constipat$ or hepatitis or flush or flushes or flushing or flushed or bradycardi$).mp.
45. (diverticulitis or diverticulitus or arrhythmia$ or palpitat$ or sweat$ or syncope$ or vasospasm$ or ecchymosis).mp.
46. (peripheral ischemia$ or peripheral ischaemia$).mp.
47. (haematoma$ or hematoma$ or fatigue$ or tired$ or anxiety or anxious or drowsiness or drowsy or dizziness or dizzy).mp.
48. (interstitial pneumonitis or interstitial fibrosis).mp.
49. (insomnia$ or sleepless$ or confusion or confused or agitation or agitated or amnesia$ or forgetful$ or vaginitis or myalgia or arthralgia or polyarthralgia or alopecia or hair loss or bald$).mp.
50. endophthalmia.mp.
51. (rash or rashes or exathema or examthemic or hyper-keratosis or hyperkeratosis or skin pigmentation).mp.
52. Adverse Drug Reaction Reporting Systems/
53. drug eruptions/ or erythema nodosum/
54. Drug Hypersensitivity/
55. Drug Toxicity/
56. treatment emergent.tw.
57. (safe or safety).ti,ab.
58. (tolerability or toxicity or adrs or harm$).ti,ab.
59. (hypersensiti$ or hyper sensiti$).ti,ab.
60. (undesir$ adj2 (outcome$ or event$ or reaction$ or effect or effects)).ti,ab.
61. (side effects or side effect).tw.
62. (adverse adj2 (event$ or effect or effects or outcome$ or reaction$)).ti,ab.
63. (po or ae or de or co or to).fs.
64. Fever/ci
65. Nausea/ci
66. Abnormalities, Drug-Induced/
67. (fever or temperature or nausea or nauseous).ti,ab.
68. muscl$ pain.ti,ab.
69. randomized controlled trial.pt.
70. exp randomized controlled trials/
71. random allocation/
72. double blind method/
73. single blind method/
74. clinical trial.pt.
75. exp clinical trials/
76. controlled clinical trials/
77. clin$ trial$.ti,ab.
78. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).ti,ab.
79. placebo$.ti,ab.
80. placebos/
81. random$.ti,ab.
82. exp evaluation studies/
83. follow up studies/
84. exp research design/
85. prospective studies/
86. (control$ or prospectiv$ or volunteer$).ti,ab.
87. or/69-86
88. animals/
89. human/
90. 88 not (88 and 89)
91. (infliximab or remicade).mp.
92. or/1-68
93. 92 and 87
94. 93 not 90
95. 94 and 91

EMBASE (OVID Online – http://www.ovid.com/): 1980–2004 week 20

This search retrieved 1287 references.

1. (hypertens$ or hyper tens$ or hypo tens$ or hypotens$).mp.
2. (oesophagitis or esophagitis or infection$ or immunocompromise$ or immuno compromise$ or immunosuppress$ or immuno suppress$).mp.
3. (cholecystitis or dyspn?ea).mp.
4. ((gastrointestinal or gastro intestinal) adj1 (haemorrhage$ or hemorrhage$)).mp.
5. (demyelinat$ adj1 (disorder$ or syndrome$ or disease$ or condition$)).mp.
6. seizure$.mp.
7. (chest pain$ or urticaria or serum sickness or angiodema or anaphyla$ or hyspep$ or diarrhoea$ or diarrhea$).mp.

8. (constipat$ or hepatitis or flush or flushes or flushing or flushed or bradycardi$).mp.
9. (diverticulitis or diverticulitus or arrhythmia$ or palpitat$ or sweat$ or syncope$ or vasospasm$ or ecchymosis).mp.
10. (peripheral ischemia$ or peripheral ischaemia$).mp.
11. (haematoma$ or hematoma$ or fatigue$ or tired$ or anxiety or anxious or drowsiness or drowsy or dizziness or dizzy).mp.
12. (interstitial pneumonitis or interstitial fibrosis).mp.
13. (insomnia$ or sleepless$ or confusion or confused or agitation or agitated or amnesia$ or forgetful$ or vaginitis or myalgia or arthralgia or polyarthralgia or alopecia or hair loss or bald$).mp.
14. endophthalmia.mp.
15. (rash or rashes or exathema or examthemic or hyper-keratosis or hyperkeratosis or skin pigmentation).mp.
16. treatment emergent.tw.
17. (safe or safety).ti,ab.
18. (tolerability or toxicity or adrs or harm$).ti,ab.
19. (hypersensiti$ or hyper sensiti$).ti,ab.
20. (undesir$ adj2 (outcome$ or event$ or reaction$ or effect or effects)).ti,ab.
21. (side effects or side effect).tw.
22. (adverse adj2 (event$ or effect or effects or outcome$ or reaction$)).ti,ab.
23. (fever or temperature or nausea or nauseous).ti,ab.
24. muscl$ pain.ti,ab.
25. drug surveillance program/
26. exp Drug Toxicity/
27. drug safety/ or drug tolerability/
28. treatment emergent.tw.
29. (si or it or ae or to or po).fs.
30. injection/
31. injection site/
32. Erythema Nodosum/si
33. Pruritus/si
34. Skin Tingling/si
35. Pain/si
36. Fever/si
37. Nausea/si
38. vomiting/si
39. Infection/si
40. Abdominal Pain/si
41. Immune Deficiency/si
42. Immunosuppressive Agent/ae, it, to
43. Hypotension/si
44. hypertension/si
45. Cholecystitis/si
46. Gastrointestinal Hemorrhage/si
47. Upper Gastrointestinal Bleeding/si
48. Dyspnea/si
49. Demyelinating Disease/si
50. Seizure/si
51. Esophagitis/si
52. Thorax Pain/si
53. Urticaria/si
54. Serum Sickness/si
55. Anaphylaxis/si
56. Dyspepsia/si
57. Diarrhea/si
58. Constipation/si
59. Hepatitis/si
60. Diverticulitis/si
61. flushing/
62. Bradycardia/si
63. Heart Arrhythmia/si
64. sweating/
65. Syncope/si
66. Ecchymosis/si
67. Hematoma/si
68. INTERSTITIAL LUNG DISEASE/si
69. FIBROSING ALVEOLITIS/si
70. Fibrosis/si
71. Fatigue/si
72. anxiety/
73. Vertigo/si
74. Insomnia/si
75. Confusion/si
76. Amnesia/si
77. Vaginitis/si
78. Arthralgia/si
79. Rash/si
80. Alopecia/si
81. skin pigmentation/
82. Heart Palpitation/si
83. Vasospasm/si
84. Hyperkeratosis/si
85. or/1-84
86. randomized controlled trial/
87. randomization/
88. double blind procedure/ or single blind procedure/
89. exp clinical trial/
90. controlled study/
91. clin$ trial$.ti,ab.
92. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).ti,ab.
93. placebo$.ti,ab.
94. Placebo/
95. random$.ti,ab.
96. evaluation/
97. follow up/
98. exp methodology/
99. prospective study/
100. (control$ or prospectiv$ or volunteer$).ti,ab.
101. or/86-100

102. (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
103. exp ANIMAL/
104. Animal Experiment/
105. Nonhuman/
106. Human/
107. Human Experiment/
108. or/102-105
109. 106 or 107
110. 108 not (108 and 109)
111. 101 not 110
112. 85 and 111
113. Infliximab/
114. (infliximab or remicade).mp.
115. 113 or 114
116. 112 and 115

National Research Register (NRR) (CD-ROM): 2004 Issue 1

This search retrieved 50 references.

#1 INFLIXIMAB or REMICADE

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm): 2004 Issue 2

#1 ADVERSE DRUG REACTION REPORTING SYSTEMS single term (MeSH)
#2 DRUG ERUPTIONS single term (MeSH)
#3 ERYTHEMA NODOSUM single term (MeSH)
#4 DRUG HYPERSENSITIVITY single term (MeSH)
#5 DRUG TOXICITY single term (MeSH)
#6 (treatment next emergent)
#7 (safe or safety)
#8 (tolerability or toxicity or adrs or harm*)
#9 (hypersensiti* or (hyper next sensiti*))
#10 ((undesir* next outcome*) or (undesir* next event*) or (undesir* next reaction*) or (undesir* next effect) or (undesir* next effects))
#11 ((side next effects) or (side next effect))
#12 ((adverse next event*) or (adverse next effect) or (adverse next effects) or (adverse next outcome*) or (adverse next reaction*))
#13 FEVER {ci} single term (MeSH)
#14 NAUSEA {ci} single term (MeSH)
#15 INFECTION {ci} single term (MeSH)
#16 IMMUNOCOMPROMISED HOST single term (MeSH)
#17 IMMUNOSUPPRESSIVE AGENTS {ae} single term (MeSH)
#18 ABNORMALITIES DRUG-INDUCED single term (MeSH)
#19 ((site next reaction*) or (injection* next reaction*) or erythema or itching or pain or swelling or swollen or swelled)
#20 (fever or temperature or nausea or nauseous)
#21 (myalgia or (muscle* next pain) or infection* or immunocompromise* or (immuno next compromise*))
#22 (immunosuppress* or (immuno next suppress*))
#23 HYPERTENSION {ci} single term (MeSH)
#24 HYPOTENSION {ci} single term (MeSH)
#25 CHOLECYSTITIS {ci} single term (MeSH)
#26 GASTROINTESTINAL HEMORRHAGE {ci} single term (MeSH)
#27 DYSPNEA {ci} single term (MeSH)
#28 DEMYELINATING DISEASES {ci} single term (MeSH)
#29 SEIZURES {ci} single term (MeSH)
#30 CHEST PAIN {ci} single term (MeSH)
#31 URTICARIA {ci} single term (MeSH)
#32 SERUM SICKNESS {ci} single term (MeSH)
#33 ANAPHYLAXIS {ci} single term (MeSH)
#34 DYSPEPSIA {ci} single term (MeSH)
#35 DIARRHEA {ci} single term (MeSH)
#36 CONSTIPATION {ci} single term (MeSH)
#37 HEPATITIS single term (MeSH)
#38 DIVERTICULITIS {ci} single term (MeSH)
#39 FLUSHING {ci} single term (MeSH)
#40 BRADYCARDIA {ci} single term (MeSH)
#41 ARRHYTHMIA {ci} single term (MeSH)
#42 SWEATING {ci} single term (MeSH)
#43 SYNCOPE {ci} single term (MeSH)
#44 ECCHYMOSIS {ci} single term (MeSH)
#45 HEMATOMA {ci} single term (MeSH)
#46 LUNG DISEASES INTERSTITIAL {ci} single term (MeSH)
#47 FIBROSIS {ci} single term (MeSH)
#48 FATIGUE {ci} single term (MeSH)
#49 ANXIETY {ci} single term (MeSH)
#50 DIZZINESS {ci} single term (MeSH)
#51 SLEEP INITIATION AND MAINTENANCE DISORDERS {ci} single term (MeSH)
#52 CONFUSION {ci} single term (MeSH)
#53 AMNESIA {ci} single term (MeSH)
#54 VAGINITIS {ci} single term (MeSH)
#55 ARTHRALGIA {ci} single term (MeSH)
#56 EXANTHEMA {ci} single term (MeSH)
#57 ALOPECIA {ci} single term (MeSH)
#58 SKIN PIGMENTATION {de} single term (MeSH)
#59 (hypertens* or (hyper next tens*) or (hypo next tens*) or hypotens*)

#60 (oesophagitis or esophagitis or infection* or seizure* or cholecystitis or dyspnea or dyspnoea)
#61 ((gastrointestinal next haemorr*) or (gastrointestinal next hemorr*) or (gastro next intestinal next haemorr*) or (gastro next intestinal next hemorr*))
#62 ((demyelinat* next disorder*) or (demyelinat* next syndrome*) or (demyelinat* next disease*) or (demyelinat* next condition*))
#63 ((chest next pain*) or urticaria or (serum next sickness) or angiodema or anaphyla* or hyspep* or diarrhoea* or diarrhea*)
#64 (constipat* or hepatitis or flush or flushes or flushing or flushed or bradycardi*)
#65 (diverticulitis or diverticulitus or arrhythmia* or palpitat* or sweat* or syncope* or vasospasm* or ecchymosis)
#66 ((peripheral next ischemia*) or (peripheral next ischaemia*))
#67 (haematoma* or hematoma* or fatigue* or tired* or anxiety or anxious or drowsiness or drowsy or dizziness or dizzy)
#68 ((interstitial next pneumonitis) or (interstitial next fibrosis))
#69 (insomnia* or sleepless* or confusion or confused or agitation or agitated or amnesia*)
#70 (forgetful* or vaginitis or myalgia or arthralgia or polyarthralgia or alopecia or (hair next loss) or bald*)
#71 endophthalmia
#72 (rash or rashes or exathema or examthemic or hyper-keratosis or hyperkeratosis or (skin next pigmentation))
#73 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)
#74 (#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40)
#75 (#41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60)
#76 (#61 or #62 or #63 or #64 or #65 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75)
#77 (infliximab or remicade)
#78 (#76 and #77)

CenterWatch (Internet – http://www.centerwatch.com/): searched 24 May 2004

This search retrieved 103 references.

Infliximab OR remicade

Current Controlled Trials (Internet – http://www.controlled-trials.com/): searched 24 May 2004

This search retrieved 27 references.

Infliximab OR remicade

ClinicalTrials.gov (Internet – http://clinicaltrials.gov/): searched 24 May 2004

This search retrieved 12 references.

Infliximab OR remicade {all-fields}

ISI Science and Technology Proceedings (Web of Knowledge): 1990–2004 (15 May update) Social Science Citation Index and Science Citation Index (Web of Science – http://wos.mimas.ac.uk/): 1981–2004 (24 May update)

The same strategy was used in both instances. The search of ISI Science and Technology Proceedings retrieved seven references and that of Social Science Citation Index and Science Citation Index retrieved 22 references.

#1 TS=(((study or studies) SAME design*))
#2 TS=(((singl* or doubl* or trebl* or tripl*) SAME (blind* or mask*)))
#3 TS=(((clinic* same trial*) or placebo* or random* or (control* or prospectiv* or volunteer*)))
#4 #1 or #2 or #3
#5 TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*)
#6 #4 not #5
#7 TS=(hypertens* or (hyper SAME tens*) or (hypo SAME tens*) or hypotens*)
#8 TS=(oesophagitis or esophagitis or infection* or seizure* or cholecystitis or dyspnea or dyspnoea)
#9 TS=((gastrointestinal SAME haemorr*) or (gastrointestinal SAME hemorr*) or (gastro SAME intestinal SAME haemorr*) or (gastro SAME intestinal SAME hemorr*))
#10 TS=((demyelinat* SAME disorder*) or (demyelinat* SAME syndrome*) or #11 (demyelinat* SAME disease*) or (demyelinat* SAME condition*))
#12 TS=((chest SAME pain*) or urticaria or (serum SAME sickness) or angiodema or anaphyla* or hyspep* or diarrhoea* or diarrhea*)
#13 TS=(constipat* or hepatitis or flush or flushes or flushing or flushed or bradycardi*)

#14 TS=(diverticulitis or diverticulitus or arrhythmia* or palpitat* or sweat* or syncope* or vasospasm* or ecchymosis)
#15 TS=((peripheral SAME ischemia*) or (peripheral SAME ischaemia*))
#16 TS=(haematoma* or hematoma* or fatigue* or tired* or anxiety or anxious or drowsiness or drowsy or dizziness or dizzy)
#17 TS=((interstitial SAME pneumonitis) or (interstitial SAME fibrosis))
#18 TS=(insomnia* or sleepless* or confusion or confused or agitation or agitated or amnesia*)
#19 TS=(forgetful* or vaginitis or myalgia or arthralgia or polyarthralgia or alopecia or (hair SAME loss) or bald*)
#20 TS=(endophthalmia or rash or rashes or exathema or examthemic or hyper-keratosis or hyperkeratosis or (skin SAME pigmentation))
#21 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#22 #6 and #20
#23 TS=(infliximab or remicade)
#24 #21 and #22

All databases were searched from inception date.

Search D: reports of adverse events of comparators treatments

The following resources were searched for references to adverse events:

BMJ Publishing Group. *Clinical evidence*. London: BMJ Publishing Group; 2004.

Dukes MNG, Aronson JK, editors. *Meyler's side effects of drugs: an encyclopedia of adverse reactions and interactions*, 14th edn. Oxford: Elsevier; 2000.

British Medical Association. *British National Formulary, No. 47*. London: British Medical Association, 2004. URL: http://bnf.org.

Sweetman SC, editor. *Martindale: the complete drug reference* [CD-ROM]. London: Pharmaceutical Press; 200.

EMC Trust. *Medicines compendium* [CD-ROM]. Alton: Virtual Health Network; Version 3.4, 3rd quarter 2003.

Aronson JK, editor. *Side effects of drugs annual*. Oxford: Elsevier; 2004.

United States Pharmacopeial Convention. USPDI, *Vol. 1: drug information for the health care professional*. Rockville, MD: United States Pharmacopeial Convention; 2004.

Cost-effectiveness evidence

Searching for the cost-effectiveness component of this review addressed several questions:

- to locate economic evaluations of etanercept or infliximab in PsA
- to locate economic evaluations of comparator treatments in PsA
- to locate reports of QoL measures in PsA
- to locate economic models for PsA
- to locate reports of treatment pathways for PsA
- Internet searches to locate guidelines for psoriatic arthritis.

Separate strategies were devised for each topic. Full details of the databases searched and search strategies used are provided below.

Search 1: economic evaluations of etanercept or infliximab in PsA

MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/): 1966–2004/June week 2

This search retrieved eight references.

1. economics/
2. exp "Costs and Cost Analysis"/
3. VALUE OF LIFE/
4. economics, dental/
5. exp economics, hospital/
6. economics, medical/
7. economics, nursing/
8. economics, pharmaceutical/
9. or/1-8
10. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom$).ti,ab.
11. (expenditure$ not energy).ti,ab.
12. (value adj1 money).ti,ab.
13. budget$.ti,ab.
14. or/10-13
15. 9 or 14
16. letter.pt.
17. editorial.pt.
18. historical article.pt.
19. or/16-18
20. 15 not 19
21. animals/
22. human/
23. 21 not (21 and 22)
24. 20 not 23
25. (metabolic adj cost).ti,ab.
26. ((energy or oxygen) adj cost).ti,ab.
27. 24 not (25 or 26)
28. arthritis, psoriatic/
29. (psoria$ adj2 (arthrit$ or arthropath$)).mp.
30. or/28-29
31. (etanercept or enbrel).mp.
32. (infliximab or remicade).mp.
33. or/31-32
34. 27 and 30 and 33

EMBASE (OVID Online – http://www.ovid.com/): 1980–2004 week 25
This search retrieved 93 references.

1. economics/ or exp health economics/
2. cost/ or exp health care cost/
3. exp fee/ or exp health insurance/ or exp pharmacoeconomics/ or health care organization/ or exp health care quality/
4. economic aspect/ or budget.mp.
5. economic aspect/ or budget/
6. exp disease management/
7. or/1-6
8. (econom$ or cost or costs or costly or costing or costed or price or prices or pricing or pharmacoeconom$).tw.
9. (expenditure$ not energy).tw.
10. (value adj5 money).tw.
11. budget$.tw.
12. or/9-11
13. 7 or 12
14. 13 not (editorial or letter or note).pt.
15. exp ANIMAL/ or Animal Experiment/ or Nonhuman/ or (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
16. Human/ or Human Experiment/
17. 15 not (15 and 16)
18. 14 not 17
19. (metabolic adj cost).mp.
20. ((energy or oxygen) adj cost).mp.
21. 18 not (19 or 20)
22. Psoriatic Arthritis/
23. (psoria$ adj2 (arthrit$ or arthropath$)).mp.
24. or/22-23
25. Etanercept/
26. Infliximab/
27. (etanercept or enbrel or infliximab or remicade).mp.
28. or/25-27
29. 21 and 24 and 28

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm): 2004 Issue 2
This search retrieved five references.

#1 ARTHRITIS PSORIATIC single term (MeSH)
#2 (psoria* next arthrit*)
#3 (psoria* next arthropath*)
#4 (#1 or #2 or #3)
#5 (etanercept or enbrel)
#6 (infliximab or remicade)
#7 (#5 or #6)
#8 (#4 and #7)

National Research Register (NRR) (CD-ROM): 2004 Issue 2
This search retrieved three references.

#1 ARTHRITIS PSORIATIC single term (MeSH)
#2 (PSORIA* next ARTHRIT*)
#3 (PSORIA* next ARTHROPATH*)
#4 (#1 or #2 or #3)
#5 (ETANERCEPT or ENBREL)
#6 (INFLIXIMAB or REMICADE)
#7 (#5 or #6)
#8 (#4 and #7)

NHS Economic Evaluation Database (NHS EED) (CRD administration database): 1990–2004/June
This search retrieved no references.

1. s psoria$(w2)arthrit$
2. s psoria$(w2)arthropath$
3. s s1 or s2
4. s sulphasalazine or sulfasalazine or mtx or methotrexate
5. s Ciclosporin$ or cyclosporin$ or neoral or sandimmun$ or cyc(w)a or cya or csa
6. s (Intramuscular$(w)gold) or (Intra(w)muscular$ gold)
7. s (Imi(w)gold) or (Im(w)gold)
8. s (inject$(w)gold)
9. s (Gold(w)preparation$) or (gold(w)salt$)
10. s (Peroral$(w)gold)
11. s (Parenteral$(w)gold)
12. s (Intramuscular$(w)administ$(w)gold)
13. s (Intra(w)muscular$(w)administ$(w)gold)
14. s Auranofin or Azathioprine or aza or Penicillamine or d(w)Penicillamine or dpa
15. s Leflunomide or Hydroxychloroquine or hxchl or hcq
16. s Salazopyrin or Salicylazosulphapyridine or Salicylazosulfapyridine or sasp or placebo$
17. s s4 or s5 or s6 or s7 or s8 or s9 or s10
18. s s11 or s12 or s13 or s14 or s15 or s16 or s17
19. s s3 and s18

Health Economic Evaluation Database (HEED) (CD-ROM): June 2004
This search retrieved no references.

(Psoriatic arthritis) or (psoriatic arthropathy)
AND
etanercept or enbrel or infliximab or remicade

EconLit (SilverPlatter on the web – http:/arc.uk.ovid.com/): 1969–2004/May
This search retrieved no references.

1. (Psoria* adj arthrit*)or(Psoria* adj arthropath*)

2. Etanercept or enbrel or inflixmab or remicade
3. (Etanercept or enbrel or inflixmab or remicade) and ((Psoria* adj arthrit*) or (Psoria* adj arthropath*))

ISI Science and Technology Proceedings (Web of Knowledge): 1990–2004 (25 June update)
Social Science Citation Index and Science Citation Index (Web of Science – http://wos.mimas.ac.uk/): 1981–2004 (27 June update)

The same strategy was used in both instances. The search of ISI Science and Technology Proceedings retrieved no references and that of Social Science Citation Index and Science Citation Index retrieved six references.

#1 TS=((econom* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom* or budget*))
#2 TS=(psoria* SAME arthrit*)
#3 TS=(psoria* SAME arthropath*)
#4 #2 or #3
#5 TS=(etanercept or enbrel or remicade or infliximab)
#6 #1 and #4 and #5
#7 TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*)
#8 #6 not #7

All databases were searched from inception date.

Search 2: economic evaluations of comparator treatments in PsA

MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/): 1996–2004/June week 3

This search retrieved nine references.

1. economics/
2. exp "Costs and Cost Analysis"/
3. VALUE OF LIFE/
4. economics, dental/
5. exp economics, hospital/
6. economics, medical/
7. economics, nursing/
8. economics, pharmaceutical/
9. or/1-8
10. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom$).ti,ab.
11. (expenditure$ not energy).ti,ab.
12. (value adj1 money).ti,ab.
13. budget$.ti,ab.
14. or/10-13
15. 9 or 14
16. letter.pt.
17. editorial.pt.
18. historical article.pt.
19. or/16-18
20. 15 not 19
21. animals/
22. human/
23. 21 not (21 and 22)
24. 20 not 23
25. (metabolic adj cost).ti,ab.
26. ((energy or oxygen) adj cost).ti,ab.
27. 24 not (25 or 26)
28. arthritis, psoriatic/
29. (psoria$ adj2 (arthrit$ or arthropath$)).mp.
30. or/28-29
31. (sulphasalazine or sulfasalazine).mp.
32. SULFASALAZINE/
33. methotrexate/ or (mtx or methotrexate).mp.
34. (Ciclosporin$ or cyclosporin$ or neoral or sandimmun$).mp.
35. exp cyclosporins/ or (cyc-a or cya or csa).mp.
36. Auranofin/ or Auranofin.mp.
37. (Intramuscular$ gold or Intra muscular$ gold).mp.
38. (Imi gold or Im gold).mp.
39. (inject$ adj2 gold).mp.
40. (Gold preparation$ or gold salt$).mp.
41. (Peroral$ adj2 gold).mp.
42. (Parenteral$ adj2 gold).mp.
43. (Intramuscular$ administ$ adj2 gold).mp.
44. (Intra muscular$ administ$ adj2 gold).mp.
45. INJECTIONS INTRAMUSCULAR/
46. GOLD/
47. 45 and 46
48. Azathioprine.mp. or Azathioprine/
49. aza.mp.
50. Penicillamine/ or (Penicillamine or d-Penicillamine).mp.
51. "Enkephalin, D-Penicillamine (2,5)-"/ or dpa.mp.
52. (Leflunomide or Hydroxychloroquine).mp. or HYDROXYCHLOROQUINE/
53. (hxchl or hcq).mp.
54. (Salazopyrin or Salicylazosulphapyridine or Salicylazosulfapyridine or sasp).mp.
55. placebo$.mp. or placebos/
56. or/31-44,47-55
57. 27 and 30 and 56

EMBASE (OVID Online – http://www.ovid.com/): 1980–2004 week 26

This search retrieved 173 references.

1. economics/ or exp health economics/
2. cost/ or exp health care cost/
3. exp fee/ or exp health insurance/ or exp pharmacoeconomics/ or health care organization/ or exp health care quality/

4. economic aspect/ or budget.mp.
5. economic aspect/ or budget/
6. exp disease management/
7. or/1-6
8. (econom$ or cost or costs or costly or costing or costed or price or prices or pricing or pharmacoeconom$).tw.
9. (expenditure$ not energy).tw.
10. (value adj5 money).tw.
11. budget$.tw.
12. or/9-11
13. 7 or 12
14. 13 not (editorial or letter or note).pt.
15. exp ANIMAL/ or Animal Experiment/ or Nonhuman/ or (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
16. Human/ or Human Experiment/
17. 15 not (15 and 16)
18. 14 not 17
19. (metabolic adj cost).mp.
20. ((energy or oxygen) adj cost).mp.
21. 18 not (19 or 20)
22. Psoriatic Arthritis/
23. (psoria$ adj2 (arthrit$ or arthropath$)).mp.
24. or/22-23
25. Salazosulfapyridine/
26. METHOTREXATE/
27. cyclosporin/ or cyclosporin a/ or cyclosporin a derivative/ or "cyclosporin a {8 dextro o (2 hydroxyethyl)serine}"/ or "cyclosporin a {1 (3,8 dihydroxy 2 methylamino 4 methyl 6 octenoic acid)}"/ or "cyclosporin a {4 leucine}"/ or cyclosporin b/ or cyclosporin c/ or cyclosporin d/ or cyclosporin derivative/ or cyclosporin f/ or cyclosporin g/ or cyclosporin h/
28. Auranofin/
29. intramuscular drug administration/
30. Gold/
31. 29 and 30
32. Gold/im
33. Azathioprine/
34. Penicillamine/
35. Leflunomide/
36. Hydroxychloroquine/
37. Placebo/
38. (sulphasalazine or sulfasalazine or mtx or methotrexate).mp.
39. (Ciclosporin$ or cyclosporin$ or neoral or sandimmun$ or cyc-a or cya or csa).mp.
40. (Intramuscular$ gold or Intra muscular$ gold).mp.
41. (Imi gold or Im gold).mp.
42. (inject$ adj2 gold).mp.
43. (Gold preparation$ or gold salt$).mp.
44. (Peroral$ adj2 gold).mp.
45. (Parenteral$ adj2 gold).mp.
46. (Intramuscular$ administ$ adj2 gold).mp.
47. (Intra muscular$ administ$ adj2 gold).mp.
48. (Auranofin or Azathioprine or aza or Penicillamine or d-Penicillamine or dpa).mp.
49. (Leflunomide or Hydroxychloroquine or hxchl or hcq).mp.
50. (Salazopyrin or Salicylazosulphapyridine or Salicylazosulfapyridine or sasp).mp.
51. placebo$.mp.
52. or/25-28,31-51
53. 21 and 24 and 52

National Research Register (NRR) (CD-ROM): 2004 Issue 2

This search retrieved 20 references.

#1 ARTHRITIS PSORIATIC single term (MeSH)
#2 (PSORIA* next ARTHRIT*)
#3 (PSORIA* next ARTHROPATH*)
#4 (#1 or #2 or #3)
#5 SULFASALAZINE single term (MeSH)
#6 METHOTREXATE single term (MeSH)
#7 CYCLOSPORINS explode tree 1 (MeSH)
#8 AURANOFIN single term (MeSH)
#9 INJECTIONS INTRAMUSCULAR single term (MeSH)
#10 GOLD single term (MeSH)
#11 (#9 and #10)
#12 AZATHIOPRINE single term (MeSH)
#13 PENICILLAMINE single term (MeSH)
#14 ENKEPHALIN D-PENICILLAMINE (25)- single term (MeSH)
#15 HYDROXYCHLOROQUINE single term (MeSH)
#16 PLACEBOS single term (MeSH)
#17 (SULPHASALAZINE or SULFASALAZINE or MTX or METHOTREXATE)
#18 (CICLOSPORIN* or CYCLOSPORIN* or NEORAL or SANDIMMUN* or CYC-A or CYA or CSA)
#19 ((INTRAMUSCULAR* next GOLD) or (INTRA-MUSCULAR* next GOLD))
#20 ((IMI next GOLD) or (IM next GOLD))
#21 (INJECT* next GOLD)
#22 ((GOLD next PREPARATION*) or (GOLD next SALT*))
#23 (PERORAL* next GOLD)
#24 (PARENTERAL* next GOLD)
#25 (INTRAMUSCULAR* next ADMINIST* next GOLD)
#26 (INTRA-MUSCULAR* next ADMINIST* next GOLD)
#27 (AURANOFIN or AZATHIOPRINE or AZA or PENICILLAMINE or D-PENICILLAMINE or DPA)

#28 (LEFLUNOMIDE or HYDROXYCHLOROQUINE or HXCHL or HCQ)
#29 (SALAZOPYRIN or SALICYLAZOSULPHAPYRIDINE or SALICYLAZOSULFAPYRIDINE or SASP)
#30 PLACEBO*
#31 (#5 or #6 or #7 or #8 or #11 or #12 or #13 or #14 or #15 or #16)
#32 (#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25)
#33 (#26 or #27 or #28 or #29 or #30 or #31 or #32)
#34 (#4 and #33)

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm): 2004 Issue 2
This search retrieved 47 references.

#1 ARTHRITIS PSORIATIC single term (MeSH)
#2 (psoria* next arthrit*)
#3 (psoria* next arthropath*)
#4 (#1 or #2 or #3)
#5 SULFASALAZINE single term (MeSH)
#6 METHOTREXATE single term (MeSH)
#7 CYCLOSPORINS explode tree 1 (MeSH)
#8 AURANOFIN single term (MeSH)
#9 INJECTIONS INTRAMUSCULAR single term (MeSH)
#10 GOLD single term (MeSH)
#11 (#9 and #10)
#12 AZATHIOPRINE single term (MeSH)
#13 PENICILLAMINE single term (MeSH)
#14 ENKEPHALIN D-PENICILLAMINE (25)- single term (MeSH)
#15 HYDROXYCHLOROQUINE single term (MeSH)
#16 PLACEBOS single term (MeSH)
#17 (sulphasalazine or sulfasalazine or mtx or methotrexate)
#18 (ciclosporin* or cyclosporin* or neoral or sandimmun* or cyc-a or cya or csa)
#19 ((intramuscular* next gold) or (intra-muscular* next gold))
#20 ((imi next gold) or (im next gold))
#21 (inject* next gold)
#22 ((gold next preparation*) or (gold next salt*))
#23 (peroral* next gold)
#24 (parenteral* next gold)
#25 (intramuscular* next administ* next gold)
#26 (intra-muscular* next administ* next gold)
#27 (auranofin or azathioprine or aza or penicillamine or d-penicillamine or dpa)
#28 (leflunomide or hydroxychloroquine or hxchl or hcq)
#29 (salazopyrin or salicylazosulphapyridine or salicylazosulfapyridine or sasp)
#30 placebo*
#31 (#5 or #6 or #7 or #8 or #11 or #12 or #13 or #14 or #15 or #16)
#32 (#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25)
#33 (#26 or #27 or #28 or #29 or #30 or #31 or #32)
#34 (#4 and #33)

NHS Economic Evaluation Database (NHS EED) (CRD administration database): June 2004 update
This search retrieved no references.

1. s psoria$(w2)arthrit$
2. s psoria$(w2)arthropath$
3. s s1 or s2
4. s sulphasalazine or sulfasalazine or mtx or methotrexate
5. s Ciclosporin$ or cyclosporin$ or neoral or sandimmun$ or cyc(w)a or cya or csa
6. s (Intramuscular$(w)gold) or (Intra(w)muscular$ gold)
7. s (Imi(w)gold) or (Im(w)gold)
8. s (inject$(w)gold)
9. s (Gold(w)preparation$) or (gold(w)salt$)
10. s (Peroral$(w)gold)
11. s (Parenteral$(w)gold)
12. s (Intramuscular$(w)administ$(w)gold)
13. s (Intra(w)muscular$(w)administ$(w)gold)
14. s Auranofin or Azathioprine or aza or Penicillamine or d(w)Penicillamine or dpa
15. s Leflunomide or Hydroxychloroquine or hxchl or hcq
16. s Salazopyrin or Salicylazosulphapyridine or Salicylazosulfapyridine or sasp or placebo$
17. s s4 or s5 or s6 or s7 or s8 or s9 or s10
18. s s11 or s12 or s13 or s14 or s15 or s16 or s17
19. s s3 and s18

Health Economic Evaluation Database (HEED) (CD-ROM): June 2004
This search retrieved three references.

(Psoriatic arthritis) or (psoriatic arthropathy)

EconLit (SilverPlatter on the web – http:/arc.uk.ovid.com/): 1969–2004/May
This search retrieved no references.

(Psoria* adj arthrit*)or(Psoria* adj arthropath*)

ISI Science and Technology Proceedings (Web of Knowledge): 1990–2004 (25 June update)
Social Science Citation Index and Science Citation Index (Web of Science – http://wos.mimas.ac.uk/): 1981–2004 (27 June update)
The same strategy was used in both instances. The search of ISI Science and Technology Proceedings retrieved one reference and that of Social Science Citation Index and Science Citation Index retrieved 12 references.

#1 TS=((econom* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom* or budget*))
#2 TS=(psoria* SAME arthrit*)
#3 TS=(psoria* SAME arthropath*)
#4 #2 or #3
#5 #1 and #4
#6 TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*)
#7 #5 not #6

All databases were searched from inception date.

Search 3: QoL measures in PsA

MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/): 1990–2004/June week 3
This search retrieved 57 references.

1. (sf36 or sf 36).tw.
2. (eq5d or eq 5d or euroqol or euro qol).tw.
3. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
4. (hrql or hrqol or h qol or hql or hqol).tw.
5. (hye or hyes or health$ year$ equivalent$ or health utilit$).tw.
6. health related quality life.tw.
7. rosser.tw.
8. (standard gamble$ or time trade off or time tradeoff or tto or willingness pay).tw.
9. (utilities or utility or daly or dalys or disability adjusted life).tw.
10. quality of life/ or (quality of life or life quality).tw.
11. health status indicators/
12. quality adjusted life year/
13. (qaly$ or quality adjusted).tw.
14. (qwb$ or hui or hui1 or hui2 or hui3 or qwi).tw.
15. (quality wellbeing or quality well being).tw.
16. preference based.tw.
17. (dermatology life quality index or health status).tw.
18. (state$ adj2 (value or values or valuing or valued or valuation)).tw.
19. (dlqi or hspv).ti,ab.
20. general health questionnaire.tw.
21. nottingham health profile.tw.
22. patient generated index.tw.
23. sickness impact profile.tw.
24. (ghq or nhp or pgi or sip or uksip or wtp).ti,ab.
25. or/1-24
26. animals/
27. human/
28. 26 not (26 and 27)
29. 25 not 28
30. 29 not (letter or editorial or comment).pt.
31. arthritis, psoriatic/
32. (psoria$ adj2 (arthrit$ or arthropath$)).mp.
33. 31 or 32
34. 30 and 33
35. limit 34 to yr=1990 - 2005

EMBASE (OVID Online – http://www.ovid.com/): 1996–2004 week 26
This search retrieved 75 references.

1. (sf36 or sf 36).tw.
2. (eq5d or eq 5d or euroqol or euro qol).tw.
3. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
4. (hrql or hrqol or h qol or hql or hqol).tw.
5. (hye or hyes or health$ year$ equivalent$ or health utilit$).tw.
6. health related quality life.tw.
7. rosser.tw.
8. (standard gamble$ or time trade off or time tradeoff or tto or willingness pay).tw.
9. (utilities or utility or daly or dalys or disability adjusted life).tw.
10. (qaly$ or quality adjusted).tw.
11. (qwb$ or hui or hui1 or hui2 or hui3 or qwi).tw.
12. (quality wellbeing or quality well being).tw.
13. preference based.tw.
14. (dermatology life quality index or health status).tw.
15. (state$ adj2 (value or values or valuing or valued or valuation)).tw.
16. (dlqi or hspv).ti,ab.
17. general health questionnaire.tw.
18. nottingham health profile.tw.
19. patient generated index.tw.
20. sickness impact profile.tw.
21. (ghq or nhp or pgi or sip or uksip or wtp).ti,ab.
22. (quality life or life quality).tw.
23. quality of life/ or quality adjusted life year/

24. or/1-23
25. Psoriatic Arthritis/
26. (psoria$ adj2 (arthrit$ or arthropath$)).mp.
27. or/25-26
28. 24 and 27
29. exp ANIMAL/ or Animal Experiment/ or Nonhuman/ or (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
30. Human/ or Human Experiment/
31. 29 not (29 and 30)
32. 28 not 31
33. 32 not (editorial or letter or note).pt.
34. limit 33 to yr=1990-2005

National Research Register (NRR) (CD-ROM): 2004 Issue 2

This search retrieved 10 references.

#1 (((((SF36 or SF-36) or EQ5D) or EQ-5D) or EUROQOL) or EURO-QOL)
#2 ((((SHORT next FORM-36) or SHORTFORM-36) OR (SF NEXT THIRTYSIX)) OR (SF NEXT THIRTY-SIX))
#3 ((((SHORTFORM next THIRTYSIX) or (SHORTFORM next THIRTY-SIX)) OR ((SHORT NEXT FORM) NEXT THIRTYSIX)) OR ((SHORT NEXT FORM) NEXT THIRTY-SIX))
#4 (((((((HRQL or HRQOL) or H-QOL) or HQL) or HQOL) or HYE) or HYES) OR ((HEALTH* next YEAR*) NEXT EQUIVALENT*)) OR (HEALTH NEXT UTILIT*))
#5 ((((((HEALTH next RELATED) next QUALITY) next LIFE) or ROSSER) OR (STANDARD NEXT GAMBLE*)) OR ((TIME NEXT TRADE) NEXT OFF))
#6 (((((((TIME next TRADEOFF) or TTO) OR (WILLINGNESS NEXT PAY)) OR UTILITIES) OR UTILITY) OR DALYS) OR DALY) OR ((DISABILITY NEXT ADJUSTED) NEXT LIFE))
#7 ((QUALITY next LIFE) or (LIFE next QUALITY))
#8 QUALITY-OF-LIFE single term (MeSH)
#9 QUALITY-ADJUSTED-LIFE-YEARS single term (MeSH)
#10 HEALTH-STATUS-INDICATORS single term (MeSH)
#11 (((((((QALY* or (QUALITY next ADJUSTED)) OR QWB*) OR HUI) OR HUI1) OR HUI2) OR HUI3) OR QWI)
#12 (((QUALITY next WELLBEING) or (QUALITY next WELL-BEING)) OR (PREFERENCE NEXT BASED))
#13 ((((DERMATOLOGY next LIFE) next QUALITY) next INDEX) or (HEALTH next STATUS))
#14 (DLQI or HSPV)
#15 ((((GENERAL next HEALTH) next QUESTIONNAIRE) or ((NOTTINGHAM next HEALTH) next PROFILE)) OR ((PATIENT NEXT GENERATED) NEXT INDEX))
#16 (((((((SICKNESS next IMPACT) next PROFILE) or GHQ) OR NHP) OR PGI) OR SIP) OR UKSIP) OR WTP)
#17 ((((STATE next VALUE) or (STATE next VALUES)) OR (STATE NEXT VALUING)) OR (STATE NEXT VALUED))
#18 ((((((STATES next VALUE) or (STATES next VALUES)) OR (STATES NEXT VALUING)) OR (STATES NEXT VALUED)) OR (STATES NEXT VALUATION)) OR (STATE NEXT VALUATION))
#19 (((((((((#1 or #2) or #3) or #4) or #5) or #6) or #7) or #8) or #9) or #10)
#20 (((((((#11 or #12) or #13) or #14) or #15) or #16) or #17) or #19)
#21 ARTHRITIS-PSORIATIC* single term (MeSH)
#22 ((PSORIA* next ARTHRIT*) or (PSORIA* next ARTHROPATH*))
#23 (#21 or #22)
#24 (#22 and #23)

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm): 2004 Issue 2

This search retrieved four references.

#1 (sf36 or sf-36 or eq5d or eq-5d or euroqol or euro-qol)
#2 ((short next form-36) or shortform-36 or (sf next thirtysix) or (sf next thirty-six))
#3 ((shortform next thirtysix) or (shortform next thirty-six) or (short next form next thirtysix) or (short next form next thirty-six))
#4 (hrql or hrqol or h-qol or hql or hqol or hye or hyes or (health* next year* next equivalent*) or (health next utilit*))
#5 ((health next related next quality next life) or rosser or (standard next gamble*) or (time next trade next off))
#6 ((time next tradeoff) or tto or (willingness next pay) or utilities or utility or daly or dalys or (disability next adjusted next life))
#7 ((quality next life) or (life next quality))
#8 QUALITY OF LIFE single term (MeSH)
#9 QUALITY-ADJUSTED LIFE YEARS single term (MeSH)

#10 HEALTH STATUS INDICATORS single term (MeSH)
#11 (qaly* or (quality next adjusted) or qwb* or hui or hui1 or hui2 or hui3 or qwi)
#12 ((quality next wellbeing) or (quality next well-being) or (preference next based))
#13 ((dermatology next life next quality next index) or (health next status)) 2568
#14 (dlqi or hspv)
#15 ((general next health next questionnaire) or (nottingham next health next profile) or (patient next generated next index))
#16 ((sickness next impact next profile) or ghq or nhp or pgi or sip or uksip or wtp)
#17 ((state* next value) or (state* next values) or (state* next valuing) or (state* next valuation) or (state* next valued))
#18 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)
#19 (#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)
#20 ARTHRITIS PSORIATIC single term (MeSH)
#21 ((psoria* next arthrit*) or (psoria* next arthropath*))
#22 (#20 or #21)
#23 (#19 and #22) (1990 to current date)

NHS Economic Evaluation Database (NHS EED) (CRD administration database): 1990–2004/June
This search retrieved no references.

1. s sf36 or sf(w)36 or eq5d or eq(w)5d or euroqol or euro(w)qol
2. s short(w)form(w)36 or shortform(w)36 or sf(w)thirtysix or sf(w)thirty(w)six
3. s shortform(w)thirtysix or shortform(w)thirty(w)six or short(w)form(w)thirtysix
4. s short(w)form(w)thirty(w)six or hrql or hrqol or h(w)qol or hql or hqol or hye or hyes
5. s health$(w)year$(w)equivalent$ or health(w)utilit$ or health(w)related(w)quality(w)life
6. s rosser or standard(w)gamble$ or time(w)trade(w)off or time(w)tradeoff
7. s tto or willingness(w)pay or utilities or utility or dalys or daly or disability(w)adjusted(w)life
8. s quality(w2)life or life(w)quality
9. s health(w)status(w)indicator$ or quality(w)adjusted(w)life(w)year$
10. s qaly$ or quality(w)adjusted or qwb$ or hui or hui1 or hui2 or hui3 or qwi
11. s quality(w2)wellbeing or quality(w2)well(w)being or preference(w)based
12. s dermatology(w)life(w)quality(w)index or health(w)status
13. s (state$(w2)(value or values or valuing or valued or valuation)) or dlqi or hspv
14. s general(w)health(w)questionnaire or nottingham(w)health(w)profile
15. s patient(w)generated(w)index or sickness(w)impact(w)profile
16. s ghq or nhp or pgi or sip or uksip or wtp
17. s s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14
18. s s15 or s16 or s17
19. s (psoria$(w)arthrit$) or (psoria$(w)arthropath$)
20. s s18 and s19
21. s 1990:2004/xyr
22. s s20 and s21

Health Economic Evaluation Database (HEED) (CD-ROM): 1990–2004/June
This search retrieved no references.

(Psoriatic arthritis) or (psoriatic arthropathy)

EconLit (SilverPlatter on the web – http:/arc.uk.ovid.com/): 1969–2004/May
This search retrieved no references.

1. (sf36 or sf-36 or eq5d or eq-5d or euroqol or euro-qol or (short form-36) or shortform-36 or (sf thirtysix) or (sf thirty-six))or((shortform thirtysix) or (shortform thirty-six) or (short form thirtysix) or (short form thirty-six))or(hrql or hrqol or h-qol or hql or hqol or hye or hyes or (health* year* equivalent*) or (health utilit*))
2. ((health related quality life) or rosser or (standard gamble*) or (time trade off) or (time tradeoff))or(tto or (willingness pay) or utilities or utility or daly or (disability adjusted life) or (quality of life))or((life quality) or qaly* or (quality adjusted) or qwb* or hui or hui1 or hui2 or hui3 or qwi)
3. ((quality wellbeing) or (quality well-being) or (preference based) or (dermatology life quality index))or((health status) or (state value) or (state values) or (state valuing) or (state valued) or dlqi or hspv)
4. ((general health questionnaire) or (nottingham health profile) or (patient generated index))or((sickness impact profile) or ghq or nhp or pgi or sip or uksip or wtp) 263
5. (states value) or (states values) or (states valuing) or (states valued) or (states valuation) or (state valuation) or dalys
6. (((general health questionnaire) or (nottingham health profile) or (patient generated index))or ((sickness impact profile) or ghq or nhp or pgi or sip or uksip or wtp)) or (((quality wellbeing)

or (quality well-being) or (preference based) or (dermatology life quality index))or((health status) or (state value) or (state values) or (state valuing) or (state valued) or dlqi or hspv)) or (((health related quality life) or rosser or (standard gamble*) or (time trade off) or (time tradeoff) or(tto or (willingness pay) or utilities or utility or daly or (disability adjusted life) or (quality of life))or((life quality) or qaly* or (quality adjusted) or qwb* or hui or hui1 or hui2 or hui3 or qwi)) or ((sf36 or sf-36 or eq5d or eq-5d or euroqol or euro-qol or (short form-36) or shortform-36 or (sf thirtysix) or (sf thirty-six))or((shortform thirtysix) or (shortform thirty-six) or (short form thirtysix) or (short form thirty-six))or(hrql or hrqol or h-qol or hql or hqol or hye or hyes or (health* year* equivalent*) or (health utilit*))) or ((states value) or (states values) or (states valuing) or (states valued) or (states valuation) or (state valuation) or dalys)

7. (psoria* arthrit*) or (psoria* arthropath*)
8. ((psoria* arthrit*) or (psoria* arthropath*)) and ((((general health questionnaire) or (nottingham health profile) or (patient generated index))or((sickness impact profile) or ghq or nhp or pgi or sip or uksip or wtp)) or (((quality wellbeing) or (quality well-being) or (preference based) or (dermatology life quality index))or((health status) or (state value) or (state values) or (state valuing) or (state valued) or dlqi or hspv)) or (((health related quality life) or rosser or (standard gamble*) or (time trade off) or (time tradeoff))or(tto or (willingness pay) or utilities or utility or daly or (disability adjusted life) or (quality of life))or ((life quality) or qaly* or (quality adjusted) or qwb* or hui or hui1 or hui2 or hui3 or qwi)) or ((sf36 or sf-36 or eq5d or eq-5d or euroqol or euro-qol or (short form-36) or shortform-36 or (sf thirtysix) or (sf thirty-six))or((shortform thirtysix) or (shortform thirty-six) or (short form thirtysix) or (short form thirty-six))or(hrql or hrqol or h-qol or hql or hqol or hye or hyes or (health* year* equivalent*) or (health utilit*))) or ((states value) or (states values) or (states valuing) or (states valued) or (states valuation) or (state valuation) or dalys))

ISI Science and Technology Proceedings (Web of Knowledge): 1990–2004 (25 June update)
Social Science Citation Index and Science Citation Index (Web of Science – http://wos.mimas.ac.uk/): 1981–2004 (27 June update)

The same strategy was used in both instances. The search of ISI Science and Technology Proceedings retrieved four references and that of Social Science Citation Index and Science Citation Index retrieved 54 references.

#1 TS=(sf36 or sf-36 or eq5d or eq-5d or euroqol or euro-qol or (short SAME form-36) or shortform-36 or (sf SAME thirtysix) or (sf SAME thirty-six))
#2 TS=((shortform SAME thirtysix) or (shortform SAME thirty-six) or (short SAME form SAME thirtysix) or (short SAME form SAME thirty-six))
#3 TS=(hrql or hrqol or h-qol or hql or hqol or hye or hyes or (health* SAME year* SAME equivalent*) or (health SAME utilit*))
#4 TS=(tto or (willingness SAME pay) or utilities or utility or daly or dalys or (disability SAME adjusted SAME life) or (quality SAME life))
#5 TS=((quality SAME wellbeing) or (quality SAME well-being) or (preference SAME based) or (dermatology SAME life SAME quality SAME index))
#6 TS=((health SAME status) or (state* SAME value) or (state* SAME values) or (state* SAME valuing) or (state* SAME valuation) or (state* SAME valued) or dlqi or hspv)
#7 TS=((health SAME related SAME quality SAME life) or rosser or (standard SAME gamble*) or (time SAME trade SAME off) or (time SAME tradeoff))
#8 TS=((life SAME quality) or qaly* or (quality SAME adjusted) or qwb* or hui or hui1 or hui2 or hui3 or qwi)
#9 TS=((general SAME health SAME questionnaire) or (nottingham SAME health SAME profile) or (patient SAME generated SAME index))
#10 TS=((sickness SAME impact SAME profile) or ghq or nhp or pgi or sip or uksip or wtp)
#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 TS=((psoria* SAME arthrit*) or (psoria* SAME arthropath*))
#13 #11 and #12
#14 TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*)
#15 #13 not #14

All databases were searched from 1990 to date.

Search 4: economic models for PsA

MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/): 1990–2004/July week 3

This search retrieved 26 references.

1 exp decision support techniques/ or exp survival analysis/
2 exp models, economic/ or decision trees/
3 markov.mp. or exp models, statistical/
4 (decision analytic model$ or decision tree$ or simulation model$ or decision analysis).ti,ab.
5 (explanatory model$ or statistical model$ or monte carlo or decision model$).ti,ab.
6 (survival analy$ or mathematical model$).ti,ab.
7 or/1-6
8 animals/
9 human/
10 8 not (8 and 9)
11 7 not 10
12 11 not (letter or editorial or comment).pt.
13 arthritis, psoriatic/
14 (psoria$ adj2 (arthrit$ or arthropath$)).mp.
15 13 or 14
16 12 and 15
17 exp decision support techniques/ or exp survival analysis/
18 exp models, economic/ or decision trees/
19 markov.mp. or exp models, statistical/
20 (decision analy$ model$ or decision tree$ or simulation model$ or decision analy$).ti,ab.
21 (explanatory model$ or statistical model$ or monte carlo or decision model$).ti,ab.
22 (survival analy$ or mathematical model$).ti,ab.
23 or/17-22
24 animals/
25 human/
26 24 not (24 and 25)
27 23 not 26
28 27 not (letter or editorial or comment).pt.
29 arthritis, psoriatic/
30 (psoria$ adj2 (arthrit$ or arthropath$)).mp.
31 29 or 30
32 28 and 31
33 from 32 keep 1-26

EMBASE (OVID Online – http://www.ovid.com/): 1980–2004 week 29

This search retrieved 24 references.

1 decision support system/
2 medical decision making/
3 decision theory/
4 survival/
5 statistical model/
6 probability/
7 monte carlo method/
8 (decision support technique$ or economic model$ or decision tree$).tw.
9 (decision analytic model$ or simulation model$ or decision analysis).tw.
10 (explanatory model$ or markov or statistical model$ or monte carlo or decision model$).tw.
11 (survival analy$ or mathematical model$).tw.
12 or/1-11
13 exp psoriasis/
14 (psoria$ or antipsoria$ or anti-psoria$).mp.
15 13 or 14
16 12 and 15
17 16 not (editorial or letter or note).pt.
18 exp ANIMAL/ or Animal Experiment/ or Nonhuman/ or (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
19 Human/ or Human Experiment/
20 18 not (18 and 19)
21 17 not 20
22 decision support system/
23 medical decision making/
24 decision theory/
25 survival/
26 statistical model/
27 probability/
28 monte carlo method/
29 (decision support technique$ or economic model$ or decision tree$).tw.
30 (decision analy$ model$ or simulation model$ or decision analy$).tw.
31 (explanatory model$ or markov or statistical model$ or monte carlo or decision model$).tw.
32 (survival analy$ or mathematical model$).tw.
33 or/22-32
34 Psoriatic Arthritis/
35 (psoria$ adj2 (arthrit$ or arthropath$)).mp.
36 34 or 35
37 33 and 36
38 37 not (editorial or letter or note).pt.
39 exp ANIMAL/ or Animal Experiment/ or Nonhuman/ or (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamsters or feline or ovine or bovine or canine or sheep).ti,ab,de.
40 Human/ or Human Experiment/
41 39 not (39 and 40)
42 38 not 41 (24)
43 from 42 keep 1–24

National Research Register (NRR) (CD-ROM): 2004 Issue 2

This search retrieved one reference.

#1 DECISION SUPPORT TECHNIQUES explode all trees (MeSH)
#2 SURVIVAL ANALYSIS explode all trees (MeSH)
#3 MODELS ECONOMIC explode all trees (MeSH)
#4 DECISION TREES single term (MeSH)

#5 MODELS STATISTICAL explode all trees (MeSH)
#6 (MARKOV:TI or MARKOV:AB)
#7 ((DECISION next ANALY* next MODEL*) or (SIMULATION next MODEL*) or (DECISION next ANALY*) or (DECISION netx TREE*))
#8 ((EXPLANATORY next MODEL*) or (STATISTICAL next MODEL*) or (MONTE next CARLO) or (DECISION next MODEL*))
#9 ((SURVIVAL next ANALY*) or (MATHEMATICAL next MODEL"))
#10 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)
#11 ARTHRITIS PSORIATIC single term (MeSH)
#12 PSORIA* near ARTHRIT*
#13 PSORIA* near ARTHROPATH*
#14 (#11 or #12 or #13)
#15 (#10 and #14)

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm): 2004 Issue 2
This search retrieved one reference.

#1 DECISION SUPPORT TECHNIQUES (explode all trees)
#2 SURVIVAL ANALYSIS (explode all trees)
#3 MODELS ECONOMIC (explode all trees)
#4 DECISION TREES (single term)
#5 MODELS STATISTICAL (explode all trees)
#6 (markov:ti or markov:ab)
#7 ((decision next analy* next model*) or (simulation next model*) or (decision next analy*) or (decision next tree*))
#8 ((explanatory next model*) or (statistical next model*) or (monte next carlo) or (decision next model*))
#9 ((survival next analy*) or (mathematical next model*))
#10 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)
#11 ARTHRITIS PSORIATIC (single term)
#12 psoria* near arthrit*
#13 (psoria* near arthropath*)
#14 (#11 or #12 or #13)
#15 (#10 and #14)

NHS Economic Evaluation Database (NHS EED) (CRD administration database): 1990–2004/June
This search retrieved no references.

1. s decision(w)analysis(w)model$
2. s decision(w)analyses(w)model$
3. s decision(w)analytic(w)model$
4. s simulation(w)model$
5. s decision(w)analy$
6. s decision(w)tree$
7. s explanatory(w)model$
8. s statistical(w)model$
9. s monte(w)carlo
10. s decision(w)model$
11. s survival(w)analy$
12. s mathematical(w)model$
13. s markov
14. s s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13
15. s psoria$(2w)arthrit$
16. s psoria$(2w)arthropath$
17. s s15 or s16
18. s s14 and s17

Health Economic Evaluation Database (HEED) (CD-ROM): 1990–2004/June
This search retrieved no references.

1. AX='decision analy* model*'
2. AX= 'simulation model*'
3. AX= 'decision analy*'
4. AX= 'decision tree*'
5. AX= 'explanatory model*'
6. AX= 'statistical model*'
7. AX= 'monte carlo'
8. AX= 'decision model*'
9. AX= 'survival analy*'
10. AX= 'mathematical model*'
11. markov
12. CS=1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11
13. AX= 'psoria* arthrit*' within 2
14. AX= 'psoria* arthropath*' within 2
15. CS=13 OR 14
16. CS=12 AND 15

EconLit (SilverPlatter on the web – http:/arc.uk.ovid.com/): 1969–2004/June
This search retrieved no references.

#1 markov
#2 decision analy* model* or simulation model* or decision analy* or decision tree*
#3 explanatory model* or statistical model* or monte carlo or decision model*
#4 survival analy* or mathematical model*
#5 #1 or #2 or #3 or #4
#6 psoria* near arthrit*
#7 psoria* near arthropath*
#8 #6 or #7
#9 #5 and #8

ISI Science and Technology Proceedings (Web of Knowledge): 1990–2004 (16 July update)
Social Science Citation Index and Science Citation Index (Web of Science – http://wos.mimas.ac.uk/): 1981–2004 (16 July update)
The same strategy was used in both instances. The searches of both ISI Science and Technology Proceedings and Social Science Citation Index and Science Citation Index retrieved no references.

#1 markov
#2 decision analy* model* or simulation model* or decision analy* or decision tree*
#3 explanatory model* or statistical model* or monte carlo or decision model*
#4 survival analy* or mathematical model*
#5 #1 or #2 or #3 or #4
#6 psoria* same arthrit*
#7 psoria* same arthropath*
#8 #6 or #7
#9 #5 and #8

All databases were searched from inception date.

Search 5: treatment pathways for PsA

MEDLINE and In-Process Citations (OVID Online – http://www.ovid.com/): 1990–2004/June week 2
This search retrieved 28 references.

1 guideline.pt.
2 practice guideline.pt.
3 exp guidelines/
4 health planning guidelines/
5 treatment$ pathway$.mp.
6 treatment$ path way$.mp.
7 care pathway$.mp.)
8 care path way$.mp.
9 clinical pathway$.mp.
10 clinical path way$.mp.
11 treatment$ path$.mp.
12 (treatment$ route$ or guideline$ or guide line$).mp.
13 or/1-12
14 arthritis, psoriatic/
15 (psoria$ adj2 (arthrit$ or arthropath$)).mp.
16 14 or 15
17 13 and 16
18 from 17 keep 1-28

EMBASE (OVID Online – http://www.ovid.com/): 1980–2004 week 27
This search retrieved 48 references.

1. exp practice guideline/
2. (treatment pathway$ or treatment path way$).mp.
3. (care pathway$ or care path way$).mp.
4. (clinical path way$ or clinical pathway$).mp.
5. (treatment$ path$ or treatment$ route$).mp.
6. (guide line$ or guideline$).mp.
7. or/1-6
8. Psoriatic Arthritis/
9. (psoria$ adj2 (arthrit$ or arthropath$)).mp.
10. or/8-9
11. 7 and 10

National Research Register (NRR) (via the Internet – http://www.update-software.com/projects/nrr/): 2004 Issue 2
This search retrieved two references.

#1 GUIDELINES explode all trees (MeSH)
#2 HEALTH PLANNING GUIDELINES single term (MeSH)
#3 ((TREATMENT next PATHWAY*) or (TREATMENT next PATH next WAY*) or (TREATMENTS next PATHWAY*) or (TREATMENTS next PATH next WAY*))
#4 ((CARE next PATHWAY*) or (CARE next PATH next WAY*) or (CLINICAL next PATHWAY*) or (CLINICAL next PATH next WAY*))
#5 ((TREATMENT next PATH*) or (TREATMENTS next PATH*) or (TREATMENT next ROUTE*) or (TREATMENTS next ROUTE*))
#6 (GUIDELINE* or (GUIDE next LINE*))
#7 (#1 or #2 or #3 or #4 or #5 or #6)
#8 ARTHRITIS PSORIATIC single term (MeSH)
#9 (PSORIA* near ARTHRIT*)
#10 (PSORIA* near ARTHROPATH*)
#11 (#9 or #10)
#12 (#7 and #11)

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library via the Internet – http://www.update-software.com/clibng/cliblogon.htm): 2004 Issue 2
This search retrieved two references.

#1 GUIDELINES explode all trees (MeSH)
#2 HEALTH PLANNING GUIDELINES single term (MeSH)
#3 ((treatment next pathway*) or (treatment next path-way*) or (treatments next pathway*) or (treatments next path-way*))
#4 ((care next pathway*) or (care next path-way*) or (clinical next pathway*) or (clinical next path-way*))

#5 ((treatment next path*) or (treatments next path*) or (treatment next route*) or (treatments next route*))
#6 (guideline* or guide-line*)
#7 (#1 or #2 or #3 or #4 or #5 or #6)
#8 ARTHRITIS PSORIATIC single term (MeSH)
#9 psoria* near arthrit*
#10 psoria* near arthropath*
#11 (#9 or #10)
#12 (#7 and #11)

NHS Economic Evaluation Database (NHS EED) (CRD administration database): 1990–2004/June
This search retrieved no references.

1. S treatment$(w)pathway$ or treatment$(w)path(w)way$
2. S care(w)pathway$ or care$(w)path(w)way$
3. S clinical(w)pathway$ or clinical$(w)path(w)way$
4. S treatment$(w)path$
5. S treatment$(w)route$
6. S guideline$ or guide(w)line$
7. S s1 or s2 or s3 or s4 or s5 or s6
8. S psoria$(2w)arthrit$ or psoria$(2w)arthropath$
9. S s7 and s8

Health Economic Evaluation Database (HEED) (CD-ROM): 1990–2004/June
This search retrieved no references.

1 ax=psoria*
2 ax=path* or guide*
3 cs=1 and 2

EconLit (SilverPlatter on the web – http:/arc.uk.ovid.com/): 1969–2004/May
This search retrieved no references.

#1 guideline*
#2 treatment* pathway*
#3 treatment* path-way*
#4 treatment* path way*
#5 care pathway*
#6 care path way*
#7 care path-way*
#8 clinical pathway*
#9 clinical path way*
#10 clinical path-way*
#11 treatment* path*
#12 treatment* route* or guideline* or guide line* or guide-line*
#13 (care pathway*) or (treatment* path way*) or (treatment* path-way*) or (treatment* route* or guideline* or guide line* or guide-line*) or (treatment* pathway*) or (treatment* path*) or (guideline*) or (clinical path-way*) or (clinical path way*) or (clinical pathway*) or (care path-way*) or (care path way*)
#14 psoria* near arthrit*
#15 psoria* near arthropath*
#16 (psoria* near arthrit*) or (psoria* near arthropath*)
#17 ((care pathway*) or (treatment* path way*) or (treatment* path-way*) or (treatment* route* or guideline* or guide line* or guide-line*) or (treatment* pathway*) or (treatment* path*) or (guideline*) or (clinical path-way*) or (clinical path way*) or (clinical pathway*) or (care path-way*) or (care path way*)) and ((psoria* near arthrit*) or (psoria* near arthropath*))

ISI Science and Technology Proceedings (Web of Knowledge): 1990–2004 (25 June update)
Social Science Citation Index and Science Citation Index (Web of Science – http://wos.mimas.ac.uk/): 1981–2004 (27 June update)
The same strategy was used in both instances. The search of ISI Science and Technology Proceedings retrieved one reference and that of Social Science Citation Index and Science Citation Index retrieved no references.

#1 ((treatment* same pathway*) or (treatment* same path-way*) or (care same pathway*) or (care same path-way*))
#2 ((clinical* same pathway*) or (clinical* same path-way*) or (treatment* same path*) or (treatment* same route*))
#3 (guideline* or guide-line*)
#4 #1 or #2 or #3
#5 ((psoria* same arthrit*) or (psoria* same arthropath*))
#6 #4 and #5

All databases were searched from their inception. In total, 113 references were retrieved for this topic.

Search 6: Internet searches to locate guidelines for PsA

The following websites were searched on 21 June 2004 using the keyword Psoriatic:

NeLH Guidelines Finder (http://rms.nelh.nhs.uk/guidelinesfinder/)
This search retrieved one reference.

eGuidelines (http://www.eguidelines.co.uk/)
This search retrieved five references.

Health Services/Technology Assessment Text (HSTAT) (http://hstat.nlm.nih.gov/hq/Hquest/screen/HquestHome/s/52877)
This search retrieved no references.

National Guidelines Clearinghouse (http://www.guideline.gov/)
This search retrieved one references.

Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/index.html)
This search retrieved no reference.

Clinicians Health Channel (http://www.clinicians.vic.gov.au/guidelines/index.html)
This search retrieved no references.

Medical Services Advisory Committee (MSAC) (http://www.health.gov.au/msac/msacapps.htm)
This search retrieved no references.

New Zealand Health Technology Assessment (NZHTA) (http://nzhta.chmeds.ac.nz/)
This search retrieved no references.

National Health and Medical Research Council (NHMRC) (http://www.health.gov.au/nhmrc/publications/cphome.htm)
This search retrieved no references.

New Zealand Guidelines Group (NZGG) (http://www.nzgg.org.nz/)
This search retrieved no references.

Australian Safety and Efficacy Register of New Interventional Procedures (ASERNIP) (http://www.surgeons.org/asernip-s/)
This search retrieved no references.

Centre for Clinical Effectiveness (CCE – Monash) (http://www.med.monash.edu.au/healthservices/cce)
This search retrieved no references.

All resources were searched from inception date.

Additional searches

Citation searching

Social Science Citation Index and Science Citation Index (Web of Science – http://wos.mimas.ac.uk/): 1981–2004 (searched on 19 November 2004)
This search retrieved 17 references.

To identify cohort studies of PsA, a search was carried out for articles that had cited the following studies:

Sokoll KB, Helliwell PS. Comparison of disability and quality of life in rheumatoid and psoriatic arthritis. *J Rheumatol* 2001;**28**:1842–6.

Kane D, Stafford L, Bresnihan B, FitzGerald O. A classification study of clinical subsets in an inception cohort of early psoriatic peripheral arthritis – 'DIP or not DIP revisited'. *Rheumatology* 2003;**42**:1469–76.

Kane D, Stafford L, Bresnihan B, FitzGerald O. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. *Rheumatology* 1460;**42**:1460–8.

Kay L, Walker D. Therapy for psoriatic arthritis: sometimes a conflict for psoriasis. *Br J Rheumatol* 1998; **37**:234–5.

Search for cohort studies

Few suitable RCTs were identified, so a focused, pragmatic search was carried out in OVID MEDLINE to identify cohort studies of psoriatic arthritis.

MEDLINE (OVID Online – http://www.ovid.com/): 1990–2004/November week 2
This search retrieved 151 references.

1 *ARTHRITIS, PSORIATIC/
2 psoriatic arthritis.ti.
3 1 or 2
4 COHORT STUDIES/
5 LONGITUDINAL STUDIES/
6 PROSPECTIVE STUDIES/
7 DISEASE PROGRESSION/
8 Follow-Up Studies/
9 or/4-8
10 9 and 3

Search for publications about the Toronto Psoriatic Arthritis Program

A search was undertaken to find research relating to this database.

MEDLINE (OVID Online – http://www.ovid.com/): 1990–2004/November week 2
This search retrieved 14 references.

1 ARTHRITIS, PSORIATIC/
2 psoriatic.ti,ab.
3 1 or 2
4 toronto.ti,ab.
5 gladman dd.au.
6 3 and 4 and 5

Further author searches

The following searches were undertaken to check for relevant publications by key authors.

MEDLINE (OVID Online – http://www.ovid.com/): 1990–2004/November week 3

This search retrieved 13 references.

1. ARTHRITIS, PSORIATIC/
2. psoriatic arthritis.ti,ab.
3. 1 or 2
4. (emery p or emery pc or emery pe or emery pj or emery pt or emery pw).au.
5. 3 and 4

MEDLINE (OVID Online – http://www.ovid.com/): 1990–2004/November week 3

This search retrieved 13 references.

1. ARTHRITIS, PSORIATIC/
2. psoriatic arthritis.ti,ab.
3. 1 or 2
4. (mchugh n or mchugh nj).au.
5. 3 and 4

ISI Science and Technology Proceedings (Web of Knowledge – http://wos.mimas.ac.uk/): 1990–2004 (searched on 26 November 2004)

This search retrieved 1 reference.

#1 AU=emery P*
#2 TS=psoriatic arthritis
#3 #1 and #2

This search retrieved 10 references.

#1 AU=McHugh

Appendix 2

Quality assessment tool

All of the criteria listed below should be scored with one of the following responses:

Yes (Y)	Not stated (NS)
No (N)	Not applicable (NA)
Partial (P)	Unclear (U).

Study:

1	Were the eligibility criteria for the study adequately specified? *Adequate: study population clearly defined*	
2	Was an *a priori* power calculation for adequate sample size performed?	
3	Was the sample size adequate for the analysis of the primary outcome variable?	
4	Was the number of participants who were randomised stated?	
5	Was the method used to assign participants to treatment groups truly random? *Adequate: computer-generated random numbers, random number tables* *Inadequate: alternation, case record numbers, birth dates, days of the week*	
6	Was the trial described as double-blind?	
7	Was allocation of treatment concealed? *Adequate: centralised or pharmacy-controlled assignment, serially numbered containers, serially numbered opaque envelopes, on-site computer-based systems where assignment is unreadable until after allocation, other robust measures to prevent revelation of a participant's treatment* *Inadequate: alternation, case record numbers, days of the week, open random number lists*	
8	Were the individuals administering the treatment blinded to the treatment allocation?	
9	Were the outcome assessors blinded to the treatment allocation?	
10	Were the participants blinded to the treatment allocation?	
11	Was the blinding procedure successful?	
12	Were adequate details of the treatment groups at baseline presented? Adequate: information on age, nature and severity of psoriasis, previous treatments	
13	Were the treatment groups comparable at baseline? *Answer 'Yes' if no important differences or if appropriate adjustments had been made for any differences in the baseline characteristics of the treatment groups*	
14	Were the treatment groups similar in terms of co-interventions that could influence the results?	
15	Was participant compliance with the assigned treatment adequate?	
16	Were all participants who were randomised accounted for at the end of the trial?	
17	Was a valid ITT analysis performed? *Adequate: all participants randomised included in efficacy analysis, all randomised participants who took at least one dose of trial medication included in efficacy analysis*	
18	Were at least 80% of those randomised included in the follow-up assessment? *Answer 'Yes' if at least 80% of those randomised provided complete data with regard to the primary outcome(s)*	

Quality rating =

Excellent: The answer is 'Yes' to all of the criteria.
Good: The answer is 'Yes' to all of the following criteria: 1, 3, 4, 6, 10, 12–14, 16–18.
Satisfactory: The answer is 'Yes' to all of the following criteria: 1, 3, 6, 13, 17.
Poor: The answer is NOT 'Yes' to one or more of the criteria listed for 'Satisfactory'.

Appendix 3

Excluded studies

No trials were excluded from the review because they compared different regimens of the same DMARD or compared a DMARD with or without a concomitant agent.

Appendix 4

Data extraction tables: intervention efficacy

Data extraction tables: intervention efficacy – etanercept

Study details and design	Participant details	Intervention/outcome/analyses details
Mease, 2000,[60] USA **Type of publication** Full publication Industry Trial Report **Other publications/ reports** Industry Trial Report: protocol number 016.0612[150] **Funding** Immunex Corporation **Study design** Stage 1: double-blind RCT, parallel group Monotherapy Stage 2: open-label follow-up **Setting** Outpatient **Duration of follow-up** Stage 1:12 weeks Stage 2: 24 weeks **Frequency of follow-up** Stage 1: baseline, 4, 8 and 12 weeks Stage 2: 16 and 36 weeks Extracted by: NW/ZK Checked by: NW	**Inclusion/exclusion criteria** Adults, aged 18–70 years, with active PsA (defined as >3 swollen joints and >3 tender or painful joints) and an inadequate response to NSAIDs and were thought candidates for immunomodulatory therapy. Patients taking a stable dose of methotrexate (<25 mg/week) were permitted to continue with that dose. DMARDs were to be discontinued at least 2 weeks prior to the trial. In patients with skin involvement psoriasis therapies had to have been discontinued (phototherapy 4 weeks before and topical therapies and oral retinoids 2 weeks before). **Number randomised and treated** 60 **Age** *Median age (range)* Etanercept: 46.0 years (30.0–70.0 years) Placebo: 43.5 years (24.0–63.0 years) **Gender (male)** Etanercept: 16/30 (53%) Placebo: 18/30 (60%) **Psoriatic arthritis history** *Duration of psoriatic arthritis [median (range)]* Etanercept: 9.0 years (1.0–31.0 years) Placebo: 9.5 years (1.0–30.0 years) *Prior systemic therapy* Median number of prior DMARDs Etanercept 1.5; placebo 2.0 **Psoriasis history** *Number (%) with psoriasis (>3% BSA)* Etanercept: 19/30 (63%) Placebo: 19/30 (63%)	***Stage 1*** **Intervention etanercept** Dose regimen: 25 mg sc twice a week Length of treatment: 12 weeks No. randomised: 30 No. completed: 30 Comparator placebo Dose regimen: equivalent Length of treatment: 12 weeks No. randomised: 30 No. completed: 26 ***Stage 2*** **Intervention etanercept** Dose regimen: 25 mg sc twice a week Length of treatment: 24 weeks No. = 58 No. completed: [**Confidential information removed**] No comparator **Primary outcome** The proportion of patients meeting the PsARC at 12 weeks **Sample size calculation** Assuming a response rate of 30% on placebo and 75% on etanercept a sample size of 30 patients per group gives 80% power at the 5% level **Statistical analyses** Proportions responding were compared using the Mantel–Haenszel χ^2 test adjusted for MTX use. Continuous variables were ranked and analysed by a general linear model with factors of treatment, MTX use and their interaction. The Breslow–Day test was used to

continued

Study details and design	Participant details	Intervention/outcome/analyses details
	Duration of psoriasis [median (range)] (all patients) Etanercept (n = 30): 19.0 years (4.0–53.0 years) Placebo (n = 30): 17.5 years (2.0–43.0 years) *PASI score [mean (range)] (only those evaluable)* Etanercept (n = 19): 10.1 (2.3–30.0) Placebo (n = 19): 6.0 (1.5–17.7) **Concurrent therapies** Patients taking a stable dose of methotrexate (<25 mg/week) were permitted to continue with that dose provided it had been stable for 4 weeks prior to study entry and remained constant during the study. Corticosteroids were allowed during the study at a dose of 10 mg/day prednisolone and if the dose had been stable at study entry and if it was maintained during the trial *Concomitant therapy during trial* Corticosteroids: etanercept group 6/30 (20%); placebo group 12/30 (40%) NSAIDS: etanercept group 20/30 (67%); placebo group 23/30 (77%) MTX: etanercept group 14/30 (47%); placebo group 14/30 (47%)	test for heterogeneity of relative response between MTX use strata **ITT analysis** All randomised patients included in the analysis. Last observation carried forward (LOCF) used for missing data **Comments**
Mease, 2000[60] ***Stage I efficacy outcomes*** **ACR20** Etanercept 25 mg 12 weeks = 22/30 (73%); placebo 12 weeks = 4/30 (13%); treatment difference 60% (95% CI: 40 to 80%); $p < 0.0001$ **ACR50** Etanercept 25 mg 12 weeks = 15/30 (50%); placebo 12 weeks = 1/30 (3%); treatment difference 47% (95% CI: 28 to 66%); $p = 0.0001$ **ACR70** Etanercept 25 mg 12 weeks = 4/30 (13%); placebo 12 weeks = 0/30 (0%); treatment difference 13% (95% CI: 1 to 26); $p = 0.0403$ **PsARC** Etanercept 25 mg 4 weeks = 23/30 (77%); placebo 4 weeks = 4/30 (14%); treatment difference 63% (95% CI: 44 to 83%); $p < 0.0001$ Etanercept 25 mg 8 weeks = 25/30 (83%); placebo 4 weeks = 8/30 (27%); treatment difference 57% (95% CI: 36 to 77%); $p < 0.0001$ Etanercept 25 mg 12 weeks = 26/30 (87%); placebo 12 weeks = 7/30 (23%); treatment difference 63% (95% CI: 44 to 83%); $p < 0.0001$	***Stage I efficacy outcomes (cont'd)*** **HAQ** Absolute values [median (25th and 75th percentiles] Etanercept 25 mg baseline 1.3 (0.9 to 1.6), 12 weeks 0.1 (0 to 1) Placebo baseline 1.2 (0.8 to 1.6), 12 weeks 1.1 (0.5 to 1.5); $p < 0.001$ Absolute values [mean (SD)] Etanercept 25 mg baseline 1.2 [**Confidential information removed**], 12 weeks 0.5 [**Confidential information removed**] Placebo baseline 1.2 [**Confidential information removed**] 12 weeks 1.1 [**Confidential information removed**] % improvement at 12 weeks [mean (SD)]: etanercept 25 mg ($n = 29$) 64.2 [**Confidential information removed**]; placebo ($n = 30$) 9.9 [**Confidential information removed**]; $p < 0.001$ **PASI (patients evaluable for psoriasis only)** PASI 75: etanercept 25 mg 12 weeks = 5/19 (26%); placebo 12 weeks = 0/30 (0%); treatment difference not stated; $p = 0.0154$	

continued

Stage 1 efficacy outcomes (cont'd)

PASI 50: etanercept 25 mg 12 weeks = 8/19 (42%); placebo 12 weeks = 4/19 (21%); treatment difference not stated $p = 0.295$

Values of disease activity [median (25th and 75th percentiles)]

Tender joint count

Etanercept 25 mg baseline 22.5 (11 to 32), 12 weeks 6.0 (1 to 11); placebo baseline 19.0 (10 to 39), 12 weeks 22.5 (11 to 47); $p < 0.001$

% improvement at 12 weeks [mean (median)]: etanercept 25 mg 59.9 (74.6); placebo –31.7 (–4.5); $p < 0.001$

Swollen joint count

Etanercept 25 mg baseline 14.0 (8 to 23), 12 weeks 3.0 (1 to 8); placebo baseline 14.7 (7 to 24), 12 weeks 11.0 (5 to 28); $p < 0.001$

% improvement at 12 weeks [mean (median)]: etanercept 25 mg 69.4 (72.1); placebo 14.9 (18.8); $p < 0.001$

Physician global assessment

% improvement at 12 weeks [mean (median)]: etanercept 25 mg 63.3 (66.7); placebo 6.9 (0.0); $p < 0.001$

Patient global assessment

% improvement at 12 weeks [mean (median)]: etanercept 25 mg 56.4 (66.7); placebo –2.5 (0.0); $p < 0.001$.

Stage 1 efficacy outcomes (cont'd)

Morning stiffness

% improvement at 12 weeks [mean (median)]: etanercept 25 mg 63.3 (83.3); placebo –5.1 (0.0); $p < 0.001$

Pain assessment

% improvement at 12 weeks [mean (median)]: etanercept 25 mg 43.9 (66.7); placebo 5.5 (0.0); $p < 0.001$

ESR

Etanercept 25 mg baseline 22 (9 to 34), 12 weeks 5 (3 to 12); placebo baseline 16 (9 to 29), 12 weeks 18 (6 to 40); $p < 0.001$

% improvement at 12 weeks [mean (median)]: etanercept 25 mg 49.4 (58.6); placebo –15.0 (15.4); $p < 0.001$

CRP

Etanercept 25 mg baseline 14 (7 to 28), 12 weeks 4 (3 to 11); placebo baseline 12 (8 to 22), 12 weeks 14 (4 to 23); $p < 0.001$

% improvement at 12 weeks [mean (median)]: etanercept 25 mg 51.8 (63.2); placebo –49.8 (–9.1); $p < 0.001$

Stage 2

PsARC

Etanercept 25 mg 16 weeks = 26/30 (87%); placebo/etanercept 16 weeks = 19/28 (68%)
Etanercept 25 mg 36 weeks = 26/30 (87%); placebo/etanercept 36 weeks = 21/28 (75%)

ACR20

Etanercept 25 mg 16 weeks = 22/30 (73%); placebo/etanercept 16 weeks = 12/28 (43%)
Etanercept 25 mg 36 weeks = 26/30 (87%); placebo/etanercept 36 weeks = 17/28 (61%)

ACR50

Etanercept 25 mg 16 weeks = 13/30 (43%); placebo/etanercept 16 weeks = 8/28 (29%)
Etanercept 25 mg 36 weeks = 19/30 (63%); placebo/etanercept 36 weeks = 13/28 (46%)

ACR70

Etanercept 25 mg 16 weeks = 7/30 (23%); placebo/etanercept 16 weeks = 0/28
Etanercept 25 mg 36 weeks = 10/30 (33%); placebo/etanercept 36 weeks = 7/28 (25%)

HAQ

Etanercept 25 mg 16 weeks [**Confidential information removed**]; placebo/etanercept 16 weeks [**Confidential information removed**]

% improvement at 16 weeks: etanercept 25 mg [**Confidential information removed**]; placebo/etanercept [**Confidential information removed**]

Stage 2 *(cont'd)*

Etanercept 25 mg 36 weeks [**Confidential information removed**]; placebo/etanercept 36 weeks [**Confidential information removed**]

% improvement at 36 weeks: etanercept 25 mg [**Confidential information removed**]; placebo/etanercept [**Confidential information removed**]

PASI (patients evaluable for psoriasis only)

PASI 75: etanercept 25 mg 36 weeks = 7/19 (37%); placebo/etanercept 36 weeks = 5/18 (28%)

PASI 50: etanercept 25 mg 36 weeks = 11/19 (58%); placebo/etanercept 36 weeks = 10/18 (56%)

Values of disease activity

Tender joint count

Etanercept 25 mg 16 weeks [**Confidential information removed**]; placebo/etanercept 16 weeks [**Confidential information removed**]

Stage 2 *(cont'd)*

% improvement at 16 weeks [mean (median)]: etanercept 25 mg [**Confidential information removed**]; placebo/etanercept [**Confidential information removed**]

continued

Stage 2 ***(cont'd)***

Etanercept 25 mg 36 weeks [**Confidential information removed**]; placebo/etanercept 36 weeks [**Confidential information removed**];
% improvement at 36 weeks [mean (median)]: etanercept 25 mg [**Confidential information removed**]; placebo/etanercept [**Confidential information removed**]

Swollen joint count
Etanercept 25 mg 16 weeks [**Confidential information removed**]; placebo/etanercept 16 weeks [**Confidential information removed**];
% improvement at 16 weeks [mean (median)]: etanercept 25 mg [**Confidential information removed**]; placebo/etanercept [**Confidential information removed**]

Etanercept 25mg 36 weeks [**Confidential information removed**]; placebo/etanercept 36 weeks [**Confidential information removed**];
% improvement at 36 weeks [mean (median)]: Etanercept 25 mg [**Confidential information removed**]; placebo/etanercept [**Confidential information removed**]

Physician global assessment
% improvement at 36 weeks [mean (median)]: etanercept 25 mg [**Confidential information removed**]

Patient global assessment
% improvement at 36 weeks [mean (median)]: etanercept 25 mg [**Confidential information removed**]

Stage 2 ***(cont'd)***

Morning stiffness
% improvement at 36 weeks [mean (median)]: etanercept 25 mg [**Confidential information removed**]

Pain assessment
% improvement at 36 weeks [mean (median)]: etanercept 25 mg [**Confidential information removed**]

ESR
Etanercept 25 mg 36 weeks [**Confidential information removed**]; placebo/etanercept 36 weeks [**Confidential information removed**];
% improvement at 36 weeks: etanercept 25 mg [**Confidential information removed**]; placebo/etanercept [**Confidential information removed**]

CRP
Etanercept 25mg 36 weeks [**Confidential information removed**]; placebo/etanercept 36 weeks [**Confidential information removed**];
% improvement at 36 weeks: etanercept 25 mg [**Confidential information removed**]; placebo/etanercept [**Confidential information removed**]

continued

Adverse events
Stage 1 (12 weeks treatment)

	Placebo	*Etanercept*
Any adverse event:	25 (83%);	28 (93%)
Non-infectious adverse events		
occurring in ≥ 5% of patients by treatment:		
Injection site bruise	5 (17%)	6 (20%)
Injection site reaction	1 (3%)	6 (20%)
Rhinitis	4 (13%)	5 (17%)
Headache	3 (10%)	4 (13%)
Fatigue (asthenia)	0	4 (13%)
Sinusitis	2 (7%)	3 (10%
Rash	1 3%)	3 (10%)
Nausea	2 (7%)	2 (7%)
Diarrhoea	1 (3%)	2 (7%)
Accidental injury	1 (3%)	2 (7%)
Lung disorder	1 (3%)	2 (7%)
Hypertension	0	2 (7%)
Dyspepsia	2 (7%)	0
Dizziness	2 (7%)	0
Infectious adverse events including any serious infections		
occurring in ≥ 5% of patients by treatment:		
Respiratory tract infection	4 (13%)	8 (27%)
Pharyngitis	3 (10%)	5 (17%)
Influenza syndrome	6 (20%)	0
Monilia vagina	0	3 (10%)

Cancer: none

Other non-infectious serious adverse events
Etanercept: none;
Placebo: *n* = 1 (repair of rectal tear)

Deaths: none

Withdrawals due to adverse events: none

Positive test for antibodies
Samples from 50 patients were tested at week 12; all were negative

Other important adverse event results: none reported

Adverse events
Stage 2 (24 weeks treatment, n = 58)

	Placebo	*Etanercept*
	n = 28	*n* = 30
Any adverse event:	21 (75%);	22 (73%)
Non-infectious adverse events		
occurring in ≥ 5% of patients by treatment:		
Injection site reaction	4 (14%)	0
Headache	4 (14%)	2 (7%)
Sinusitis	1 (4%)	3 (10%)
Nausea	0	3 (10%)
Diarrhoea	2 (7%)	1 (3%)
Vomiting	2 (7%)	1 (3%)
Tooth disorder	2 (7%)	0
Anxiety	0	2 (7%)
Menopause	0	2 (7%)
Infectious adverse events including any serious infections		
occurring in >5% of patients by treatment:		
Respiratory tract infection	9 (32%)	7 (23%)
Pharyngitis	2 (7%)	1 (3%)
Influenza syndrome	4 (14%)	3 (10%)
Urinary tract infection	2 (7%)	0
Infection (not specified)	0	2 (7%)

Cancer: none

Other non-infectious serious adverse events
n = 1 (multiple sclerosis diagnosed)

Deaths: **[Confidential information removed]**

Withdrawals due to adverse events: [**Confidential information removed**]

Positive test for antibodies: [**Confidential information removed**]

Other important adverse event results: [**Confidential information removed**]

Comments
All efficacy data in Stage 2 relates to non-randomised patients. All patients in Stage 2 had received etanercept

Study details and design	Participant details	Intervention/outcome/analyses details
Mease, 2004,[36] USA **Type of publication** Full publication **Other publications/reports** Wyeth, 2001[151] Ory, 2002 (abstract)[152] Krueger 2002 (abstract)[153] Wyeth, 2003[154] **Funding** Immunex Corporation **Study design** Stage 1: double-blind placebo-controlled RCT Stage 2: maintenance period Stage 3: open-label follow-up **Setting** Outpatient **Duration of follow-up** Stage 1: 24 weeks Stage 2: <24 weeks Stage 3: 48 weeks **Frequency of follow-up** Stage 1: baseline, 4, 12 and 24 weeks Stage 2: 12 week intervals thereafter Stage 3: 48 weeks Extracted by: AK/ZK/NW Checked by: NW/AK	**Inclusion/exclusion criteria** Patients between 18 and 70 years of age with active PsA and stable plaque psoriasis (target lesion >2 cm diameter) with >3 swollen joints and >3 painful/tender points with at least one of the following subtypes of psoriatic arthritis: DIP involvement; polyarticular arthritis; arthritis mutilans; asymmetric peripheral arthritis; or ankylosing spondylitis-like. Arthritis had to have demonstrated an inadequate response to NSAID therapy **Number randomised and treated** Stage 1: 205 Stage 2: [**Confidential information removed**] Stage 3: 168 **Age** Stage 1: Total: mean [**Confidential information removed**] years (range 18–76 years) Etanercept: mean 47.6 years (range 18–76 years) Placebo: mean 47.3 years (range 21–73 years) **Gender** Stage 1: Etanercept: male 57% (n = 58) Placebo: male 45% (n = 47) **Psoriatic arthritis history** *Duration of psoriatic arthritis (mean)* Etanercept: 9.0 years Placebo: 9.2 years *Subtypes of psoriatic arthritis (%)* DIP joints of hands and feet: etanercept 50%; placebo 51% Arthritis mutilans: etanercept 2%; placebo 1% Polyarticular arthritis: etanercept 83%; placebo 86% Asymmetric peripheral arthritis: etanercept 38%; placebo 41% Ankylosing spondylitis like: etanercept 4%; placebo 3% *Prior systemic therapy* Patients were permitted to have received previous DMARD therapy, but this was not a requirement for entry into the trial. Patients previously treated with etanercept or metallo-proteinase inhibitors were excluded, as were those receiving investigational drugs or biologics within 4 weeks of the trial	**Intervention etanercept** *Stage 1:* Dose regimen: 25 mg sc twice per week Duration/frequency of treatment: 24 weeks No. of participants: 101 *Stage 2:* After completing Stage 1, patients could choose to continue on their blinded study treatment in this maintenance period until all patients had completed 24 weeks of study treatment and the database was locked Dose regimen: 25 mg S.C. twice per week Duration/frequency of treatment: < 24 weeks No. of participants: [**Confidential information removed**] *Stage 3:* After the database was locked all patients [**Confidential information removed**] were eligible to enter a 48-week open-label extension. Dose regimen: 25 mg S.C. twice per week Duration/frequency of treatment: 48 weeks No. of participants: 168 (87 previously on etanercept; 81 Stage 1 previously on placebo) [**Confidential information removed**] **Comparator placebo** *Stage 1:* Placebo (n = 104): equivalent *Stage 2:* Placebo (n = [**Confidential information removed**]; equivalent **Primary outcome** The proportion of patients meeting the ACR 20 at 24 weeks **Sample size calculation** Assuming an ACR 20 rate of 60% on etanercept and 30% on placebo a sample size of 100 patients per group gives >90% power at the 5% level

continued

Study details and design	Participant details	Intervention/outcome/analyses details
	Psoriasis history Duration of psoriasis (mean) Etanercept: 18.3 years Placebo: 19.7 years **Concurrent therapies** Patients taking a stable dose (minimum 2 months) of MTX (<25 mg/week) and corticosteroids (≤10 mg/day prednisolone) were permitted to continue with that dose. Other DMARDs were to be discontinued at least 4 weeks prior to the trial. In patients with skin involvement psoriasis therapies had to have been discontinued (phototherapy at least 2 weeks prior). Topical therapies were permitted on scalp, axillae and groin only *Concomitant therapy at baseline* MTX: etanercept 45 (42%); placebo 51 (49%) Corticosteroids: etanercept 19 (19%); placebo 16 (15%) NSAIDS: etanercept 89 (88%); placebo 86 (83%)	**Statistical analyses** Binary response rates were compared using the Cochran–Mantel–Haenszel test or Fisher's exact test. Continuous variables were analysed by Wilcoxon's rank sum test using LOCF for missing data or early termination **ITT analysis** All randomised patients who received at least one dose of blinded study drug were included in the analysis **Safety assessment** All patients who were randomised and received at least one dose of study drug were evaluated for adverse events. [**Confidential information removed**] **Comments** Patients taking MTX were randomised separately

Results (Mease, 2004[36])

Stage 1 efficacy outcomes

ACR20

No. (%) of patients achieving ACR 20

Etanercept 25 mg 4 weeks = 38 (38%); placebo 4 weeks = 11 (11%); ($p < 0.001$)
Etanercept 25 mg 12 weeks = 60 (59%); placebo 12 weeks = 16 (15%); ($p < 0.001$)
Etanercept 25 mg 24 weeks = 50 (50%); placebo 24 weeks = 14 (13%); ($p < 0.001$)

Subgroup analysis (with and without MTX):
Etanercept + MTX 12 weeks = 26/42 (62%); placebo 12 weeks = 8/43 (19%)
Etanercept – MTX 12 weeks = 34/59 (58%); placebo 12 weeks = 8/61 (13%)

Etanercept + MTX 24 weeks = 23/42 (55%); placebo 24 weeks = 8/43(19%)
Etanercept – MTX 24 weeks = 27/59 (46%); placebo 24 weeks = 6/61 (10%)

ACR50

No. (%) of patients achieving ACR 50

Etanercept 25 mg 4 weeks = 11 (11%); placebo 4 weeks = 2 (2%); ($p = 0.009$)
Etanercept 25 mg 12 weeks = 38 (38%); placebo 12 weeks = 4 (4%); ($p < 0.001$)
Etanercept 25 mg 24 weeks = 37 (37%); placebo 24 weeks = 4 (4%); ($p < 0.001$)

Subgroup analysis (with and without MTX):
Etanercept + MTX 12 weeks = 17/42 (40%); placebo 12 weeks = 1/43 (2%)
Etanercept – MTX 12 weeks = 21/59 (36%); placebo 12 weeks = 3/61 (5%)

Stage 1 efficacy outcomes (cont'd)

Etanercept + MTX 24 weeks = 16/42 (38%); placebo 24 weeks = 3/43 (7%)
Etanercept – MTX 24 weeks = 21/59 (36%); placebo 24 weeks = 1/61 (2%)

ACR70

No. (%) of patients achieving ACR 70

Etanercept 25 mg 4 weeks = 1 (1%); placebo 4 weeks = 0; ($p = 0.493$)
Etanercept 25 mg 12 weeks = 11 (11%); placebo 12 weeks = 0; ($p < 0.001$)
Etanercept 25 mg 24 weeks = 9 (9%); placebo 24 weeks = 1 (1%); ($p = 0.009$)

Subgroup analysis (with and without MTX):
Etanercept + MTX 12 weeks = 4/42 (10%); placebo 12 weeks = 0/43 (0%)
Etanercept – MTX 12 weeks = 7/59 (12%); placebo 12 weeks = 0/61 (0%)

Etanercept + MTX 24 weeks = 2/42 (5%); placebo 24 weeks = 0/43 (0%)
Etanercept – MTX 24 weeks = 7/59 (12%); placebo 24 weeks = 0/61 (0%)

PsARC

No. (%) of patients achieving PsARC

Etanercept 25 mg 4 weeks = 57 (56%); placebo 4 weeks = 25 (24%); ($p < 0.001$)
Etanercept 25 mg 12 weeks = 73 (72%); placebo 12 weeks = 32 (31%); ($p < 0.001$)
Etanercept 25 mg 24 weeks = 71 (70%); placebo 24 weeks = 24 (23%); ($p < 0.001$)

continued

Stage 1 efficacy outcomes (cont'd)

Subgroup analysis (with and without MTX):
Etanercept + MTX 12 weeks = 32/42 (76%); placebo 12 weeks = 14/43 (33%)
Etanercept – MTX 12 weeks = 41/59 (69%); placebo 12 weeks = 18/61 (30%)

Etanercept + MTX 24 weeks = 31/42 (74%); placebo 24 weeks = 11/43 (26%)
Etanercept – MTX 24 weeks = 40/59 (68%); placebo 24 weeks = 13/61 (21%)

HAQ

Mean (SD) absolute values:
Etanercept 25 mg baseline (n = 101) 1.1 [**Confidential information removed**]; placebo baseline (n = 104) 1.1 [**Confidential information removed**]
Etanercept 25 mg 12 weeks (n = 101) 0.6 [**Confidential information removed**]; placebo 12 weeks (n = 104) 1.0 [**Confidential information removed**]
Etanercept 25 mg 24 weeks (n = 101) 0.5 [**Confidential information removed**]; placebo 24 weeks (n = 104) 1.0 [**Confidential information removed**]

Mean (SD) % changes from baseline:
Etanercept 25 mg 4 weeks (n = 96) 35.1 [**Confidential information removed**]; placebo 4 weeks (n = 99) 8.0 [**Confidential information removed**]; $p < 0.001$
Etanercept 25 mg 12 weeks (n = 96) 53.5[**Confidential information removed**]; placebo 12 weeks (n = 99) 6.3 [**Confidential information removed**]; $p < 0.001$
Etanercept 25 mg 24 weeks (n = 96) 53.6 [**Confidential information removed**]; placebo 24 weeks (n = 99) 6.4 [**Confidential information removed**]; $p < 0.001$

Total Sharp Score (TSS)

Mean (SD) annualised rate of progression at 6 months:
Etanercept (n = 101) [**Confidential information removed**]; placebo (n = 104) [**Confidential information removed**]

Subgroup analysis (with and without MTX) mean (SD):
Etanercept + MTX [**Confidential information removed**]; placebo [**Confidential information removed**]
Etanercept – MTX [**Confidential information removed**]; placebo [**Confidential information removed**]

PASI 75

No. (%) improvement in PASI 75
Etanercept 25 mg 24 weeks (n = 66): 15 (23%); placebo 24 weeks (n = 62): 2 (3%); $p = 0.001$

PASI 50

No. (%) improvement in PASI 50
Etanercept 25 mg 24 weeks (n = 66): 31 (47%); placebo 24 weeks (n = 62): 11 (18%); $p < 0.001$

Stage 1 efficacy outcomes (cont'd)

PASI 90

No. (%) improvement in PASI 90
Etanercept 25 mg 24 weeks (n = 66): 4 (6%); placebo 24 weeks (n = 62): 2 (3%); $p = 0.681$

Tender joint count
Mean (median) % improvement from baseline:
Etanercept 25 mg 4 weeks 33.3 (40); placebo 4 weeks 6.6 (13); $p < 0.001$
Etanercept 25 mg 12 weeks 57.7 (70); placebo 12 weeks 9.6 (16.7); $p < 0.001$
Etanercept 25 mg 24 weeks 53.3 (75); placebo 24 weeks 11.4 (13.4); $p < 0.001$

Swollen joint count
Mean (median) % improvement from baseline:
Etanercept 25 mg 4 weeks 12.3 (25); placebo 4 weeks 4.7 (11.3); $p < 0.001$
Etanercept 25 mg 12 weeks 44.7 (56.6); placebo 12 weeks 6.9 (16.7); $p < 0.001$
Etanercept 25 mg 24 weeks 46.6 (61.1); placebo 24 weeks 15.2 (21.5); $p < 0.001$

Physician global assessment
Mean (median) % improvement from baseline:
Etanercept 25 mg 4 weeks 36.0 (50.0); placebo 4 weeks 2.9 (0); $p < 0.001$
Etanercept 25 mg 12 weeks 44.9 (50); placebo 12 weeks 0.3 (0); $p < 0.001$
Etanercept 25 mg 24 weeks 47.2 (50); placebo 24 weeks 2.3 (0); $p < 0.001$

Patient global assessment
Mean (median) % improvement from baseline:
Etanercept 25 mg 4 weeks 21.6 (25.0); placebo 4 weeks 1.3 (0); $p < 0.001$
Etanercept 25 mg 12 weeks 36.1 (33.3); placebo 12 weeks –0.3 (0); $p < 0.001$
Etanercept 25 mg 24 weeks 40.4 (50.0); placebo 24 weeks –3.9 (0); $p < 0.001$

Morning stiffness (minutes)
Mean (median) % improvement from baseline:
Etanercept 25 mg 4 weeks 12.7 (50.0); placebo 4 weeks 3.7 (0); $p < 0.001$
Etanercept 25 mg 12 weeks 45.4 (68.3); placebo 12 weeks –47.2 (25.0); $p < 0.001$
Etanercept 25 mg 24 weeks 48.3 (78.9); placebo 24 weeks –56.7 (0); $p < 0.001$

Pain assessment
Mean (median) % improvement from baseline:
Etanercept 25 mg 4 weeks 29.8 (33.3); placebo 4 weeks –1.3 (0); $p < 0.001$
Etanercept 25 mg 12 weeks 47.6 (50.0); placebo 12 weeks –1.2 (0); $p < 0.001$
Etanercept 25 mg 24 weeks 45.5 (50.0); placebo 24 weeks –2.5 (0); $p < 0.001$

ESR
Not reported

continued

Stage 1 efficacy outcomes (cont'd)

C-reactive protein
Mean (median) % improvement from baseline:
Etanercept 25 mg 4 weeks 58.1 (75.0); placebo 4 weeks –76.5 (–2.9); $p < 0.001$
Etanercept 25 mg 12 weeks 46.7 (74.2); placebo 12 weeks –33.3 (–6.3); $p < 0.001$
Etanercept 25 mg 24 weeks 51.9 (77.8); placebo 24 weeks –37.1 (0); $p < 0.001$

SF-36 – mental component score:
Mean (median) % changes from baseline:
Etanercept 25 mg 4 weeks 2.3 (0.9); placebo 4 weeks 1.7 (0.9); $p = 0.748$
Etanercept 25 mg 12 weeks 2.3 (1.0); placebo 12 weeks 0.8 (0.3); $p = 0.392$
Etanercept 25 mg 24 weeks 2.7 (1.1); placebo 24 weeks –0.1 (–0.1); $p = 0.062$

Stage 2 efficacy outcomes
Not reported

Stage 3 efficacy outcomes
ACR 20/50/70 responses were maintained or improved over the open follow-up stage of the trial in those patients who had taken etanercept from baseline. Data reported in graphical form only (not extractable)

Radiographic results

Total Sharp Score (TSS)
Mean (SD) annualised rate of progression at 12 months:
Etanercept ($n = 101$) –0.03 [**Confidential information removed**]; placebo ($n = 104$) 1.00 [**Confidential information removed**]; $p = 0.0001$

Subgroup analysis (with and without MTX): mean (SD):
Etanercept + MTX [**Confidential information removed**]; placebo [**Confidential information removed**]
Etanercept – MTX [**Confidential information removed**]; placebo [**Confidential information removed**]

Total Sharp Score (TSS) excluding DIP joints
Mean (SE) annualised rate of progression at 12 months:
Etanercept [**Confidential information removed**]; placebo [**Confidential information removed**]

Stage 1 efficacy outcomes (cont'd)

SF-36 – physical component score:
Mean (median) % changes from baseline:
Etanercept 25 mg 4 weeks 5.8 (5.1); placebo 4 weeks 0.5 (0.7); $p < 0.001$
Etanercept 25 mg 12 weeks 8.9 (6.8); placebo 12 weeks 1.2 (1.6); $p < 0.001$
Etanercept 25 mg 24 weeks 9.3 (7.7); placebo 24 weeks 0.7 (0.5); $p < 0.001$

Stage 3 efficacy outcomes (cont'd)

Erosion score: mean rate of change (units/year)
Etanercept ($n = 101$) –0.08; placebo ($n = 104$) 0.69; $p = 0.0001$

Joint space narrowing: mean rate of change (units/year)
Etanercept ($n = 101$) 0.06; placebo ($n = 104$) 0.35; $p = 0.04$

PsA-specific radiographic features
No. (%) patients

[**Confidential information removed**]

continued

Adverse events

Stage 1

Non-infectious adverse events

occurring in >5% patients in any group (no. of patients)

	Etanercept	*Placebo*
Any adverse event	65 (64%)	69 (66%)
Injection site reaction	36 (36%)	9 (9%)
Injection site ecchymosis	12 (12%)	11 (11%)
Accidental injury	8 (8%)	5 (5%)
Headache	8 (8%)	5 (5%)
Rash	5 (5%)	7 (7%)
Cough increase	4 (4%)	6 (6%)
Dizziness	4 (4%)	5 (5%)
Nausea	2 (2%)	7 (7%)
Rhinitis	1 (1%)	7 (7%)
Diarrhoea	1 (1%)	6 (6%)
Dyspepsia	1 (1%)	6 (6%)
Immunisation reaction	0 (0%)	6 (6%)
Pruritus	1 (1%)	5 (5%)

Infectious adverse events including any serious infections

occurring in >5% patients in any group (no. of patients)

	Etanercept	*Placebo*
Any infection	40 (40%)	45 (43%)
Upper respiratory tract infection	21 (21%)	24 (23%)
Sinusitis	6 (6%)	8 (8%)
Urinary tract infection	6 (6%)	6 (6%)

Infections that required hospitalisation or use of intravenous antibiotics (no. of patients):
Etanercept: 0
Placebo: gastroenteritis 1

Cancer

None

Other non-infectious serious adverse events

Etanercept: total 4 (4 patients); chest pain 1; renal calculus 1; multiple sclerosis 1; synscope 1
Placebo: total 8 (4 patients); angina pectoris 1; gastroenteritis 1; gastritis 1; atrial fibrillation 1; gastrointestinal haemorrhage 1; heart failure 1; perforated large intestine 1; surgery complications for perforated bowel (intraperitoneal haemorrhage 1

Stage 1 *(cont'd)*

Deaths

Etanercept: 0
Placebo: total 1; surgery complications for perforated bowel (intraperitoneal haemorrhage) 1

Withdrawals due to adverse events

Etanercept: total 1; elevated liver enzymes 1
Placebo: total 1; increased psoriasis 1

Positive test for anti-etanercept antibody

All samples were negative for anti-etanercept antibodies

Other important adverse event results

[**Confidential information removed**]

Stage 2 (<24 weeks maintenance period)

Non-infectious adverse events

[**Confidential information removed**]

Infectious adverse events including any serious infections

Not reported

Cancer

[**Confidential information removed**]

Other non-infectious serious adverse events

[**Confidential information removed**]

Deaths

[**Confidential information removed**]

Withdrawals due to adverse events (no. of patients)

[**Confidential information removed**]

Positive test for anti-etanercept antibody

[**Confidential information removed**]

Other important adverse event results

[**Confidential information removed**]

continued

Adverse events

Stage 3 (48-week open-label follow-up)
Non-infectious adverse events
[Confidential information removed]

Serious infection *n* = 1 (pneumonia)
Infectious adverse events including any serious infections
[Confidential information removed]

Cancer
[Confidential information removed]

Other non-infectious serious adverse events
[Confidential information removed]

Deaths
[Confidential information removed]

Withdrawals due to adverse events (no. of patients)
[Confidential information removed]

Positive test for anti-etanercept antibody
[Confidential information removed]

Other important adverse event results
[Confidential information removed]

Stage 2 and Stage 3 combined

Non-infectious adverse events
[Confidential information removed]

Infectious adverse events including any serious infections
[Confidential information removed]

Cancer
[Confidential information removed]

Other non-infectious serious adverse events
[Confidential information removed]

Deaths
[Confidential information removed]

Withdrawals due to adverse events (no. of patients)
[Confidential information removed]

Positive test for anti-etanercept antibody
[Confidential information removed]

Other important adverse event results
[Confidential information removed]

Comments
[Confidential information removed]

Data extraction tables: intervention efficacy – infliximab

Study details and design	Participant details	Intervention/outcome/analyses details
Antoni, 2005,[61] USA **Type of publication** Industry trial report **Other publications/reports** **Centocor 2003[127]** Industry submission Schering-Plough submission, 2004[62] Antoni, 2002[155] Antoni, 2003[156] **Funding** Centocor **Study design** Double-blind RCT, parallel Monotherapy Two stages: Stage I RCT, Stage II open uncontrolled follow-up **Setting** Outpatient **Duration of follow-up** Stage I: 16 weeks Stage II: >34 weeks **Frequency of follow-up** Stage I: baseline, 2, 6, 14, 16 weeks Stage II: 18, 22, 30, 46, 50 weeks	**Inclusion/exclusion criteria** Patients aged 18 years and above diagnosed with peripheral polyarticular PsA at least 6 months previously and active disease including 5+ swollen/tender joints. Subjects must have failed on at least one DMARD. They were not required to have active psoriasis at baseline Of the included patients [**Confidential information removed**]. 42.3% of infliximab patients and 32.7 % of placebo patients had psoriasis (defined as baseline PASI score of >2.5. The proportion of patients with spine involvement, arthritis mutilans and erosions at baseline was not reported **Number randomised and treated** 104 **Age** Mean age (SD) Infliximab 45.7 years (11.1); placebo 45.2 years (9.7) **Gender** Infliximab male 57.7%; placebo male 57/7% **Psoriatic arthritis history** ***Duration of psoriatic arthritis*** *Diagnosis duration [mean (SD)(range)]:* Infliximab mean [**Confidential information removed**]; placebo [**Confidential information removed**] *Symptom duration, years (mean (SD):* Infliximab 11.7 (9.8); placebo 11.0 (6.6) **Psoriasis history** *Symptom duration: years [mean (SD)(range)]* Infliximab 16.9 (10.9); placebo 19.4 (11.6) *PASI score [mean (SD)]* Infliximab (n = 42) 5.1 (5.9); placebo (n = 40) 4.2 (5.8)	*Stage I* **Intervention infliximab** Dose regimen: 5 mg/kg at weeks 0, 2, 6, 14 Length of treatment: 16 weeks No. randomised: 52 No. completed: [**Confidential information removed**] **Comparator placebo** Dose regimen: equivalent Length of treatment: 16 weeks No. randomised: 52 No. completed: [**Confidential information removed**] *Stage II* Patients in the placebo group in Stage I received 5 mg/kg infliximab at weeks 16, 18, 22, 30, 38 and 46. Patients who were in the infliximab group in Stage I received placebo at weeks 16 and 18 and 5 mg/kg infliximab at weeks 22, 30, 38 and 46 **Primary outcome** ACR 20 response at week 16 **Sample size calculation** Based on prediction of 50% ARC 20 on infliximab and 20% on placebo, it was calculated that a sample size of 45 patients per treatment arm would achieve 80% power at the 5% level [**Confidential information removed**] **Statistical analyses** Categorical outcomes including the ACR 20 were compared using the χ^2 test [**Confidential information removed**] **ITT analysis** Yes. Consisting of a subset of all randomised patients Subgroup analysis of 16-week data for patients who used MTX during the study compared with those who did not

continued

Study details and design	Participant details	Intervention/outcome/analyses details
Extracted by: ZK/NW Checked by: NW/AK	*Concurrent therapies* *DMARD use (not MTX)* Infliximab [**Confidential information removed**]; placebo [**Confidential information removed**] *MTX use* Infliximab [**Confidential information removed**]; placebo [**Confidential information removed**] ***Concomitant therapy during trial*** MTX was permitted if it had been taken continuously for at least 3 months prior to trial and if its dose was a stable dose of ≥15 mg/week taken for at least 4 weeks prior to the trial. Patients taking MTX were also given folic acid. Patients receiving one of the following DMARDs were eligible; MTX, leflunomide, SSZ, hydroxychloroquine, i.m. gold, penicillamine and azathioprine. Patients were permitted to maintain use of NSAIDs and corticosteroids if on a stable dose 2 weeks prior to screening. Stable doses of soft topicals were also permitted	

Results

Stage I efficacy outcomes

ACR 20 response
Infliximab 2 weeks: 42.3% (22/52); placebo 2 weeks: 5.8% (3/52); $p < 0.01$
Infliximab 6 weeks: 61.5% (32/52); placebo 6 weeks: 7.7% (4/52); $p < 0.01$
Infliximab 10 weeks: 53.8% (28/52); placebo 10 weeks: 13.5% (7/52); $p < 0.01$
Infliximab 14 weeks: 67.3% (35/52); placebo 14 weeks: 11.5% (6/52); $p < 0.01$
Infliximab 16 weeks: 65.4% (34/52); placebo 16 weeks: 9.6% (5/52); $p < 0.01$

Subgroup results (baseline MTX or no baseline MTX) at 16 weeks
Infliximab + MTX 16 weeks: 62.5%; placebo + MTX 16 weeks: [**Confidential information removed**]
Infliximab – MTX 16 weeks: 67.9%); placebo – MTX 16 weeks: [**Confidential information removed**]

ACR 50 response
Infliximab 2 weeks: 17.3% (9/52); placebo 2 weeks: 0% (0/52); $p = 0.01$
Infliximab 6 weeks: 26.9% (14/52); placebo 6 weeks: 0% (0/52); $p < 0.01$
Infliximab 10 weeks: 32.7% (17/52); placebo 10 weeks: 1.9% (1/52); $p < 0.01$
Infliximab 14 weeks: 36.5% (19/52); placebo 14 weeks: 1.9% (1/52); $p < 0.01$
Infliximab 16 weeks: 46.2% (24/52); placebo 16 weeks: 0% (0/52); $p < 0.01$

Stage I efficacy outcomes (cont'd)

ACR 70 response
Infliximab 2 weeks: 1.9% (1/52); placebo 2 weeks: 0% (0/52); $p > 0.99$
Infliximab 6 weeks: 9.6% (5/52); placebo 6 weeks: 0% (0/52); $p = 0.07$
Infliximab 10 weeks: 13.5% (7/52); placebo 10 weeks: 0% (0/52); $p = 0.02$
Infliximab 14 weeks: 21.2% (11/52); placebo 14 weeks: 0% (0/52); $p < 0.01$
Infliximab 16 weeks: 28.8% (15/52); placebo 16 weeks: 0% (0/52); $p < 0.01$

PsARC
Infliximab 2 weeks: 55.8% (29/52); placebo 2 weeks: 17.3% (9/52); $p < 0.01$
Infliximab 6 weeks: 76.9% (40/52); placebo 6 weeks: 17.3% (9/52); $p < 0.01$
Infliximab 10 weeks: 65.4% (34/52); placebo 10 weeks: 21.2% (11/52); $p < 0.01$
Infliximab 14 weeks: 76.9% (40/52); placebo 14 weeks: 13.5% (7/52); $p < 0.01$
Infliximab 16 weeks: 75.0% (39/52); placebo 16 weeks: 21.2% (11/52); $p < 0.01$

HAQ (0 to3)
Absolute values mean (SE)
Infliximab baseline [**Confidential information removed**]; 16 weeks [**Confidential information removed**]
Placebo baseline [**Confidential information removed**]; 16 weeks [**Confidential information removed**]

continued

Stage 1 efficacy outcomes (cont'd)

Absolute change from baseline: mean (SE)
Infliximab 16 weeks: –0.6 [**Confidential information removed**]; placebo 16 weeks: 0.0 [**Confidential information removed**]; between-group difference [**Confidential information removed**]; $p < 0.01$.

HAQ (0 to3): mean (SE) % improvement from baseline
Infliximab 16 weeks ($n = 48$): 49.8 (8.2); placebo 16 weeks ($n = 47$): –1.6 (8.3); between-group difference: [**Confidential information removed**]

Change in PASI: mean (SE) % change from baseline
Infliximab 16 weeks ($n = 42$) –4.1 (0.6); placebo 16 weeks ($n = 38$): 0.9 (0.6); between-group difference –5 (95% CI: –6.8 to –3.3); $p < 0.01$.

Mean (SD) % ACR improvement
[**Confidential information removed**]

Swollen joint count (0 to 66): mean (SE) % improvement
Infliximab 16 weeks ($n = 52$): –59.9 (9.1); placebo 16 weeks ($n = 51$): 1.8 (9.2)

Pain/tender joint count (0 to 68): mean (SE) % improvement
Infliximab 16 weeks ($n = 52$): –55.2 (9.7); placebo 16 weeks ($n = 51$): 23.6 (9.8)

Stage 1 efficacy outcomes (cont'd)

Subject's VAS of pain: mean (SE) % improvement
Infliximab 16 weeks ($n = 52$): –53.7(7.7); placebo 16 weeks ($n = 51$): 8.7 (7.8)
Patient's VAS of global disease activity: mean (SE) % improvement
Infliximab 16 weeks ($n = 52$): –47.5 (7.4); placebo 16 weeks ($n = 51$): 13.9 (7.5)
Physician's VAS of global disease activity: mean (SE) % improvement
Infliximab 16 weeks ($n = 51$): –58.4 (6.0); placebo 16 weeks ($n = 51$): 4.7 (6.0)
CRP (C reactive protein): mean (SE) % improvement
Infliximab 16 weeks ($n = 48$): –57.1 (9.5); placebo 16 weeks ($n = 48$): –3.6 (9.5)
DAS 28 (Disease Activity Score assessing 28 joints): mean (SE) % change from baseline
Infliximab 16 weeks: ($n = 51$) –45.5 (3.2); placebo: 16 weeks: ($n = 50$): –2.8 (3.2)

Stage 2 efficacy outcomes

ACR 20 response
Infliximab 18 weeks: 77.6% (38/49); placebo/infliximab 18 weeks: 52.0% (26/50)
Infliximab 22 weeks: 71.4% (35/49); placebo/infliximab 22 weeks: 62.0% (31/50)
Infliximab 30 weeks: 65.3% (32/49); placebo/infliximab 30 weeks: 66.0% (33/50)
Infliximab 38 weeks: 57.1% (28/49); placebo/infliximab 38 weeks: 62.0% (31/50)
Infliximab 46 weeks: 57.1% (28/49); placebo/infliximab 46 weeks: 66.0% (33/50)
Infliximab 50 weeks: 69.4% (34/49); placebo/infliximab 50 weeks: 68.0% (34/50)

Subgroup results (baseline MTX or no baseline MTX) at 50 weeks
[**Confidential information removed**]

ACR 50 response
Infliximab 18 weeks: 49.0% (24/49); placebo/infliximab 18 weeks: 26.0% (13/50)
Infliximab 22 weeks: 38.8% (19/49); placebo/infliximab 22 weeks: 36.0% (18/50)
Infliximab 30 weeks: 42.9% (21/49); placebo/infliximab 30 weeks: 44.0% (22/50)
Infliximab 38 weeks: 40.8% (20/49); placebo/infliximab 38 weeks: 48.0% (24/50)
Infliximab 46 weeks: 49.0% (24/49); placebo/infliximab 46 weeks: 46.0% (23/50)
Infliximab 50 weeks: 53.1% (26/49); placebo/infliximab 50 weeks: 42.0% (21/50)

ACR 70 response
Infliximab 18 weeks: 28.6% (14/49); placebo/infliximab 18 weeks: 8.0% (4/50)
Infliximab 22 weeks: 22.4% (11/49); placebo/infliximab 22 weeks: 20.0% (10/50)
Infliximab 30 weeks: 26.5% (13/49); placebo/infliximab 30 weeks: 22.0% (11/50)

Stage 2 efficacy outcomes (cont'd)

Infliximab 38 weeks: 26.5% (13/49); placebo/infliximab 38 weeks: 28.0% (14/50)
Infliximab 46 weeks: 32.7% (16/49); placebo/infliximab 46 weeks: 24.0% (12/50)
Infliximab 50 weeks: 38.8% (19/49); placebo/infliximab 50 weeks: 34.0% (17/50)

PsARC
Infliximab 18 weeks: 81.6% (40/49); placebo/infliximab 18 weeks: 70.0% (35/50)
Infliximab 22 weeks: 77.6% (38/49); placebo/infliximab 22 weeks: 74.0% (37/50)
Infliximab 30 weeks: 73.5% (36/49); placebo/infliximab 30 weeks: 78.0% (39/50)
Infliximab 38 weeks: 71.4% (35/49); placebo/infliximab 38 weeks: 82.0% (41/50)
Infliximab 46 weeks: 69.4% (34/49); placebo/infliximab 46 weeks: 74.0% (37/50)
Infliximab 50 weeks: 73.5% (36/49); placebo/infliximab 50 weeks: 76.0% (38/50)

HAQ (0 to3)
Absolute values: mean (SE)
[**Confidential information removed**]

Absolute change from baseline mean (SE)
[**Confidential information removed**]

HAQ (0 to3): mean (SE) % improvement from baseline
Infliximab 50 weeks ($n = 45$): –42.5 (8.8)

Change in PASI mean (SE) % change from baseline
Infliximab 50 weeks ($n = 35$): –4.8 (1.0); placebo/infliximab 50 weeks ($n = 37$): –2.7 (1.0)

continued

Stage 2 efficacy outcomes (cont'd)

Mean (SD) % ACR improvement
[**Confidential information removed**]

Swollen joint count (0 to 66): mean (SE) % improvement
Infliximab 50 weeks (n = 49): –72.5 (5.1)
Pain/tender joint count (0 to 68): mean (SE) % improvement
Infliximab 50 weeks (n = 49): –66.9 (5.9)

Subject's VAS of pain: mean (SE) % improvement
Infliximab 50 weeks (n = 49): –54.1 (6.1)

Adverse events

Stage 1

	Placebo n = 51	*Infliximab* n = 52
Any adverse event	33/51(65%)	38/52 (73%)
Non-infectious adverse events occurring in ≥ 5% patients [**Confidential information removed**]		
Infusion reactions	5 (10%)	4 (8%)
Infectious adverse events including any serious infections occurring in ≥ 5% patients [**Confidential information removed**]		

Serious infection: 1 patient (infliximab) – infection and synovitis

Cancer
[**Confidential information removed**]

Other non-infectious serious adverse events
Placebo: 1 patient-rectal bleeding resulting from diverticulitis
[**Confidential information removed**]

Deaths
Withdrawals due to adverse events
[**Confidential information removed**]

Positive test for antibodies
[**Confidential information removed**]

Other important adverse event results
[**Confidential information removed**]

Stage 2 efficacy outcomes (cont'd)

Patient's VAS of global disease activity: mean (SE) % improvement
Infliximab 50 weeks (n = 49): –50.0 (7.3)
Physician's VAS of global disease activity: mean (SE) % improvement
Infliximab 50 weeks (n = 49): –70.3 (4.4)
CRP: mean (SE) % improvement
Infliximab 50 weeks (n = 46): –25.7 (17.2)
DAS 28: mean (SE) % change from baseline
Infliximab 50 weeks (n = 48) –48.2 (3.6)

Adverse events

Stage 2

	Placebo/infliximab n = 50	*Infliximab* n = 49
Any adverse event	44/50 (88%)	41/49 (84%)
Non-infectious adverse events occurring in ≥5% patients [**Confidential information removed**]		
Infectious adverse events including any serious infections occurring in ≥ 5% patients [**Confidential information removed**]		
Infusion reactions	7 (14%)	4 (8%)

Serious infection: 1 patient on infliximab/placebo – *Salmonella* infection

Cancer
[**Confidential information removed**]

Other non-infectious serious adverse events
[**Confidential information removed**]

Deaths
[**Confidential information removed**]

Withdrawals due to adverse events
[**Confidential information removed**]

Positive test for antibodies
[**Confidential information removed**]

Other important adverse event results
[**Confidential information removed**]

Comments
[**Confidential information removed**]

Appendix 5

Data extraction tables: intervention adverse events

Data extraction tables: intervention adverse events – etanercept

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Bathon, 2000,[78] USA **Genovese, 2002,[157] USA** **Type of publication** Full publication **Other publications/reports** Bathon, 2003,[158] full publication **Funding** Immunex **Study design** Stage 1: double-blind RCT Stage 2: open–label follow-up **Duration of follow-up** Stage 1: 12 months Stage 2: 12 months **Study objective** To compare the efficacy and safety of etanercept and MTX in patients with early RA Extracted by: AK Checked by: NW	**Indication** Early RA **Inclusion criteria** Patients ≥18 years of age who had had RA for no more than 3 years, had not been treated with MTX and had no other important concurrent illness. Patients were required to have positive RF or at least 3 bone erosions of the hand, wrists or feet; at least 10 swollen joints; and at least 12 tender or painful joints. DMARDs were discontinued at least 4 weeks before the study began **Total no. of participants** Stage 1: 632 Stage 2: 512 **Age** Etanercept 10 mg: mean 50.0 years (SD 13, range 19–84) Etanercept 25 mg: mean 51.0 years (SD 13, range 21–82) **Gender** Etanercept 10 mg: male 25% Etanercept 25 mg: male 26% **Concurrent therapies** All patients received 1 mg folic acid per day. Other drugs permitted were stable doses of NSAIDs, prednisodone	**Intervention etanercept** Dose regimen: 10 mg s.c. twice per week Duration/frequency of treatment: 24 months No. of participants: Stage 1 208; Stage 2 166 **Intervention etanercept** Dose regimen: 25 mg s.c. twice per week Duration/frequency of treatment: 12 months No. of participants: Stage 1 207; Stage 2 177 **Comparators** MTX (Stage 1 $n = 217$; Stage 2 $n = 169$): 2.5 mg oral three times per week titrated to 2.5 mg oral eight times per week after 8 weeks **Assessment** Adverse events were graded on a scale derived from the Common Toxicity Criteria for the National Cancer Institute. Patients were assessed every 3 months for adverse events **Comments** Patients who discontinued either study drug received standard care and continued to be evaluated for the duration of the study	**Stage 1 (months 0–12)** **Non-infectious adverse events** occurring in ≥10% patients in any etanercept group (no. of patients) *Etanercept 10 mg n = 208* / *Etanercept 25 mg n = 207* Low peripheral lymphocyte count: (56%) / Not reported Injection site reaction: 63 (30%) / 77 (37%) Headache: 52 (25%) / 46 (22%) Nausea: 29 (14%) / 35 (17%) Sporadic neutropenia: Not reported / (16%) Rhinitis: 36 (17%) / 31 (15%) Diarrhoea: 26 (12%) / 30 (14%) Bleeding at injection site: 30 (14%) / 29 (14%) Asthenia: 19 (9%) / 27 (13%) Influenza-like syndrome: 20 (10%) / 26 (13%) Rash: 33 (16%) / 25 (12%) Dyspepsia: 21 (10%) / 25 (12%) Dizziness: 10 (5%) / 24 (12%) Back pain: 12 (6%) / 22 (11%) Abdominal pain: 23 (11%) / 20 (10%) Sinusitis: 28 (13%) / 20 (10%) **Other non-infectious adverse events (no. of patients)** Etanercept 10 mg: Grade 3 neutropenia 1 Etanercept 25 mg: Grade 3 neutropenia 2 **Infectious adverse events including any serious infections** occurring in ≥10% patients in any etanercept group (no. of patients) *Etanercept 10 mg* / *Etanercept 25 mg* Upper respiratory tract infection: 57 (27%) / 72 (35%) Skin infection: 22 (11%) / 28 (14%) All types of infection occurred at a rate of 1.5 events per patient year across the two etanercept groups

continued

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
	(≤10 mg per day), glucocorticoids		Infection requiring hospitalisation or i.v. antibiotics occurred in <3% of patients
	Comments		There were no opportunistic infections
			The rate of serious infections was similar to that in months 13–24
			Cancer (no. of patients)

	Etanercept 10 mg	*Etanercept 25 mg*
Breast cancer	1	0
Lung cancer	1	0
Carcinoid lung cancer	0	1
Hodgkin's disease	0	1
Prostate cancer	0	1

Other non-infectious serious adverse events
Not reported

Deaths (no.)

	Etanercept 10 mg	*Etanercept 25 mg*
Metastatic lung cancer	1	0
Non-infectious complications from dissection of pre-existing aortic aneurysm	0	1

Withdrawals due to adverse events (no.)
Etanercept 10 mg: 2 (10.6%) Etanercept 25 mg: 5 (4.8%)

Positive test for anti-etanercept antibody
<3% of etanercept patients were positive. The positives tests were not associated with adverse events

Other important adverse event results
Not reported

continued

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results

Stage 2 (months 13–24)

Non-infectious adverse events

Not reported

Infectious adverse events including any serious infections (no. of patients)

	Etanercept 10 mg $n = 166$	*Etanercept 25 mg* $n = 177$
Cellulitis	1	1
Bronchitis	1	0
Pneumonia	1	0
Cystitis	0	2

There were no tuberculosis infections

Cancer (no. of patients)

Etanercept 10 mg: 1 *Etanercept 25 mg: 1*

Other non-infectious serious adverse events (no. of patients)

Not reported

Deaths

There were no deaths

Withdrawals due to adverse events (no. of patients)

Etanercept 10 mg: 2 *Etanercept 25 mg: 5*

Positive test for anti-etanercept antibody

Not reported

Other important adverse event results

Not reported

continued

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results

Stage 1 and 2 combined (months 0–24)

Non-infectious adverse events

occurring in ≥ 10% patients in any group (no. of patients)

	Etanercept 10 mg $n = 208$	*Etanercept 25 mg* $n = 207$
Low peripheral lymphocyte count	Not reported	Not reported
Injection site reaction	66 (32%)	81 (39%)
Headache	56 (27%)	51 (25%)
Nausea	30 (14%)	42 (20%)
Rash	40 (19%)	37 (18%)
Rhinitis	41 (20%)	37 (18%)
Diarrhoea	28 (14%)	35 (17%)
Asthenia	25 (12%)	33 (16%)
Bleeding at injection site	31 (15%)	32 (16%)
Sporadic neutropenia	Not reported	Not reported
Dyspepsia	33 (16%)	31 (15%)
Dizziness	15 (7%)	30 (15%)
Abdominal pain	26 (13%)	26 (13%)
Back pain	17 (8%)	25 (12%)
Accidental injury	24 (12%)	23 (11%)
Pain	17 (8%)	22 (11%)
Ecchymosis	19 (9%)	23 (11%)
Vomiting	7 (3%)	20 (10%)
Hypertension	23 (11%)	18 (9%)
Peripheral oedema	23 (11%)	14 (7%)

Infectious adverse events including any serious infections

occurring in > 10% patients in any etanercept group (no. of patients)

Not reported

There were no opportunistic infections

Infection requiring hospitalisation or i.v. antibiotics (no. of patients)

Etanercept 10 mg: 5 (2.4%) Etanercept 25 mg: 7 (3.4%)

Cancer (no. of patients)

Etanercept 10 mg: 3 Etanercept 25 mg: 4

continued

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
			Other serious non-infectious adverse events Not reported **Deaths (no.)** See Stage 1 (months 0–12) data **Withdrawals due to adverse events (no.)** Etanercept 10 mg: 11 (6.6%) Etanercept 25 mg: 15 (7.3%) **Positive test for anti-etanercept antibody** 14 (3.5%) etanercept patients were positive: etanercept 10 mg 6 (2.9%) patients; etanercept 25 mg 8 (3.9%) patients. The positives tests were not associated with adverse events **Other important adverse event results** Not reported **Comments** Withdrawal data reported for Stage 1 and 2 combined (months 0–24) do not tally with withdrawal data reported for Stage 1 (months 0–12). Using Stage 1 data (months 0–12) and Stage 2 data (months 13–24), withdrawal figures tally to: Etanercept 10 mg: 24 (11.5%) Etanercept 25 mg: 15 (7.2%) The reporting of infection and serious adverse events across the different periods and different publications was inconsistent

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Davis, 2003,[74] USA, Canada and Europe **Type of publication** Full publication **Other publications/reports** None **Funding** Immunex Corp. **Study design** Double-blind placebo-controlled RCT **Duration of follow-up** 24 weeks **Study objective** To determine the safety and efficacy of etanercept in adults with moderate to severe ankylosing spondylitis Extracted by: AK Checked by: NW	**Indication** Ankylosing spondylitis **Inclusion criteria** Patients aged between 18 and 70 years with ankylosing spondylitis. Patients were excluded if they had complete ankylosis (fusion) of the spine, had previously received TNF inhibitor therapy, had serious infection within 4 weeks of starting the study, were pregnant or had received DMARDs (except for hydroxychloroquine, SSZ, or MTX) within 4 weeks of starting **Total no. of participants** 277 **Age** Etanercept: mean 42.1 years (range 24–70) Placebo: mean 41.9 years (range 16–65) **Gender** Etanercept: male 76% (n = 105) Placebo: male 76% (n = 105) **Concurrent therapies** Hydroxychloroquine, SSZ, MTX, NSAIDs and prednisone; analgesics were permitted od **Comments**	**Intervention etanercept** Dose regimen: 25 mg s.c. twice per week Duration/frequency of treatment: 24 weeks No. of participants: 138 **Comparators** Placebo (n = 139): equivalent **Assessment** All patients who were randomised and received at least one dose of study drug were evaluated for adverse events, which were graded on a scale derived from the Common Toxicity Criteria for the National Cancer Institute. Patient diaries were used to record any adverse events. Study staff reviewed the diary with the patient at each visit **Comments**	**Non-infectious adverse events** occurring in ≥5% patients (no. of patients) *Placebo* / *Etanercept* Injection site reaction 13 (9%) / 41 (30%) Injection site bruising 23 (17%) / 29 (21%) Headache 16 (12%) / 19 (14%) Accidental injury 6 (4%) / 17 (12%) Diarrhoea 13 (9%) / 11 (8%) Rash 9 (6%) / 11 (8%) Rhinitis 9 (6%) / 8 (6%) Abdominal pain 7 (5%) / 8 (6%) Dizziness 3 (2%) / 8 (6%) Flu syndrome 10 (7%) / 5 (4%) **Infectious adverse events including any serious infections** occurring in ≥5% patients (no. of patients) *Placebo* / *Etanercept* Upper respiratory tract infection 16 (12%) / 28 (20%) There were no opportunistic or TB infections **Serious infections (no. of patients)** Etanercept: wound infection after cat bite 1 Placebo: viral infection 1 **Cancer** Not reported **Other non-infectious serious adverse events (no. of patients)** *Placebo* / *Etanercept* Chest pain 1 Accidental injury 2 Suicide attempt 1 Lymphadenopathy / 1 Staphylococcal cellulitis after spider bite 1 Fever with injection site reaction / 1 Ulcerative colitis / 1 Intestinal obstruction due to adhesions / 1 Bone fracture after trauma / 3

continued

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results

Deaths
Not reported

Withdrawals due to adverse events (no.)

	Placebo	*Etanercept*
Total	1	7
Fever with injection site reaction		1
Ulcerative colitis		1
Intestinal obstruction due to adhesions		1
Bone fracture after trauma		2
Gastrointestinal haemorrhage secondary to haemorrhoids		1
Ileitis secondary to Crohn's disease		1

Positive test for anti-etanercept antibody
3 etanercept patients tested positive for non-neutralising anti-etanercept antibodies

Other important adverse event results
Not reported

Comments

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Elewski, 2004,[81] USA, Canada and Europe **Type of publication** Conference poster **Other publications/reports** Wyeth, 2003,[159] industry trial report Wyeth, 2003,[160] industry trial report Gordon 2004,[161] conference poster Gottlieb 2004,[162] conference poster Industry submission (study no. 20021642), 2004[163] **Funding** Immunex Corp. (wholly owned subsidiary of Amgen Inc.); Wyeth Pharmaceuticals Inc. **Study design** Double-blind RCT, parallel with open follow-up Monotherapy The trial was conducted in two stages: Stage 1 RCT; Stage 2 open follow-up **Duration of follow-up** Stage 1: 12 weeks Stage 2: 36 weeks Extracted by: NW Checked by: ZK	**Indication** Psoriasis **Inclusion/exclusion criteria** Active clinically stable plaque psoriasis involving ≥10% BSA, minimum PASI score of 10, previously treated with at least one systemic therapy or phototherapy or to be a candidate for such therapy. Aged ≥18 years. Those previously treated with etanercept or with antibodies to TNF or who had received investigational drugs, biologics, systemic psoriasis therapy, systemic corticosteroids or PUVA within previous 4 weeks or had received UVB, topical steroids, topical vitamin A or D analogues or anthralin within 2 weeks were excluded **Number randomised and treated** 583 **Age** *Mean age (SD)* Etanercept 25 mg: 45.4 years [**Confidential information removed**] Etanercept 50 mg: 45.2 years [**Confidential information removed**] Placebo: 44.8 years [**Confidential information removed**]	*Stage 1* **Intervention etanercept** Dose regimen: 25 mg s.c. twice per week Length of treatment: 12 weeks No. randomised: 196 No. completed: [**Confidential information removed**] **Intervention etanercept** Dose regimen: 50 mg s.c. twice per week Length of treatment: 12 weeks No. randomised: 194 No. completed: [**Confidential information removed**] **Comparator placebo** Dose regimen: equivalent Length of treatment: 12 weeks No. randomised: 193 No. completed: [**Confidential information removed**] *Stage 2* **Intervention etanercept** Dose regimen: 25 mg s.c. twice per week Length of treatment: 36 weeks No.: 557 **Assessment** [**Confidential information removed**]	*Stage 2* All patients on etanercept 25 mg twice per week Results expressed as exposure-adjusted rate per 100 patient years Previous group: *Placebo* [**Confidential information removed**]; *Etanercept 25 mg* [**Confidential information removed**]; Etanercept 50 mg [**Confidential information removed**]; All *n* = 557 [**Confidential information removed**] **Non-infectious adverse events** Any non-infectious adverse events: [**Confidential information removed**] Headache: [**Confidential information removed**] Accidental injury: [**Confidential information removed**] Injection site ecchymosis: [**Confidential information removed**] Migraine: [**Confidential information removed**] **Infectious adverse events including any serious infections** Infections: [**Confidential information removed**] **Serious infections (no.):** [**Confidential information removed**] **Cancer** [**Confidential information removed**] **Other non-infectious serious adverse events (no.)** [**Confidential information removed**] **Deaths (no.)** [**Confidential information removed**] **Withdrawals due to adverse events** [**Confidential information removed**] **Positive test for anti-etanercept antibody** [**Confidential information removed**] **Other important adverse event results** [**Confidential information removed**]

continued

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
	Total 45.2 years [**Confidential information removed**] **Gender** Etanercept 25 mg: male 65%; [**Confidential information removed**] Etanercept 50 mg: male 67%; [**Confidential information removed**] Placebo: male 64%; (124/193) Total: male 66% (382/583) **Concurrent therapies** [**Confidential information removed**] **Comments** [**Confidential information removed**]; 583 treated		**Comments** 48-week data were not available for many patients

BSA, bovine serum albumin.

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Geborek, 2002,[76] Sweden **Type of publication** Full publication **Other publications/reports** None **Funding** Not stated **Study design** Prospective study **Duration of follow-up** 2 years **Study objective** To apply a clinical protocol adapted to monitor new treatments in RA to evaluate tolerability and efficacy of etanercept, infliximab and leflunomide under post-marketing conditions. Extracted by: AK Checked by: NW	**Indication** RA **Inclusion criteria** Patients who had failed on at least two DMARDs, including MTX, who started on treatment with etanercept, infliximab or leflunomide **Total no. of participants** 369 **Age** Etanercept: mean 54.0 years **Gender** Etanercept: male 22% **Concurrent therapies** Prednisolone, systemic glucocorticoid, DMARDs **Comments**	**Intervention etanercept** Dose regimen: 25 mg s.c. twice per week No. of participants: 166 **Comparators** Infliximab (n = 135): 3 mg/kg infusion at start, weeks 2, 6, 12 and thereafter every 8th week. Later the dose could be individually tailored and increased. Leflunomide (n = 103): 100 mg oral days 1–3 and thereafter 20 mg per day **Assessment** For assessment, the patient was included in the new treatment group when starting on a new regimen. If restarted on one treatment after a pause, the patient was considered to have continued to receive the original therapeutic regimen **Comments** All adverse events were recorded using WHO terminology Patients were allowed to switch between etanercept, infliximab and leflunomide if withdrawn from any of the three treatments. 33 patients tried two treatments and one tried all three	**Non-infectious adverse events** Not reported **Infectious adverse events including any serious infections** Not reported **Serious infections (no.)** Etanercept: bacterial infection 3 (days 130, 150, 270) **Cancer** Not reported Other non-infectious serious adverse events (no.) *Etanercept* Myocardial infarction: 4, days 41, 63, 130, 501 Uterine cervical carcinoma: 2, days 160, 413 Acute myeloic leukaemia: 1, day 440 General malaise: 1, day 350 Leucopenia: 1, day 91 Bell's paralysis: 1, day 130 Cutaneous vasculitis: 1, day 368 Discoid lupus: 1, day 69 **Deaths (no.)** *Etanercept* Gastroenteritis: 1, day 180 Immunocytoma of breast: 1, day 220 Myocardial infarction: 1, day 413 **Withdrawals due to adverse events** Etanercept: adverse reactions were the main cause of withdrawal throughout the study **Positive test for anti-etanercept antibody** Not reported **Other important adverse event results** The total no. of observational years for etanercept was 232.8

continued

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
			Graded side-effects per 100 years (no.)
			Etanercept
			Fatal 1.3 ($n = 3$)
			Life-threatening 0 ($n = 0$)
			Serious 7 ($n = 15$)
			Moderate 16 ($n = 36$)
			Mild 27 ($n = 61$)
			Not graded 2 ($n = 5$)
			Comments

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse events Results
Gottlieb, 2003,[83] USA **Type of publication** Full publication **Other publications/reports** Wyeth, 2003,[164] industry trial report Gaspari, 2002,[165] abstract Gottlieb, 2004,[166] abstract Gordon, 2004,[161] conference poster Gottlieb, 2004,[162] conference poster Industry submission (study no. 20021632), 2004[163] **Funding** Immunex Corp. (wholly owned subsidiary of Amgen Inc.) **Study design** Double-blind RCT, parallel Monotherapy The study was in 2 stages: Stage 1: RCT Stage 2: Follow-up after discontinuation of study treatments **Duration of follow-up** Stage 1: 24 weeks [**Confidential information removed**] Extracted by: AK Checked by: NW	**Indication** Psoriasis **Inclusion/exclusion criteria** Patients aged at least 18 years, with active stable plaque psoriasis involving 10% or more of the BSA. Patients were excluded if they had guttate, erythrodermic or pustular psoriasis, other skin conditions or other significant medical conditions that might interfere with evaluations of the effect of study medications on psoriasis. Patients were to have had at least one previous systemic psoriasis therapy or phototherapy. PUVA and systemic psoriasis therapy were not allowed within 4 weeks of the trial, and UVB, topical corticosteroids, vitamin A or D analogues or anthralin were not allowed within 2 weeks of baseline measurements **No. randomised and treated** 112 **Age** *Mean (range/SD)* Etanercept: 48.2 years 25–72 years [**Confidential information removed**] Placebo: 46.5 years 18–77 years [**Confidential information removed**]	**Intervention etanercept** Dose regimen: 25 mg s.c. twice per week Length of treatment: 24 weeks No. randomised: 57 No. completed: 12 weeks 53 (93%); 24 weeks 48 (84%) **Comparator placebo** Dose regimen: equivalent Length of treatment: 24 weeks No. randomised: 55 No. completed: 12 weeks 40 (73%); 24 weeks 12 (22%) *Stage 2* Etanercept *n* = 17 Placebo *n* = 3 **Assessment** All patients who had received the drug were evaluated for adverse events and serious adverse events and premature discontinuations **Comments**	**Adverse events** *N* (%) adverse events occurring in ≥5% of groups combined: *Etanercept (n = 57)* / *Placebo (n = 55)* **Non-infectious adverse events** Any non-infectious [**Confidential information removed**] headache 9 (16%) 7 (13%) bruise at injection site 6 (11%) 5 (9%) sinusitis 8 (14%) 4 (7%) pain 4 (7%) 4 (7%) peripheral oedema 1 (2%) 5 (9%) hypertension 4 (7%) 2 (4%) accidental injury 4 (7%) 2 (4%) injection site reaction 5 (9%) 0 (0%) [**Confidential information removed**] [**Confidential information removed**] [**Confidential information removed**] [**Confidential information removed**] [**Confidential information removed**] [**Confidential information removed**] [**Confidential information removed**] **Infectious adverse events including any serious infections** Any infection [**Confidential information removed**] Upper respiratory tract infection 20 (35%) 11 (20%) Bronchitis [**Confidential information removed**] Cellulitis [**Confidential information removed**] Herpes simplex [**Confidential information removed**] **Serious infections (no.)** Etanercept: appendicitis 1/57 Placebo: pharyngitis 1/55 **Cancer** [**Confidential information removed**] **Other non-infectious serious adverse events (no.)** Etanercept: motor vehicle crash 1/57 Placebo: stroke 1/55; pustular psoriasis 1/55

continued

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
	Gender Etanercept: male 58% (33/57) Placebo: male 67% (37/55) **Concurrent therapies** Tar compounds and steroid-free topical emollients were allowed during the study. Some topical preparations (such as lower potency corticosteroids and tar-based shampoo) were allowed to continue at stable doses during therapy on the scalp, axilla and groin **Comments** 18 patients were randomised; 112 received treatment		**Deaths (no.)** [**Confidential information removed**] **Withdrawals due to adverse events** Etanercept: 2/57 Placebo: 6/55 **Positive test for anti-etanercept antibody** No patients developed antibodies to etanercept: all samples negative for anti-etanercept antibodies **Other important adverse event results** Number of patients reporting adverse events was similar between the two groups [**Confidential information removed**] Rates of adverse events per patient year: Etanercept: [**Confidential information removed**] Placebo: [**Confidential information removed**] **Comments**

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Klareskog, 2004,[75] Europe, Australia, UK and USA **Type of publication** Full publication **Other publications/reports** Industry submission (TEMPO trial), 2004[163] **Funding** Wyeth Research **Study design** Double-blind RCT **Duration of follow-up** 52 weeks **Study objective** To assess combination treatment with etanercept and MTX versus the monotherapies in patients with RA. Extracted by: AK Checked by: NW	**Indication** **RA** **Inclusion criteria** Patients aged ≥18 years with disease duration of 6 months to 20 years with active adult-onset RA (defined as ≥10 swollen and ≥12 painful joints). Patients had to have had a less than satisfactory response to ≥1 DMARD other than MTX. Patients previously treated with MTX were included provided that they had not had clinically important toxic effects or lack of response and had not been treated with MTX within 6 months of enrolment **Total no. of participants** 682 **Age** Etanercept: mean 53.2 years (SD 13.8) Combination: mean 52.5 years (SD 12.4) **Gender** Etanercept: male 23% Combination: male 26% **Concurrent therapies** NSAIDs, corticosteroids. All patients received 5 mg folic acid supplement twice per week **Comments**	**Intervention etanercept** Dose regimen: 25 mg s.c. twice per week and oral placebo once per week Duration/frequency of treatment: 52 weeks No. of participants: 223 **Comparators** MTX (n = 228): 7.5 escalated to 20 mg oral once per week and placebo s.c. twice per week Combination (n = 231): etanercept 25 mg s.c. twice per week combined with methotrexate oral once per week **Assessment** Treatment-emergent adverse events were defined as either an adverse event that was not present at baseline or an event present at baseline that worsened during the study. A serious infection was defined as need for treatment with parenteral antibiotics or admission **Comments**	**Non-infectious adverse events** Treatment-emergent adverse events occurring in ≥10% patients: *Etanercept* / *Combination* Any adverse event 192 (86%) / 187 (81%) Abdominal pain 26 (12%) / 42 (18%) Accidental injury 19 (9%) / 21 (9%) Asthenia 23 (10%) / 24 (10%) Back pain 28 (13%) / 24 (10%) Cough increased 14 (6%) / 25 (11%) Diarrhoea 23 (10%) / 19 (8%) Headache 34 (15%) / 34 (15%) Injection site reaction 46 (21%) / 23 (10%) Nausea 22 (10%) / 55 (24%) Rash 16 (7%) / 23 (10%) Vomiting 7 (3%) / 12 (5%) **Infectious adverse events including any serious infections** Etanercept: all infections 131 (59%); serious infections 10 (4%) **Cancer** Etanercept: basal cell carcinoma 1; breast cancer 1; rectal cancer 1; melanoma 1 Combination: basal cell carcinoma 1 **Other non-infectious serious adverse events (no. of patients)** Etanercept: total 25 (11%) Combination: total 19 (8%) Deaths (no.) Etanercept: heart failure and suspected sepsis 1 Combination: stroke and pneumonia 1 **Withdrawals due to adverse events** Etanercept: 25 Combination: 24 **Positive test for anti-etanercept antibody** Not reported **Other important adverse event results** Not reported **Comments**

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Leonardi, 2003,[82] USA **Type of publication** Full publication **Other publications/reports** Duggan, 2003,[167] industry trial report Krueger, 2004,[168] conference poster Gottlieb, 2004,[166] conference poster Gordon, 2004,[161] conference poster Gottlieb, 2004,[162] conference poster Industry submission (study no. 20021639), 2004[163] **Funding** Immunex Corp. (wholly-owned subsidiary of Amgen Inc.) **Study design** Stage 1: double-blind RCT, parallel Monotherapy Stage 2: double-blind follow-up Stage 3: discontinuation of treatment (for responders, i.e. those who achieved PASI 50) or open-label etanercept (for incomplete responders, i.e. those who did not achieve PASI 50) Stage 4: retreatment **Duration of follow-up** Total: 72 weeks	Indication Psoriasis **Inclusion/exclusion criteria** Aged at least 18 years, with active clinically stable plaque psoriasis involving ≥10% BSA and a PASI score of ≥10; previously received systemic or phototherapy for psoriasis or had been a candidate for such therapy. Patients with other forms of psoriasis or those who had previously received etanercept were excluded. Patients were excluded if they had received anti-CDA antibodies or interleukin-2 in the previous 6 months, other biologic or other investigational therapy or PUVA, systemic corticosteroids or systemic psoriasis therapy in previous 4 weeks, or UVB, topical steroids, vitamin A or D analogues or anthralin in previous 2 weeks or antibiotics in previous week **Number randomised and treated** 652 **Age** *Mean age (SE/SD)* Etanercept 25 mg once per week: 44.4 (0.9/12.0) years; Etanercept 25 mg twice per week: 45.4 (1.0/13.1) years;	*Stage 1* **Intervention etanercept** Dose regimen: 25 mg s.c. once per week Length of treatment: 12 weeks No. randomised: 160 No. completed: [**Confidential information removed**] (94% of total study population) **Intervention etanercept** Dose regimen: 25 mg s.c. twice per week Length of treatment: 12 weeks No. randomised: 162 No. completed: [**Confidential information removed**] (94% of total study population) **Intervention etanercept** Dose regimen: 50 mg s.c. twice per week Length of treatment: 12 weeks No. randomised: 164 No. completed: [**Confidential information removed**] (94% of total study population) **Comparator placebo** Dose regimen: equivalent Length of treatment: 12 weeks No. randomised: 166 No. completed: [**Confidential information removed**] (94% of total study population) *Stage 2* Patients continued on same doses of etanercept. Those on placebo in Stage 1 switched to etanercept 25 mg twice per week. No. completed 24 weeks	*Stage 2* Adverse events from week 13 to week 24: occurring in at least 3% of patients in any group: *Etanercept 25 mg 2/wk (was placebo)* $n = 153$ — *Etanercept 25 mg 1/wk* $n = 150$ — *Etanercept 25 mg 2/wk* $n = 149$ — *Etanercept 50 mg 2/wk* $n = 159$ **Non-infectious adverse events** Any non-infectious [**Confidential information removed**] Rash: 0 / 0 / 2 (1%) / 6 (4%) Headache: 8 (5%) / 5 (3%) / 8 (5%) / 4 (3%) Sinusitis: 5 (3%) / 3 (2%) / 3 (2%) / 1 (1%) Asthenia: 2 (1%) / 3 (2%) / 7 (5%) / 2 (1%) Myalgia: 3 (2%) / 5 (3%) / 6 (4%) / 4 (3%) Accidental injury: 6 (4%) / 6 (4%) / 6 (4%) / 4 (3%) [**Confidential information removed**] **Infectious adverse events including any serious infections** Any infectious [**Confidential information removed**] Upper respiratory infection: 9 (6%) / 8 (5%) / 9 (6%) / 11(7%) **Serious infections (no.)** [**Confidential information removed**] **Cancer** [**Confidential information removed**] **Other non-infectious serious adverse events (no.)** Etanercept 25 mg once per week: [**Confidential information removed**] Etanercept 25 mg twice per week: [**Confidential information removed**] Etanercept 50 mg twice per week: [**Confidential information removed**] **Deaths (no.)**: No data

continued

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Stage 1: 12 weeks Stage 2: 12 weeks Stage 3: variable duration with follow-up until relapse (for responders); 48 weeks (for incomplete responders) Stage 4: 24 weeks or until study conclusion Extracted by: NW Checked by: AK	Etanercept 50 mg twice per week: 44.8 (0.8/10.8) years; Placebo: 45.6 (1.0/12.9) years **Gender** Etanercept 25 mg once per week: male 74% (119/160) Etanercept 25 mg twice per week: male 67% (109/162) Etanercept 50 mg twice per week: male 65% (106/164) Placebo: male 63% (104/166) Total: male 67% (438/652) **Concurrent therapies** Stable doses of low or moderate potency topical steroids on scalp, axilla and groin were permitted. [**Confidential information removed**] **Comments** 672 randomised, 652 received one dose of study drug	Etanercept 25 mg s.c. once per week: [**Confidential information removed**] Etanercept 25 mg s.c. twice per week: [**Confidential information removed**] Etanercept 50 mg twice per week: [**Confidential information removed**] Ex-placebo: [**Confidential information removed**] Total: [**Confidential information removed**] *Stage 3* 157 patients who had not achieved a PASI 50 by 24 weeks: open-label etanercept 25 mg s.c. twice per week 409 patients who achieved a PASI 50 by 24 weeks had etanercept stopped (i.e. no treatment). *Stage 4* Of those responders who underwent treatment withdrawal in Stage 3, those whose disease relapsed (i.e. lost >50% of their initial treatment response) were re-treated with their original blinded dose of etanercept ($n = 297$) [**Confidential information removed**] **Assessment** All patients who had received the drug were evaluated for adverse events, infections, antibodies and premature discontinuations **Comments**	**Withdrawals due to adverse events** Etanercept 25 mg once per week: [**Confidential information removed**]; etanercept 25 mg twice per week; [**Confidential information removed**]; etanercept 50 mg twice per week; [**Confidential information removed**]; placebo: [**Confidential information removed**] Over the 24-week study, 27 patients withdrew owing to adverse events **Positive test for anti-etanercept antibody** 8/520 etanercept patients for whom paired baseline 24-week (or study withdrawal) samples were available had serum samples tested positive for non-neutralising anti-etanercept antibodies **Other important adverse event results** [**Confidential information removed**] *Stage 3* Adverse events at week 60 Of the 157 treated with open-label etanercept 25 mg twice per week in Stage 3, 72% received 48 weeks of therapy and 38% received 60 weeks. [**Confidential information removed**]. Exposure adjusted rates of adverse events, infections and serious adverse events were similar to those in the first phase: [**Confidential information removed**] **Serious adverse events** Any: [**Confidential information removed**] Serious infection: [**Confidential information removed**] **Withdrawals due to adverse events** [**Confidential information removed**] *Stage 4* [**Confidential information removed**] **Serious adverse events** [**Confidential information removed**]

continued

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
			Withdrawals due to adverse events [**Confidential information removed**] **Serious adverse events** [**Confidential information removed**] **Withdrawals due to adverse events** [**Confidential information removed**] **Comments** Further subgroup analyses and further results relating to the re-treatment phase are reported in the Industry Trial Report

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Mease, 2004,[36] USA **Type of publication** Full publication **Other publications/reports** Wyeth, 2001,[151] industry trial report Wyeth, 2003,[154] industry trial report Wyeth, 2001,[169] industry expert report Ory, 2002,[152] abstract **Funding** Immunex Corp. (wholly owned subsidiary of Amgen Inc.) **Study design** Stage 1: double-blind placebo controlled RCT Stage 2: maintenance period (blinded) Stage 3: open-label follow-up **Duration of follow-up** Stage 1: 24 weeks [**Confidential information removed**] Stage 3: 48 weeks **Study objective** To evaluate the safety, efficacy and effect on radiographic progression of etanercept in patients with PsA	**Indication** **PsA** **Inclusion criteria** Patients between 18 and 70 years of age with active PsA and stable plaque psoriasis (target lesion >2 cm diameter) with >3 swollen joints and >3 painful/tender points with at least one of the following subtypes of PsA: DIP involvement, polyarticular arthritis, arthritis mutilans, asymmetric peripheral arthritis, or ankylosing spondylitis-like. Arthritis had to have demonstrated an inadequate response to NSAID therapy **Total no. of participants** Stage 1: 205 [**Confidential information removed**] Stage 3: 168 **Age** Stage 1: Total: mean [**Confidential information removed**] years (range 18–76) Etanercept: mean 47.6/years (range 18–76) Placebo: mean 47.3/years (range 21–73)	**Intervention etanercept** *Stage 1* Dose regimen: 25 mg s.c. twice per week Duration/frequency of treatment: 24 weeks No. of participants: 101 *Stage 2* After completing Stage 1, patients could choose to continue on their blinded study treatment in this maintenance period until all patients had completed 24 weeks of study treatment and the database was locked Dose regimen: 25 mg s.c. twice per week Duration/frequency of treatment: [**Confidential information removed**] *Stage 3* After the database was locked, all patients who completed 12 weeks of study drug in Stage 1 [**Confidential information removed**] were eligible to enter a 48-week open-label extension. Dose regimen: 25 mg s.c. twice per week Duration/frequency of treatment: 48 weeks No. of participants: 168 (87 previously on etanercept; 81 Stage 1 previously on placebo) [**Confidential information removed**] **Comparators** *Stage 1* Placebo (n = 104): equivalent *Stage 2* Placebo [**Confidential information removed**]: equivalent	**Stage 1 (24-week double-blind RCT)** **Non-infectious adverse events** occurring in >5% patients in any group (no. of patients) *Etanercept* / *Placebo* Any adverse event: 65 (64%) / 69 (66%) Injection site reaction: 36 (36%) / 9 (9%) Injection site ecchymosis: 12 (12%) / 11 (11%) Accidental injury: 8 (8%) / 5 (5%) Headache: 8 (8%) / 5 (5%) Sinusitis: 6 (6%) / 8 (8%) Rash: 5 (5%) / 7 (7%) Cough increase: 4 (4%) / 6 (6%) Dizziness: 4 (4%) / 5 (5%) Nausea: 2 (2%) / 7 (7%) Rhinitis: 1 (1%) / 7 (7%) Diarrhoea: 1 (1%) / 6 (6%) Dyspepsia: 1 (1%) / 6 (6%) Immunisation reaction: 0 (0%) / 6 (6%) Pruritus: 1 (1%) / 5 (5%) **Infectious adverse events including any serious infections** occurring in >5% patients in any group (no. of patients) *Etanercept* / *Placebo* Any infection: 40 (40%) / 45 (43%) Upper respiratory infection: 21 (21%) / 24 (23%) Urinary tract infection: 6 (6%) / 6 (6%) **Infections that required hospitalisation or use of intravenous antibiotics (no. of patients)** Etanercept: 0 Placebo: gastroenteritis 1 **Cancer** None **Other non-infectious serious adverse events** Etanercept: total 4 (4 patients); chest pain 1; renal calculus 1; multiple sclerosis 1; synscope 1

continued

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Extracted by: AK Checked by: NW	**Gender** Stage 1: Etanercept: male 57% (n = 58) Placebo: male 45% (n = 47) **Concurrent therapies** MTX, NSAIDs, corticosteroids, topical preparations (for scalp, axilla or groin only). **Comments**	**Assessment** All patients who were randomised and received at least one dose of study drug were evaluated for adverse events [**Confidential information removed**] **Comments**	Placebo: total 8 (4 patients); angina pectoris 1; gastroenteritis 1; gastritis 1; atrial fibrillation 1; gastrointestinal haemorrhage 1; heart failure 1; perforated large intestine 1; surgery complications for perforated bowel (intraperitoneal haemorrhage 1 **Deaths** Etanercept: 0 Placebo: total 1; surgery complications for perforated bowel (intraperitoneal haemorrhage) 1 **Withdrawals due to adverse events** Etanercept: total 1; elevated liver enzymes 1 Placebo: total 1; increased psoriasis 1 **Positive test for anti-etanercept antibody** All samples were negative for anti-etanercept antibodies **Other important adverse event results** [**Confidential information removed**] **Stage 2 (<24 weeks maintenance period)** **Non-infectious adverse events** [**Confidential information removed**] **Infectious adverse events including any serious infections** [**Confidential information removed**] **Cancer** [**Confidential information removed**] **Other non-infectious serious adverse events** Etanercept: [**Confidential information removed**] Placebo: [**Confidential information removed**] **Deaths** None **Withdrawals due to adverse events (no. of patients)** Etanercept: [**Confidential information removed**] Placebo: [**Confidential information removed**]

continued

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
			Positive test for anti-etanercept antibody **[Confidential information removed]** **Other important adverse event results** **[Confidential information removed]** **Stage 3 (48-week open-label follow-up)** **Non-infectious adverse events** **[Confidential information removed]** **Infectious adverse events including any serious infections** **[Confidential information removed]** **Cancer** **[Confidential information removed]** **Other non-infectious serious adverse events** **[Confidential information removed]** **Deaths** **[Confidential information removed]** **Withdrawals due to adverse events (no.)** **[Confidential information removed]** **Positive test for anti-etanercept antibody** **[Confidential information removed]** **Other important adverse event results** **[Confidential information removed]** **Stage 2 and Stage 3 combined** **Non-infectious adverse events** **[Confidential information removed]** **Infectious adverse events including any serious infections** **[Confidential information removed]** **Cancer** **[Confidential information removed]**

continued

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
			Other non-infectious serious adverse events **[Confidential information removed]** **Deaths** **[Confidential information removed]** **Withdrawals due to adverse events (no.)** **[Confidential information removed]** **Positive test for anti-etanercept antibody** **[Confidential information removed]** **Other important adverse event results** **[Confidential information removed]** **Comments** **[Confidential information removed]**

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Moreland, 1999,[77] USA **Type of publication** Full publication **Other publications/reports** None **Funding** Immunex Corp. (wholly owned subsidiary of Amgen Inc.) **Study design** Double-blind RCT **Duration of follow-up** 26 weeks **Study objective** To establish the benefit of etanercept in the treatment of RA over time with simplified dosing Extracted by: ZK Checked by: NW	**Indication** RA **Inclusion criteria** Patients were adults aged ≥ 18 years with active RA that had an inadequate response to one of any four DMARDs. Use of DMARDs stopped at least 4 weeks prior to study **Total no. of participants** 234 **Age** Etanercept 10 mg: mean 53 years Etanercept 25 mg: mean 53 years Placebo: mean 51 years **Gender** Etanercept 10 mg: male 16% Etanercept 25 mg: male 26% Placebo: male 24% **Concurrent therapies** Oral corticosteroids, NSAIDs and analgesics (except 24 h before joint examinations) were permitted **Comments**	**Intervention etanercept** Dose regimen: 10 mg s.c. twice per week Duration/frequency of treatment: 26 weeks No. of participants: 76 **Intervention etanercept** Dose regimen: 25 mg s.c. twice per week Duration/frequency of treatment: 26 weeks No. of participants: 78 **Comparators** Placebo (n = 80): equivalent **Assessment** Not reported **Comments**	**Non-infectious adverse events (no. of events per patient-year)** occurring in ≥ 10% of patients *Placebo* / *Etanercept 10 mg* / *Etanercept 25 mg* Injection-site reaction: 0.79 (13%) / 7.39 (43%) / 11.76 (49%) Headache: 0.65 (10%) / 0.81 (20%) / 0.46 (14%) Sinusitis: 0.42 (11%) / 0.26 (11%) / 0.34 (12%) Rhinitis: 0.54 (11%) / 0.36 (12%) / 0.37 (10%) Diarrhoea: 0.28 (6%) / 0.33 (11%) / 0.18 (5%) **Infectious adverse events including any serious adverse events (no.)** occurring in ≥ 10% of patients *Placebo* / *Etanercept 10 mg* / *Etanercept 25 mg* Upper respiratory tract infection: 0.93 (16%) / 0.85 (29%) / 1.11 (33%) **Cancer** Not reported **Other non-infectious serious adverse events** Not reported **Deaths** Not reported **Withdrawals due to adverse events (no.)** Etanercept 10 mg: injection-site reactions 1 Etanercept 25 mg: total 0 **Positive test for anti-etanercept antibody** 1 etanercept 10 mg patient tested positive for non-neutralising anti-etanercept antibodies at 3 and 4 months **Other important adverse events** Not reported **Comments**

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Phillips, 2002[80] **Type of publication** Full publication **Other publications/reports** None **Funding** National Institutes of Health grants and Arthritis Foundation Investigator Award **Study design** Retrospective review of medical records **Duration of follow-up** 6 months **Study objective** To investigate the long-term safety and tolerability of etanercept in patients with systemic rheumatic diseases Extracted by: ZK Checked by: NW	**Indication** Rheumatic diseases: RA 49 (66%) Juvenile RA 25 (14%) PsA 17 (9%) Ankylosing spondylitis 4 (2%) Dermatomyositis, Stills disease or undifferentiated inflammatory arthritis (9%) **Inclusion criteria** Patients receiving 25 mg etanercept twice weekly **Total no. of participants** 168 **Age** Mean 52.8 years (SD 15.6) **Gender** Etanercept: male 19% **Concurrent therapies** MTX (56%) Other DMARDs (8%) Corticosteroids (62%) **Comments**	**Intervention etanercept** Dose regimen: 25 mg twice per week Duration of treatment: median 10 months (range 1–19) No. of participants: 180 **Assessment** Not reported **Comments** Medically important or serious adverse events defined as those requiring i.v. antibiotics or hospitalisation The records of 180 patients were reviewed but as 12 patients were lost to follow-up during the period of the study, only 168 patients were included in the final calculations	**Non-infectious adverse events** Minor adverse events (no. of patients): Injection site reactions 6 Chest pain 5 Skin rash 14 Depression 5 **Infectious adverse events including any serious infections** Upper respiratory infection/cough/sinusitis 16 patients Serious infections (no of patients): Acute cholecystitis 1 Septic wrist 1 Arthroplastic hip infection 1 Bacteraemia 1 Psoas abscess/internal perforation 1 **Cancer** None **Other non-infectious serious adverse events** 5 (2.9%) patients experienced serious adverse events **Deaths (no.)** Total 2 (both infection related) **Withdrawals due to adverse events (no.)** Total 10; minor adverse event 6; serious infection 4 **Positive test for anti-etanercept antibody** Not reported **Other important adverse event results** 91 (54%) of patients experienced an adverse event 86 (51%) patients experienced a minor adverse event **Comments**

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Willis, 2001,[79] Europe **Type of publication** Abstract (interim analysis) **Other publications/reports** Wajdula, 2000,[170] abstract **Funding** Wyeth-Ayerst **Study design** Open-label study **Duration of follow-up** 1–2 years **Study objective** To evaluate the long-term safety and efficacy of etanercept in patients who completed prior double-blind studies comparing etanercept to placebo Extracted by: AK Checked by: NW	**Indication** RA **Inclusion criteria** Patients with inadequate responses to DMARDs **Total no. of participants** 549 **Age** Not stated **Gender** Not stated **Concurrent therapies** Not stated **Comments**	**Intervention etanercept** Dose regimen: 25 mg s.c. twice per week Duration/frequency of treatment: 1–2 years No. of participants: 549 [479 (87%) completed 1 year of follow-up, 94 (17%) completed 2 years of follow-up)] **Comparators** None **Assessment** Not stated **Comments**	**Non-infectious adverse events** The most frequent adverse events were injection-site reactions **Infectious adverse events including any serious infections** The most frequent adverse events were upper respiratory infections Rate of serious infections remained unchanged over the course of the study **Cancer** Rate of malignancies remained unchanged over the course of the study **Other non-infectious serious adverse events** Not stated **Deaths** Not stated **Withdrawals due to adverse events** The rate of withdrawal for tolerance-related reasons was 8% **Positive test for anti-etanercept antibody** Not stated **Other important adverse event results** Not stated **Comments**

Data extraction tables: intervention adverse events – infliximab

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Baert, 2003,[102] USA **Type of publication** Full publication **Other publications/reports** None **Funding** Not stated **Study design** Prospective cohort of consecutive patient records **Duration of follow-up** Mean 10 months **Study objective** To evaluate the clinical significance of the development of antibodies to infliximab in patients with Crohn's disease Extracted by: NW Checked by: ZK	**Indication** Crohn's disease. 50 patients had enterocutaneous fistulas and 115 had active inflammatory Crohn's disease without fistulas **Inclusion criteria** Patients with refractory luminal or fistulising Crohn's disease who started treatment with infliximab between December 1998 and July 2000 **Total no. of participants** 125 **Age** Mean 35 years (range 17–73) **Gender** 43/125 (34%) male **Concurrent therapies** Corticosteroids 53/125 (42%) Azathioprine/mercaptopurine 56/125 (45%) MTX 3/125 (2%) Mesalamine 50/125 (40%) None 18/125 (14%) **Comments**	**Intervention infliximab** Dose regimen: 5 mg/kg i.v. infusion Duration/frequency of treatment: patients with fistulas received induction therapy at weeks 0, 2 and 6. Patients who responded were retreated upon relapse of the disease. Patients with non-fistulising disease (active luminal) were treated with a single infusion at week 0. Patients who responded were retreated upon relapse of the disease Mean number of infusions per patient: 3.9 (range 1–17) **Comparators** None used **Assessment** Patients were evaluated before and every 4 weeks after each infusion. Side-effects, and early reactions (infusion reactions) and late reactions (rash, arthralgia, fatigue, myalgia and influenza-like symptoms) were recorded Serum concentrations of infliximab and anti-infliximab antibodies were measured at each visit and before each infusion **Comments**	**Non-infectious adverse events** Overall rate of infusion reactions: 27% No infusion reactions were seen with the first infusion but the incidence increased during subsequent infusions: after 2nd around 17%, after 3rd around 20%, after 4th and 5th around 23% and after 6th around 25% (numbers all read off graph). There was a strong association between concentration of antibodies and occurrence of infusion reaction **Infectious adverse events including any serious infections** Not reported **Cancer** Not reported **Other non-infectious serious adverse events (no.)** Not reported **Deaths** None stated **Withdrawals due to adverse events** Not reported **Positive test for anti-infliximab antibody** At baseline no patient tested positive for anti-infliximab antibodies. After the first infusion around 45% had detectable antibodies. After the 5th infusion, this had risen to 61%. The incidence did not increase with a higher number of infusions Use of immunosuppressive agents was associated with a lower incidence of antibodies [43% compared with 75%)] and lower titres of antibodies There was a weak positive association between the use of the three-infusion induction and the development of antibodies ($p = 0.04$) Duration of response was significantly longer in those with antibody titres <8 μg/ml than in those with a higher titre: median 71 days (95% CI: 57 to 88) compared with 35 days (95% CI: 28 to 42) **Other important adverse event results** Not reported **Comments** Data on late reactions not reported

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results

Baeten, 2003,[94] Belgium

Type of publication
Full publication

Other publications/reports
None

Funding
Vlaanderen (FWO-Vlaanderen)

Study design
Prospective observational. Three separate cohorts from different studies

Duration of follow-up
Total 191.5 patient-years

Study objective
To assess the long-term safety data of a large cohort of patients receiving infliximab

Extracted by: ZK

Checked by: NW

Indication
Spondyloarthropathy (SpA) including some patients with PsA

Inclusion criteria
Patients with active SpA meeting the European Spondylarthropathy Study Group criteria with inflammatory back pain and/or at least 1 swollen joint or enthesis

Total no. of participants
107

Age
Infliximab (cohort 1): median 43 years (range 26–73)
Infliximab (cohort 2): median 47 years (range 26–66)
Infliximab (cohort 3): median 46 years (range 28–72)

Gender
Infliximab (cohort 1): male 80%
Infliximab (cohort 1): male 70%
Infliximab (cohort 1): male 60%

Concurrent therapies

	Cohort 1	*Cohort 2*	*Cohort 3*
MTX	1/31	0	18/36
Corticosteroids	2	2	4

Comments
Cohort 1: intake of patients between November 1999 and March 2000
Cohort 2: intake of patients between November 2000 and February 2001
Cohort 3: intake of patients between March 2001 and October 2001

	Cohort 1	*Cohort 2*	*Cohort 3*
Ankylosing spondylitis	16	19	26
Psoriatic arthritis	11	18	3
Undifferentiated spondylarthropathy	4	3	7

Intervention infliximab

Cohort 1
Dose regimen: 5 mg/kg i.v.
Duration/frequency of treatment: loading regimen 5 mg/kg i.v. dose given at weeks 0, 2, 6. Maintenance therapy 5 mg/kg every 14 weeks thereafter for 1st year, 5 mg/kg every 10 weeks for 2nd year, 5 mg/kg every 8 weeks for 3rd year
Total duration of follow-up: 83.1 patient-years
No. of participants: 31

Cohort 2
Dose regimen: 5 mg/kg i.v. and 10 mg/kg i.v.
Duration/frequency of treatment: loading regimen 5 mg/kg i.v. dose given at weeks 0, 2, 6. Maintenance therapy 10 mg/kg every 14 weeks thereafter for 1st year, 5 mg/kg every 8 weeks for 2nd year
Total duration of follow-up: 63.6 patient-years
No. of participants: 40

Cohort 3
Dose regimen: 5 mg/kg i.v.
Duration/frequency of treatment: loading regimen 5 mg/kg i.v. dose given at weeks 0, 2, 6. Maintenance therapy 5 mg/kg every 8 weeks
Total duration of follow-up: 44.8 patient-years
No. of participants: 36

Comparators
None used

Assessment
Only adverse events that were serious or were possibly treatment related were registered

Comments
Minor adverse effects, e.g. headache, dizziness, were not considered in this study

Non-infectious adverse events

	No. of patients (all cohorts)
Pyelonephritis	1
Mild infusion reaction	1

Infectious adverse events
including any serious infections

Tooth abscess	2
Anal abscess	1
Erysipelas	1
Pneumonia	1
Palmoplantar pustulosis	3
Serious infections (no.)	
Disseminated tuberculosis	2
Wound infection	1
Septic-like arthritis	1
Sepsis	1
Retropharyngeal abscess	3
Infusion reaction	1

Cancer

Spinocellular carcinoma of the skin	1

Other non-infectious serious adverse events (no.)
None reported

Deaths
None reported

Withdrawals due to adverse events
5 patients (serious infections)

Positive test for anti-etanercept antibody
More than 90% of patients developed antinuclear antibodies

Other important adverse event results

Comments

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Cheifetz, 2003,[97] USA **Type of publication** Full publication **Other publications/reports** None **Funding** Not stated **Study design** Retrospective cohort of consecutive patient records **Duration of follow-up** Total study duration 2.5 years. Follow-up varied with number of infusions and time between infusions **Study objective** To assess the incidence and management if infusion reactions to infliximab in patients with Crohn's disease Extracted by: NW Checked by: ZK	**Indication** Crohn's disease. 50 patients had enterocutaneous fistulas and 115 had active inflammatory Crohn's disease without fistulas **Inclusion criteria** Review of chart data for patients with Crohn's disease; no further details provided **Total no. of participants** 165 **Age** Not reported **Gender** Not reported **Concurrent therapies** Not reported **Comments**	**Intervention infliximab** Dose regimen: not stated (infusion) Duration/frequency of treatment: the 50 patients with fistulas received induction therapy at weeks 0, 2 and 6. Patients were then retreated as necessary according to disease symptoms. These patients received 205 infusions over the study period, with a mean interval between infusions of 7.9 (SD 11.0) weeks The 115 patients with non-fistulising disease were treated with a single infusion at week 0, then treated periodically as required according to symptoms induction therapy only; 55 patients received only one infusion, the remaining 60 had multiple infusions (total 219, with a mean interval between infusions of 13.1 (SD 13.7) weeks **Comparators** None used **Assessment** Focused on infusion reactions **Comments**	**Non-infectious adverse events** *All patients* $n = 165$ / *Fistula* $n = 50$ / *Non-fistula* $n = 115$ Acute infusion reactions: 14 (8.4%) / 3 (6%) / 11 (9.6%) Delayed infusion reactions: 3 (0.6%) / 0 / 3 (0.6%) In both groups of patients the mean interval between infusions did not differ between those who did or did not develop an infusion reaction **Infectious adverse events including any serious infections** *Serious infections* Not reported **Cancer** Not reported **Other non-infectious serious adverse events (no.)** Severe infusion reactions (dyspnoea, hypotension or cardiopulmonary symptoms combined with urticaria): 4/165 **Deaths** None stated **Withdrawals due to adverse events** Not reported **Positive test for anti-etanercept antibody** Not reported **Other important adverse event results** Overall infusion reactions occurred after 26/479 (5.4%) infusions **Comments** 6 of 14 patients who developed infusion reaction were taking azathrioprine/6-mercaptopurine or MTX

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Cohen, 2000,[99] USA **Type of publication** Full publication **Other publications/reports** Cohen, 2001,[171] USA **Funding** The Reva and David Logan Gastrointestinal Clinical Research Center, University of Chicago **Study design** Prospective follow-up **Duration of follow-up** 1 year **Study objective** To determine whether the efficacy and safety of infliximab reported in previous trials can be achieved in clinical practice Extracted by: ZK Checked by: NW	**Indication** Moderate to severe luminal or fistulous Crohn's disease **Inclusion criteria** All patients with Crohn's disease receiving infliximab for the year following its commercial release. Patients were refractory to conventional therapies **Total no. of participants** 129 **Age (mean)** Luminal disease 35.7 years; fistulous disease 38.7 years **Gender** Luminal disease males 47%; fistulous disease male 38% **Concurrent therapies** % on corticosteroids: 67% (luminal), 40% (fistulous) % on MTX: 9% (luminal), 8% (fistulous) % on mercaptopurine/ azathroprine: 37% (luminal), 60% (fistulous) **Comments**	**Intervention infliximab** Dose regimen: unclear Duration/frequency of treatment: unclear – on average patients received 2.7 infusions each (2.38 for luminal and 2.23 for fistulous). Number of infusions per patient usually 1–2 but some received as many as 6 over the year. No. of patients: luminal $n = 81$, fistulous $n = 48$ **Comparators** None used **Assessment** Interviews were conducted with patients at home or via telephone at weeks 1, 3, 7, 12 and at 3-month intervals following initial infusion. **Comments**	**Non-infectious adverse events** Adverse events were experienced by 24% of patients Infusion reactions 5–13% Immediate infusion reactions ~6% After 1 week reactions ~10% Possible increase in immediate reactions on first, but not second, re-infusion **Infectious adverse events including any serious infections** *Serious infections (no.):* None reported **Cancer** None stated **Other non-infectious serious adverse events (no.)** Infusion reaction (anaphylactic-type); one patient suffered a delayed serum sickness-like reaction after the second infusion **Deaths** None **Withdrawals due to adverse events** None reported **Positive test for anti-etanercept antibody** Not reported **Other important adverse event results** None reported **Comments** Overall reporting of adverse events very limited

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Colombel, 2004,[104] USA **Type of publication** Full publication **Other publications/reports** None **Funding** Unclear **Study design** Retrospective cohort (review of consecutive patients' records) **Duration of follow-up** Median 17 months (range 0–48) 38 patients followed for <4 weeks; 202 patients followed for 0–12 months; 121 patients followed for 13–24 months; 114 patients followed for 25–36 months; 63 patients followed for 37–48 months **Study objective** To determine the safety profile of infliximab in patients with Crohn's disease in clinical practice Extracted by: ZK Checked by: NW	**Indication** Crohn's disease; including inflammatory luminal disease (65%), fistulising disease (24%), Crohn's disease of the ileoanal pouch (6%), in addition to other types **Inclusion criteria** Patients with Crohn's disease treated with infliximab at the Mayo Clinic, Rochester, MN between October 1998 and October 2002. All concurrent therapies were noted **Total no. of participants** 500 **Age** Infliximab: median 37 years (range 5–85) 28/500 (6%) patients were children (≤17 years) **Gender** Infliximab: male 44% (n = 219) **Concurrent therapies** Corticosteroids 156 (31%) Azathioprine/ 6-mercaptopurine 374 (75%) MTX 53 (11%) Corticosteroids plus azathioprine, 6-mercaptopurine or MTX 111 (22%) No immunosuppressant treatment 37 (7%)	**Intervention infliximab** Dose regimen: 5 mg/kg i.v. Duration/frequency of treatment: 1–3 doses over 8 weeks (induction for fistulising disease), 1–2 doses over 8 weeks (induction for inflammatory disease) or induction followed by tailored maintenance therapy No. of participants: 500 **Comparators** None used **Assessment** Patient records were reviewed. Only serious or possibly related adverse events considered **Comments** 245 (49%) patients received the induction therapy alone, 159 (32%) patients received induction therapy plus maintenance therapy on demand, 75 (15%) patients received induction therapy plus maintenance therapy every 8 weeks and 21 (4%) patients received induction therapy plus maintenance therapy with increased/reduced dosing intervals	**Non-infectious adverse events** *No of patients (%) (n = 500)* Infusion reaction 19 (3.8%) Drug induced lupus 3 (0.6%) Serum sickness 19 (3.8%) **Infectious adverse events including any serious infections** Any infection 48 Possibly related to treatment 41 (8.2%) Upper respiratory tract infection 9[a] Abscess 8[a] Cutaneous infections 4[a] Shingles 2[a] Chicken pox 1[a] Genital herpes 1[a] Mononucleosis 1[a] Urinary tract infection 1[a] Catheter infection 1[a] *Serious infections* Any 15 Pneumonia 8 Sepsis 2 Abdominal abscess requiring surgery 2 Viral gastroenteritis with dehydration 1 Arm cellulitis 1 Histoplasmosis 1 Other 3 **Cancer** 9 cases; lung cancer, metastatic cancer, non-Hodgkin's lymphoma, Hodgkin's lymphoma, abdominal carcinomatosis, squamous cell carcinoma (2 patients), basal cell carcinoma (2 patients) **Other non-infectious serious adverse events** Serum sickness 5 (1.0%) Drug induced lupus 3 (0.6%) Serious infusion reactions 2 Worsening of heart failure 1

continued

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
	Comments		**Deaths** 10 deaths: sepsis 1; sepsis, pneumonia and multiple organ failure 1; pneumonia and respiratory failure 1; pneumonia 1; lung cancer 1; abdominal carcinomatosis 1; unknown cause 4 **Withdrawals due to adverse events** Unclear **Positive test for anti-etanercept antibody** All 3 patients with drug-induced lupus had antinuclear antibodies (2 had anti double-stranded DNA antibodies and 2 had anti-histone antibodies) Overall data not reported **Other important adverse event results** 5 deaths (0.8%) judged as potentially related to infliximab. 14/19 infusion reaction occurred after 2nd infusion **Comments** [a] Only those possibly related to infliximab treatment

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Farrell, 2000,[96] USA **Type of publication** Full publication **Other publications/reports** None **Funding** Not stated **Study design** Prospective cohort of consecutive patient records **Duration of follow-up** 6 months **Study objective** To determine the effectiveness and safety of infliximab in clinical practice and to establish its potential as a steroid-sparing agent Extracted by: ZK Checked by: NW	**Indication** Crohn's disease, including active disease, fistulous disease and steroid dependency **Inclusion criteria** Review of chart data for patients with Crohn's disease as confirmed by medical records, barium radiography or endoscopy studies **Total no. of participants** 100 **Age** Mean 41.4 ± 13.9 SD (range 15–84 years) **Gender** Male 47% **Concurrent therapies** At time of first infusion the number of patients taking medications were azathroprine/mercaptopurine 32%, NSAIDS 96%, prednisone 61%. No patient was taking MTX Patients with a history of severe infusion reaction received premedication with diphenhydramine and acitomenophen (paracetamol) **Comments**	**Intervention infliximab** Dose regimen: 5 mg/kg i.v. Duration/frequency of treatment: induction therapy only. Some patients received a single infusion, others received multiple infusions No. of patients: 100 **Comparators** None used **Assessment** Adverse events that were believed to be potentially infliximab related were recorded **Comments** Infliximab was not given as maintenance therapy over a long period	**Non-infectious adverse events** Any 47 (47%) Infusion reactions 25 (25%) Lethargy 3 Arthralgia, myalgia 3 Rash, pruritus 2 Headache 2 Nausea, vomiting 2 Abdominal cramps 2 Bowel obstruction 1 Pulmonary embolism 1 Bowel perforation 1 Leakage around pouch 1 Epistaxis 1 Lichen planus, mouth ulcers 1 Alopecia 1 **Infectious adverse events including any serious infections** Any 14 Acne rosacea exacerbation 5 Upper respiratory tract infection 3 Pneumonia 1 Varicella zoster 1 Bilateral mastitis 1 Conjunctivitis 1 Divertculitis 1 Influenza 1 *Serious infections* Not reported **Cancer** None stated **Other non-infectious serious adverse events (no.)** Severe infusion reaction 16 (16%) **Deaths** None stated

continued

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
			Withdrawals due to adverse events Not stated **Positive test for anti-etanercept antibody** Not reported **Other important adverse event results** Severe infusion reaction symptoms included anaphylactic shock, significant hypotension, lightheadedness, chest pain, palpitations, wheeze, cough, dyspnoea, pruritis, erythema, rash, pancreatitis and vomiting **Comments**

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Geborek, 2002,[76] Sweden **Type of publication** Full publication **Other publications/reports** None **Funding** Not stated **Study design** Prospective observational study **Duration of follow-up** Study duration 2 years; individual patients followed for various durations. Total no. of observational years: 232.8 (etanercept) and 111.1 (infliximab). **Study objective** To apply a clinical protocol adapted to monitor new treatments in RA to evaluate tolerability and efficacy of etanercept, infliximab and leflunomide under post-marketing conditions Extracted by: AK, ZK Checked by: NW	**Indication** RA **Inclusion criteria** Patients who had failed on at least two DMARDs, including MTX, who started on treatment with etanercept, infliximab or leflunomide **Total no. of participants** 369 **Age** Etanercept: mean 54.0 years Infliximab: mean 55.4 years **Gender** Etanercept: male 22% Infliximab: male 21% **Concurrent therapies** Prednisolone, systemic glucocorticoid, DMARDs **Comments** Monotherapy (without other DMARDs): Etanercept 46% Infliximab 14% Prednisolone: Etanercept 83% Infliximab 81%	**Intervention infliximab** Infliximab (n = 135): 3 mg/kg infusion at start, weeks 2, 6, 12 and thereafter every 8th week. Later the dose could be individually tailored and increased **Comparators** Etanercept Dose regimen: 25 mg s.c. twice per week No. of participants: 166 **Assessment** All adverse events were recorded using WHO terminology. No details of how adverse events were elicited were reported. For assessment, the patient was included in the new treatment group when starting on a new regimen. If restarted on one treatment after a pause, the patient was considered to have continued to receive the original therapeutic regimen **Comments** Patients were allowed to switch between etanercept, infliximab and leflunomide if withdrawn from any of the three treatments. 33 patients tried two treatments and one tried all three	**Non-infectious adverse events** Not reported **Infectious adverse events including any serious infections** Not reported **Serious infections (no.)** Etanercept: bacterial infection 3 (days 130, 150, 270) Infliximab: bacterial infection 2 (days 108, 210) **Cancer** |	*Etanercept*	*Infliximab*
---	---	---
Uterine cervical carcinoma	2, days 160, 413	
Acute myeloic leukaemia	1, day 440	
Hodgkin lymphoma		1, day 129
Non-Hodgkin lymphoma		1, day 180
Mesothelioma		1, day 42 | **Other non-infectious serious adverse events (no.)** |	*Etanercept*	*Infliximab*
---	---	---
Myocardial infarction	4, days 41, 63, 130, 501	
General malaise	1, day 350	
Leucopenia	1, day 91	
Bell's paralysis	1, day 130	
Cutaneous vasculitis	1, day 368	
Discoid lupus	1, day 69	1, day 20
Thrombocytopenia		1, day 250
Lupus-like reaction		1, day 230
Pharyngitis		1, day 480
Anaphylactoid reaction		1, day 320
Allergic reactions		4, days 41, 201, 230, 573 | **Deaths (no.)** |	*Etanercept*	*Infliximab*
---	---	---
Gastroenteritis	1, day 180	None
Immunocytoma of breast	1, day 220	
Myocardial infarction	1, day 413	

continued

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results

Withdrawals due to adverse events
Etanercept: adverse reactions were the main cause of withdrawal throughout the study. Details not reported

Positive test for anti-etanercept antibody
Not reported

Other important adverse event results
Graded side-effects per 100 years (no.)

	Etanercept	*Infliximab*
Fatal	1.3 (n = 3)	
Life-threatening	0 (n = 0)	2.8 (n = 3)
Serious	7 (n = 15)	10 (n = 11)
Moderate	16 (n = 36)	31 (n = 34)
Mild	27 (n = 61)	54 (n = 59)
Not graded	2 (n = 5)	

Comments

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Gottlieb, 2004,[172] USA **Type of publication** Full publication **Other publications/reports** None **Funding** Centocor Inc. **Study design** Double-blind RCT **Duration of follow-up** 30 weeks (mean by treatment group: placebo 20 weeks, 3 mg/kg dose 29.6 weeks, 5 mg/kg dose 30.7 weeks) **Study objective** To assess the safety and efficacy of infliximab in the treatment of psoriasis Extracted by: ZK Checked by: NW	**Indication** Psoriasis **Inclusion criteria** Adults with plaque psoriasis for at least 6 months were eligible if previously treated with PUVA or other systemics. Patients needed minimum PASI of 12 and ≥10% BSA covered with psoriatic plaques. Patients were excluded if history of infectious diseases or suffering from such disease in 2 months prior to enrolment, TB, pregnancy or planned pregnancy within 12 months of enrolment. Also excluded if malignancy or history of malignancy within 5 years of enrolment **Total no. of participants** 197 **Age** Infliximab 3 mg/kg: median 45 years Infliximab 5 mg/kg: median 44 years Placebo: median 45 years **Gender** Infliximab 3 mg/kg: male 70.7% Infliximab 5 mg/kg: male 73.7% Placebo: male 60.8%	**Intervention infliximab** Dose regimen: 3 or 5 mg/kg i.v. infusion Duration/frequency of treatment: 0, 2, 6 weeks. If at week 26 PGA score was ≥ 3 then patient could have a single additional infusion. No. of participants: 3 mg/kg 99 5 mg/kg 99 **Comparators** Placebo equivalent No. of participants: 51 **Assessment** Observed and reported adverse events were included along with laboratory tests and study infusion discontinuations **Comments** 114 patients also dosed at week 26	**Non-infectious adverse events** *Placebo* $n = 51$ / *3 mg/kg* $n = 98$ / *5 mg/kg* $n = 99$ No. of patients with ≥ 1 adverse event (%): 32 (62.7) / 76 (77.6) / 78 (78.8) No. of patients with serious adverse events (%): 4 (4.1) / 8 (8.1) / 12 (6.1) No. of patients with serious infusion reactions (%): 0 (0.0) / 0 (0.0) / 0 (0.0) No. of patients with infusion reactions (%): 1 (2.0) / 18 (18.4) / 22 (22.2) No. of infusions with infusion reactions (%): 1 (0.7) / 19 (5.6) / 26 (7.6) Mild: 1 (0.7) / 11 (3.2) / 18 (5.2) Moderate: 0 (0.0) / 8 (2.3) / 6 (1.7) Severe: 0 (0.0) / 0 (0.0) / 2 (0.6) Infusion reactions include headaches, chills, flushing, nausea, dyspnea, injection-site infiltrations and taste perversion **Infectious adverse events including any serious infections** No. of patients with serious infections (%): 0 (0.0) / 0 (0.0) / 1 (1.0) **Cancer** Squamous cell carcinoma (3 mg/kg infliximab, 1 patient) **Other non-infectious serious adverse events (no.)** Cholecystitis and cholelithiasis (3 mg/kg infliximab, 1 patient); diverticulitis (5 mg/kg infliximab, 1 patient); sepsis and pyelonephritis (5 mg/kg infliximab, 1 patient) **Deaths (no.)** None stated **Withdrawals due to adverse events** None stated **Positive test for anti-etanercept antibody** *Placebo* / *3 mg/kg* / *5 mg/kg* Antinuclear antibodies (%): 1/44 (2.3%) / 19/83 (22.9%) / 20/80 (25.0%) Antibodies against double-stranded DNA: 1/48 (2.1%) / 3/91 (3.3%) / 4/94 (4.3%) Antibodies to infliximab: NA / 21/76 (27.6%) / 17/87 (19.5%)

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results
	Concurrent therapies Only emollients and shampoos containing tar or salicylic acid were permitted. All other therapy was stopped at least 1 month prior to the trial **Comments**		**Other important adverse event results** Laboratory parameters that changed significantly from baseline more often on infliximab than on placebo were alanine transferase (34% vs 16% on placebo) and aspartate transaminase (24% vs 14%). Of those retreated at week 26, the incidence of infusion reaction was higher in those known to be antibody positive compared with those known to be antibody negative

NA, not applicable.

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse events results
Hanauer, 2002,[103] USA, Europe and Israel **Type of publication** Full publication **Other publications/reports** Rutgeerts, 2004[173] **Funding** Centocor Inc. **Study design** Double-blind placebo-controlled multi-centre RCT Monotherapy **Duration of follow-up** 54 weeks **Study objective** The ACCENT I trial (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen in Patients with Fistulising Crohn's Disease) determines the safety and efficacy of infliximab administered in repeated infusions for patients with improvement after a single infusion Extracted by: ZK Checked by: NW	**Indication** Crohn's disease **Inclusion criteria** Patients with Crohn's disease for at least 3 months, with a score on the Crohn's disease activity index (CDAI) between 220 and 400. Concurrent therapies included patients previously treated with infliximab or agents targeted at TNF were excluded Consistent doses of 5-aminosalicylates or antibiotics for 4 weeks prior to screening, corticosteroids (stable dose for 3 weeks), azathioprine or 6-mercaptopurine (stable dose for 8 weeks), MTX (stable dose for 6 weeks) **Total no. of participants** 573 **Age** (median IQ range) All patients 35 years (28–46) Responders (n = 335): median 35 years (IQ range 27–46) Non-responders (n = 238): median 37 years (IQ range 30–46) **Gender** Responders: male 39% (n = 130) Non-responders: male 46% (n = 109)	**Intervention infliximab** Dose regimen: 5 mg/kg i.v. or 10 mg/kg Duration/frequency of treatment: 5 mg/kg i.v. at week 0. If response at weeks 2 then randomised to: placebo (group I) or treatment (group II and III) and given infusions at week 2, 6 and every 8 weeks thereafter until week 46. Group II received 5 mg/kg per infusion, group III received 5 mg/kg until week 14 and 10 mg/kg thereafter No. of patients (group II): 192 No. of patients (group III): 193 **Comparators** Placebo Dose regimen: equivalent No. of participants (group I): 188 **Assessment** 573 patients were included in the safety analysis at week 54. Adverse events were ascertained by direct questioning of patients at each assessment and samples were taken for	**Non-infectious adverse events** *Infliximab (group II) n = 193* / *Infliximab (group III) n = 192* / *Placebo (group I) n = 188* Infusion reactions: 44 (23%) / 36 (19%) / 17 (9%) Intestinal stenosis: 3 (2%) / 5 (3%) / 6 (3%) Serum sickness-like reactions: 5 (3%) / 6 (3%) / 3 (2%) **Infectious adverse events including any serious infections** Infections requiring antimicrobial treatment: infliximab (group II) 64/193 (33%); infliximab (group III) 52/192 (27%); placebo (group I) 70/188 (37%) *Serious infections (no.):* Infliximab (group II) 8 (4%); infliximab (group III) 6 (3%); placebo (group I) 8 (4%). One case of TB was reported. **Cancer** 6 cases: epithelial-cell skin neoplasm (1 patient, group I), natural killer-cell lymphoma (1 patient, group I), basal-cell carcinoma (1 patient, group II), hypernephroma (1 patient, group II), malignant breast neoplasm (1 patient, group II), bladder carcinoma (1 patient, group III) **Other non-infectious serious adverse events (no.)** Serious adverse events: infliximab (group II) 54 (28%); infliximab (group III) 43 (22%); placebo (group I) 55 (29%) **Deaths** 3 patient deaths (all group II): 2 from sepsis, 1 from myocardial infarction **Withdrawals due to adverse events** Infliximab (group II) 29/193 (15%); infliximab (group (III) 16/192 (8%); placebo (group I) 5/188 (3%) Reasons for withdrawal: infusion syndrome (5 patients), allergic reaction (4 patients), arthralgia (4 patients), serum sickness (4 patients), rash (3 patients). **Positive test for anti-etanercept antibody** 64/442 (14%) developed antibodies. Anti double-stranded DNA antibodies detected in 11% group I patients and 34% of group II/group III patients. Anti-nuclear antibodies detected in 35% of group I and 56% of group II/group III

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse events results
	Concurrent therapies 5-aminosalicylates 50%, corticosteroids not stated, azathioprine and 6-mercaptopurine 25%, MTX 4% **Comments**	laboratory evaluations. The patient's CDAI scores were noted **Comments** All patients received 5 mg/kg infliximab at week 0. Two groups of patients were identified responders and non-responders, all patients were randomised into either group I placebo, group II treatment with 5 mg/kg at weeks 2, 6 and every 8 weeks thereafter until week 46, group III treatment with 5 mg/kg at weeks 2 and 6 then 10 mg/kg every 8 weeks thereafter until week 46	**Other important adverse event results** None reported **Comments** Some patients in group I (placebo) received several infusions of infliximab. Reporting of adverse event data not complete

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results
Hommes, 2002,[101] The Netherlands **Other publications/reports** None **Type of publication** Full publication **Funding** Not funded by pharmaceutical industry **Study design** Prospective cohort Patient records **Duration of follow-up** Median 17 months (range 0–48 months) **Study objective** To report the experience with infliximab treatment for a large cohort of Crohn's disease patients in The Netherlands Extracted by: RR Checked by: NW	**Indication** Crohn's disease; including inflammatory luminal disease despite conventional therapy (71%) and active fistulising disease without the necessity of surgical intervention (29%) **Inclusion criteria** All patients with Crohn's disease treated at the Academic Medical Centre, Amsterdam, The Netherlands since the registration of infliximab in The Netherlands (from 1 November 1999 to 31 January 2002) Patients with a positive Mantoux test (TB) were not treated with infliximab **Total no. of participants** 134 **Age** Mean: 36 years (range 13–66) **Gender** Male/female: 52/80 **Disease duration** Mean: 10.8 years (range 1–35) **Concurrent therapies** Corticosteroids 49 (37%) Azathioprine 48 (36%) MTX 41 (31%) Other (mesalazine) 11 (8%) No immunosuppressant treatment 43 (33%) **Comments** For 2 patients reliable follow-up data were missing For 10 patients there was insufficient follow-up time to assess response For 122 patients response could be assessed	**Intervention infliximab** Dose regimen: 5 mg/kg i.v. (for 2 h) Duration/frequency of treatment: only patients with a clinical response of Crohn activity were treated again in case of recurring complaints. In total 134 patients were treated with 592 infusions of infliximab. On average 4.4 infusions per patient; 73 (55%) received 3 or less and 2 patients received more than 15. Time between infusions was on average 45 days No. of participants: 134 **Comparators** None used **Assessment** All infusion reactions were judged and recorded by a gastroenterologist Clinical response assessed with 'Physicians global assessment' **Comments**	**All adverse events** In 17% (22/127) of patients adverse events were found during treatment with infliximab. For 5/132 patients data on adverse events were incomplete Non-infectious adverse events Skin rash 9 Shortness of breath 7 Arthralgia/arthritis 2 Headache 1 Fluid retention 1 Fever 2 Shock 3 Ménière syndrome 1 Chest pain 2 Muscle ache 2 **Infectious adverse events** including any serious infections None reported. *Serious infections (no.)* None reported. **Cancer** There were no reports of lymphoma or other malignancies **Other non-infectious serious adverse events (no.)** 3 serious infusion reactions (serious allergic (anaphylactic) reactions); all 3 completely recovered and did not receive further infliximab treatment **Deaths** None reported **Withdrawals due to adverse events** None reported **Positive test for anti-etanercept antibody** Not reported **Other important adverse event results** None reported

Study details and design	Participant details	Intervention/ outcome/ analyses details	Adverse event results
Maini, 1999,[98] USA and Europe **Type of publication** Full publication **Other publications/ reports** Lipsky, 2000[174] **Funding** Centocor Inc. **Study design** Double-blind placebo-controlled RCT. Combination therapy (all patients taking MTX) **Duration of follow-up** 30 and 54 weeks **Study objective** To determine the safety and effectiveness of infliximab in patients with inadequate response to MTX Extracted by: ZK Checked by: NW	**Indication** RA **Inclusion criteria** Patients with active RA despite treatment with oral or parenteral MTX for at least 3 months, receiving a stable dose for at least 4 weeks, in addition to a stable dose of folic acid. Patients taking oral corticosteroids (10 mg/kg or less prednisone equivalent) and NSAIDs on a stable dose for at least 4 weeks were permitted. Patients were excluded if they had any current inflammatory condition, taken a DMARD (except MTX) or corticosteroids (except oral) in 4 weeks prior to screening. Patients were excluded if they failed laboratory screening for haematology and liver function. Patients were also excluded if they had had an infected joint prosthesis in previous 5 years; and serious infection in previous 3 months or any chronic infection; TB in previous 3 years or any opportunistic infection in previous 2 months; active cytomegalovirus, active *Pneumocystis carinii* or drug-resistant atypical mycobacterial infection. Other contraindications were symptoms of severe, uncontrolled, renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological or cerebral disease; any other serious condition or cancer in previous 5 years **Total no. of participants** 428 **Age** Infliximab (3 mg/kg 8 weeks): median 56 years (range 25–74) Infliximab (3 mg/kg 4 weeks): median 51 years (range 19–78) Infliximab (10 mg/kg 8 weeks): median 55 years (range 19–80) Infliximab (10 mg/kg 4 weeks): median 52 years (range 23–74) Placebo/MTX: median 51 years (range 19–75) **Gender** Infliximab (3 mg/kg 8 weeks): male 16/86 Infliximab (3 mg/kg 4 weeks): male 20/86 Infliximab (10 mg/kg 8 weeks): male 20/87	**Intervention infliximab** Dose regimen: 3 mg/kg i.v. or 10 mg/kg Duration/frequency of treatment: 0, 2, 6 weeks then every 8 weeks thereafter, or every 4 weeks thereafter. No. of participants: 3 mg/kg every 8 weeks = 86 3 mg/kg every 4 weeks = 86 10 mg/kg every 8 weeks = 87 10 mg/kg every 4 weeks = 81 **Comparators** Placebo/MTX equivalent, 4-week interval regimen *n* = 86 **Assessment** Not reported. Patients were analysed for safety indices **Comments**	**Non-infectious adverse events** *Infliximab dose* Treatment group / Placebo/MTX / 3 mg/kg 8 weeks / 3 mg/kg 4 weeks / 10 mg/kg 8 weeks / 10 mg/kg 4 weeks Headache 9 (10%) 22 (25%) 17 (20%) 21 (24%) 16 (20%) Nausea 16 (19%) 14 (16%) 12 (14%) 12 (14%) 14 (18%) Sinusitis 4 (5%) 10 (11%) 6 (7%) 12 (14%) 12 (15%) Rash 4 (5%) 5 (6%) 7 (8%) 14 (16%) 11 (14%) Coughing 3 (3%) 8 (9%) 6 (7%) 11 (13%) 12 (15%) Diarrhoea 10 (12%) 7 (8%) 8 (9%) 7 (8%) 10 (13%) Fatigue 6 (7%) 15 (17%) 5 (6%) 3 (3%) 9 (11%) Dizziness 6 (7%) 8 (9%) 5 (6%) 12 (14%) 5 (6%) Rhinitis 5 (6%) 7 (8%) 5 (6%) 10 (11%) 7 (9%) Back pain 2 (2%) 7 (8%) 7 (8%) 6 (7%) 8 (10%) Abdominal pain 7 (8%) 4 (4%) 8 (9%) 7 (8%) 6 (8%) Pain 4 (5%) 4 (4%) 3 (3%) 7 (8%) 8 (10%) Pharyngitis 4 (5%) 5 (6%) 4 (5%) 6 (7%) 6 (8%) Arthralgia 2 (2%) 6 (7%) 2 (2%) 5 (6%) 5 (6%) Hypertension 3 (3%) 5 (6%) 3 (3%) 4 (5%) 6 (8%) Stomatitis, ulcerative 2 (2%) 4 (4%) 3 (3%) 2 (2%) 9 (11%) Fever 4 (5%) 4 (4%) 7 (8%) 3 (3%) 4 (5%) Dyspepsia 3 (3%) 5 (6%) 5 (6%) 1 (1%) 6 (8%) *Infusion reaction* Overall they occurred in infliximab 14–16 (16–20%), placebo/MTX 9 (10%); $p = 0.477$. No serious infusion reactions were seen Hypersensitivity-type reactions seen in 14 patients with infliximab and 2 with placebo/MTX [*hypotension*: infliximab 8 (2.3%), placebo/MTX 2 (2.3%); *urticaria*: infliximab 4 (1.2%), placebo/MTX 0; *dyspnoea*: infliximab 2 (0.6%), placebo/MTX 0. There were no delayed hypersensitivity reactions reported after 1 h or 4 weeks]

continued

Study details and design	Participant details	Intervention/ outcome/ analyses details	Adverse event results

Infliximab (10 mg/kg 4 weeks): male 22/81
Placebo/MTX: male 18/88

Concurrent therapies	Placebo	3 mg/kg 8 weeks	3 mg/kg 4 weeks	10 mg/kg 8 weeks	10 mg/kg 4 weeks
Receiving NSAIDs	63 (72%)	68 (79%)	65 (76%)	67 (77%)	55 (68%)
Receiving corticosteroids	56 (64%)	54 (63%)	46 (53%)	50 (57%)	53 (65%)
Dose of MTX (mg/kg)	15	15	15	15	15

Comments
All 4 treatment groups and placebo/MTX control received infusions at weeks 0, 2, 6. Two treatment groups received infliximab (3 or 10 mg/kg), subsequent infusions were every 4 weeks, equivalent to the placebo/MTX group. Remaining two treatment groups received infliximab (3 or 10 mg/kg), subsequent infusions were every 8 weeks (with placebo/MTX infusions on interim 4-week visits)

Infectious adverse events including any serious infections

Any infection	34 (40%)	47 (53%)	40 (47%)	56 (64%)	58 (73%)
Upper respiratory tract infection	14 (16%)	29 (33%)	17 (20%)	21 (24 %)	18 (23%)
Urinary tract infection	3 (3%)	3 (3%)	2 (2%)	6 (7%)	7 (9%)
Infection requiring antimicrobials	18 (21%)	20 (23%)	24 (28%)	32 (37%)	30 (38%)
Serious infection					
At 30 weeks	5 (6%)	1 (1%)	5 (6%)	5 (6%)	3 (4%)
At 54 weeks	7 (8%)	2 (2%)	6 (7%)	7 (8%)	6 (7%)

Serious adverse events (unclear if includes infections or not)

At 30 weeks	14 (16%)	8 (9%)	11 (13%)	8 (9%)	10 (13%)
At 54 weeks	18 (21%)	10 (11%)	14 (16%)	17 (20%)	16 (20%)

One infliximab-treated patient developed drug-induced lupus syndrome after two treatments

Cancer
3 cases in infliximab 10 mg/kg every 4 weeks regimen: recurrence of carcinoma of the breast (1 patient), squamous cell carcinoma and melanoma (1 patient) and B cell lymphoma (1 patient).
2 cases in infliximab 10 mg/kg every 8 weeks regimen: basal-cell carcinomas (1 patient) and rectal carcinoma (1 patient)

Deaths
5 deaths: 3/88 (3%) cases in placebo/MTX; pneumonia, sepsis, intestinal gangrene and cardiopulmonary failure (1 patient), interstitial lung disease, heart failure and pericardial effusion (1 patient), ischaemic and necrotic liver and bowel causing cardiopulmonary failure (1 patient); 2/340 (1%) patients receiving infliximab, including cardiopulmonary failure resulting from pulmonary embolism or interstitial lung disease (1 patient) and pulmonary embolism secondary to venous thrombosis (1 patient)

continued

Study details and design	Participant details	Intervention/ outcome/ analyses details	Adverse event results

Withdrawals due to adverse events

Infliximab 3–6 (3–7%); placebo/MTX 7 (8%).

Infliximab: 2 patients (infusion reaction: urticaria, dyspnoea), 1 patient (dyspnoea due to MTX toxicity), 1 patient (drug-induced lupus syndrome).

Placebo: 1 patient (iron deficiency anaemia), 1 patient (thrombocytopenia)

Withdrawals may not be the total number as this is not reported

Positive test for anti-nuclear antibody

At 54 weeks:	18/69 (26%)	50/74 (68%)	40/64 (62%)	44/71 (62%)	34/64 (53%)

Positive test for anti-dsDNA antibody

At 30 weeks:	0%	all doses 16%			
At 54 weeks:	0/84	9/88 (10%)	9/85 (11%)	9/87 (10%)	6/81 (7%)

Comments

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results
Maini, 1998,[105] Europe **Type of publication** Full publication **Other publications/ reports** None **Funding** Centocor Inc. **Study design** Double-blind placebo-controlled RCT Monotherapy and combination **Duration of follow-up** 26 weeks **Study objective** To determine the safety, efficacy, pharmacokinetics and immunogenicity of multiple infusions of infliximab alone or in combination with low-dose MTX in patients with RA Extracted by: ZK Checked by: NW	**Indication** RA **Inclusion criteria** Patients with active RA treated with 7.5 mg/week MTX for at least 6 months. Patients taking oral corticosteroids and NSAIDs on a stable dose for at least 4 weeks prior to screening were permitted. Patients with ≥6 tender/painful joints on day of screening, ≥45 minutes morning stiffness and an ESR >28 mm/h or CRP level >15 mg/dl. Patients were excluded if they had taken a DMARD (except MTX) in 4 weeks prior to screening, were pregnant, severely physically incapacitated, had a previous chronic infection, a recent serious infection, or a history of malignancy. Patients that had previously received murine or chimeric MAb were also excluded **Total no. of participants** 101 **Age** [mean (SD)] Infliximab (1 mg/kg): 48.7 years (13.9) Infliximab (3 mg/kg): 47.0 years (15.0) Infliximab (10 mg/kg): 56.3 years (9.1) Infliximab (1 mg/kg) plus MTX: 53.6 years (14.0) Infliximab (3 mg/kg) plus MTX: 58.9 years (10.0) Infliximab (10 mg/kg) plus MTX: 50.4 years (13.4) Placebo plus MTX: 48.8 (12.3) **Gender** Infliximab (1 mg/kg): male 27% Infliximab (3 mg/kg): male 14% Infliximab (10 mg/kg): male 33% Infliximab (1 mg/kg) plus MTX: male 29% Infliximab (3 mg/kg) plus MTX: male 33% Infliximab (10 mg/kg) plusMTX: male 21% Placebo plus MTX: male 29%	**Intervention infliximab** Dose regimen: 1, 3 or 10 mg/kg i.v. infliximab plus oral placebo No. of participants: 1 mg/kg 15 3 mg/kg 14 10 mg/kg 15 **Intervention infliximab plus MTX** Dose regimen: 1, 3 or 10 mg/kg i.v. infliximab plus 7.5 mg/week oral MTX Duration/frequency of treatment: 4, 8, 12, 16, 26 weeks No. of participants: 1 mg/kg plus MTX 14 3 mg/kg plus MTX 15 10 mg/kg plus MTX 14 **Comparators** Placebo plus MTX Duration/frequency of treatment: equivalent No. of participants: 14 **Assessment** Follow-up assessments made at weeks 1 and 2, then every 2 weeks until week 22, final assessment week 26 whether or not patient continued with medication. Adverse events observed by study personnel, volunteered by	**Non-infectious adverse events** *All infliximab doses plus or minus MTX* Headache 12.6% Diarrhea 9.2% Rash 6.9% Pharyngitis 6.9% Rhinitis 6.9% Cough 5.7% **Infectious adverse events** Upper respiratory tract infection 4.6% Urinary tract infection 4.6% Cutaneous infection Not reported *Infections treated by antibiotics* Infliximab plus or minus MTX : 28/87 (32.2%), including 2 serious infections both on infliximab plus MTX) Placebo plus MTX: 3/14 (21.4%) ($p = 0.541$) **Cancer** None reported **Other non-infectious serious adverse events (no.)** SLE occurred in 1 patient on infliximab (3 mg/kg) plus MTX **Deaths** 1 patient after withdrawal for lack of efficacy (*Staphylococcus* infection) **Withdrawals due to adverse events** 6 or 7 patients (discrepant reporting) withdrew owing to adverse events Infliximab (1 mg/kg): 2 patients Infliximab (3 mg/kg): 1 patient Infliximab (10 mg/kg): 1 patient Infliximab (1 mg/kg) plus MTX: 1 patient Infliximab (10 mg/kg) plus MTX: 1 patient Placebo plus MTX: no patient

continued

Study details and design	Participant details	Intervention/outcome/ analyses details	Adverse event results
	Concurrent therapies No DMARDs permitted during study. Stable doses of corticosteroids were permitted. NSAIDs were permitted *% receiving corticosteroids* Infliximab (1 mg/kg): 66.7; infliximab (1 mg/kg) plus MTX 42.9 Infliximab (3 mg/kg): 50.0; infliximab (3 mg/kg) plus MTX 60.0 Infliximab (10 mg/kg): 60.0; infliximab (10 mg/kg) plus MTX 28.6 Placebo plus MTX 50.0 **Comments** 7 treatment groups: 4 groups received 1, 3, 10 mg/kg infliximab or placebo infusions concomitantly with 7.5 mg/week oral MTX (infliximab plus MTX, placebo plus MTX). 3 groups received 1, 3, 10 mg/kg infliximab with placebo tablets (infliximab)	patients or elicited by questioning were all recorded **Comments** Placebo actually equals MTX therapy. MTX always at a dose of 7.5 mg/week whether in combination with placebo or infliximab	Reasons for withdrawal: infusion reactions 5, rash 1, urinary tract infection and vaginitis 1 **Positive test for antibodies** 7 patients (8%) on infliximab with or without MTX developed anti-double stranded DNA antibodies. 12 weeks after last infliximab infusion overall incidence of human antichimeric antibodies in all patients treated with infliximab (plus of minus MTX) was 17.4%; this was dose related 53, 21 and 7% for 1, 3 and 10 mg/kg doses, respectively. In the infliximab plus MTX groups, only the respective values were 15, 7 and 0 % **Other important adverse event results** Not reported **Comments** Few adverse events data reported. Only adverse events 'reasonably related' to treatment listed, with all data for all doses of infliximab and infliximab plus MTX combined

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Sample, 2002,[95] Canada **Type of publication** Full publication **Other publications/ reports** None **Funding** Not stated **Study design** Prospective/retrospective observational follow-up **Duration of follow-up** Median 24 weeks (range 1–40) **Study objective** To determine whether the safety and efficacy of infliximab in clinical trials is apparent in diverse clinical practices Extracted by: ZK Checked by: NW	**Indication** Inflammatory and/or fistulising Crohn's disease **Inclusion criteria** Review of chart data from 109 consecutive patients receiving infliximab infusions for inflammatory and/or fistulising Crohn's disease **Total no. of participants** 109 **Age** Responders: mean 38 years (range 18–78) Non-responders: mean 40.8 years (range 25–79) **Gender** Male: 57/109 **Concurrent therapies** Mesalamine, MTX, 6-mercaptopurine, azathioprine, CSA and corticosteroids were noted as previous medications. Concurrent medications were taken by 68% MTX, 6-mercaptopurine or azathioprine, 25.5% mesalamine and 31% corticosteroids. **Comments**	**Intervention infliximab** Dose regimen: 5 mg/kg i.v. Duration/frequency of treatment: induction 1–9 infusions No. of patients: 109 Maintenance therapy: 1–8 additional infusions approximately every 8 weeks (n = 43) **Comparators** None used **Assessment** Records of patients receiving infliximab via compassionate release programmes were assessed, the records of patients who received an initial dose of infliximab through the ACCENT I and ACCENT II trials who entered the compassionate release programme were also reviewed **Comments** Patients with inflammatory disease received a single 5 mg/kg induction dose; patients with fistulising disease received three induction doses over a 6-week period	**Any adverse event** 16/109 (15.6%) **Non-infectious adverse events** *Infliximab* n = 109 Infusion reactions 8/109 (7%) Flare of gout 1 Diffuse transient joint pain 1 Chest pain 1 Rash 4 **Infectious adverse events including any serious infections** Activation of varicella zoster 1 No others reported *Serious infections (no.)* None reported **Cancer** None stated **Other non-infectious serious adverse events (no.)** Infusion reaction (anaphylactic-type) **Deaths** None stated **Withdrawals due to adverse events** 2 patients: 1 due to 'anaphylactic'-type reaction; 1 due to rash **Positive test for anti-etanercept antibody** Not reported **Other important adverse event results** None reported **Comments** Only adverse events related to infliximab reported. Overall adverse event data not well reported

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
Sands, 2004,[100] USA, Canada, Europe and Israel **Type of publication** Full publication **Other publications/ reports** None **Funding** Centocor Inc. **Study design** Double-blind placebo-controlled RCT Monotherapy **Duration of follow-up** 54 weeks **Study objective** The ACCENT II trial (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen in Patients with Fistulising Crohn's Disease) determines the safety and efficacy of infliximab administered in repeated infusions to maintain of closure of draining fistulas Extracted by: ZK Checked by: NW	**Indication** Crohn's disease with one or more draining fistulas **Inclusion criteria** Patients aged 18 years and above with Crohn's disease with single or multiple draining fistulas for at least 3 months. Patients with a stricture or abscess potentially needing surgery or previously treated with infliximab were excluded **Total no. of participants** 306 **Age** Infliximab: median 37 years (range 28–47) Placebo: median 36 years (range 29–46) **Gender** Infliximab: male 55% (n = 53) Placebo: male 48% (n = 48) **Concurrent therapies** Consistent doses of 5-aminosalicylates, oral corticosteroids, azathioprine, mercaptopurine, mycophenolate mofetil, MTX, and antibiotics were permitted. The proportions of patients taking these were as follows: 5-Aminosalicylates: infliximab 43%, placebo 49%	**Intervention infliximab** Dose regimen: 5 mg/kg i.v. Duration/frequency of treatment: induction infusions at weeks 0, 2, 6. Randomised at week 14 to treatment or placebo group and treated every 8 weeks from week 14 to 46. Randomisation separate for responders and non-responders at weeks 10 and 14. No. of participants: 282 (induction); 139 (weeks 16–54) (96 responders and 43 non-responders). After week 22, non-responding patients could have their dose increased to 10 mg/kg (n = 35) **Comparators** Placebo Dose regimen: equivalent (weeks 14–54) No. of participants: 143 (weeks 16–54) (99 responders and 44 non-responders) After week 22, non-responding patients could receive 5 mg/kg infliximab (n = 60) **Assessment** 282 patients were included in the safety analysis at week 54. Adverse events were ascertained at each assessment and samples were taken for laboratory evaluations **Comments** All patients received 5 mg/kg infliximab at weeks 0, 2 and 6. Two groups of patients were identified, responders and non-responders; all patients were randomised into either the treatment or control group at week 14 and given infusions every 8 weeks thereafter until week 46. 28/96 patients receiving infliximab in the responders group crossed over to 10 mg/kg at week 22. 50/99 patients taking placebo in	**Non-infectious adverse events** *Placebo* n = 144 / *Infliximab* n = 138 / *Total* n = 282 Infusion reactions (all): 24 (17%) / 22 (16%) / 46 (16%) Infusion reaction (induction): 11 (8%) / 9 (7%) / 20 (7%) Infusion reaction (maintenance): 4 (3%) / 13 (9%) / NA **Infectious adverse events including any serious infections** *Placebo* n = 144 / *Infliximab* n = 138 / *Total* n = 282 Infections requiring antimicrobial treatment: 39 (27%) / 47 (34%) / 86 (30%) New fistula-related abscess: 25 (17%) / 17 (12%) / 42 (15%) *Serious infections*: 9 (6%) / 4 (3%) / 13 (5%) Opportunistic infection: 0 / 2 **Cancer** 2 cases (both on infliximab), rectal carcinoma and rectal adenocarcinoma during long-term follow-up **Other non-infectious serious adverse events (no.)** All serious adverse events (including infection): placebo 33 (23%); infliximab 19 (14%); all 52 (18%) Serious infusion reactions: one case on infliximab **Deaths** 2 during long-term follow-up **Withdrawals due to adverse events** Infliximab 5/138 (4%); placebo 12/144 (8%); total 17 (6%) **Positive test for antibodies** Antinuclear antibodies: infliximab 56/122 (45.9%); placebo 24/132 (18.2%); total 80/254 (31.5%) ($p < 0.001$) Double stranded DNA antibodies: infliximab 27/116 (23.3%); placebo 8/127 (6.3%); total 35/243 (14.4%) ($p < 0.001$) Positive results for antibodies were not associated with development of lupus or lupus-like syndrome **Other important adverse event results** None reported

continued

Study details and design	Participant details	Intervention/outcome/analyses details	Adverse event results
	Oral corticosteroids infliximab 26%, placebo 30% Azathioprine, mercaptopurine: infliximab 30%, placebo 35% MTX: infliximab 1%, placebo 2% Antibiotics: infliximab 29%, placebo 26% **Comments**	the responders group crossed over to 5 mg/kg infliximab at week 22. 7/43 patients receiving infliximab in the non-responders group crossed over to 10 mg/kg at week 22. 10/44 patients taking placebo in the non-responders group crossed over to 5 mg/kg infliximab at week 22	**Comments** Adverse events reported for randomised patients only
NA, no applicable.			

Appendix 6

Adverse events data summary

Adverse effects of etanercept

Information regarding the adverse effects of etanercept was reviewed in three ways. First, information from standard reference texts was summarised. Second, information from existing reviews was summarised. Lastly, a systematic review of RCTs of etanercept in PsA and clinical studies in other indications that were of at least 24 weeks' duration and had included at least 100 patients was conducted.

Information from standard reference texts

The adverse effects of etanercept summarised from standard reference sources [84–86,175] are listed below.

Adverse events that are frequent and requiring medical attention are infection, respiratory tract infection and varicella infection. Adverse events that are frequent but require medical attention only if they continue or are bothersome are abdominal pain, headache, injection-site reaction, nausea and vomiting, pharyngitis, rhinitis and sinusitis. Adverse events that are less frequent but requiring medical attention are abdominal abscess, septic arthritis, bronchitis, cellulitis, cholecystitis, hypertension, hypotension, pneumonia, pylonephritis, sepsis and development of new positive ANA or anti-double-stranded DNA antibodies. Adverse events that are rare but requiring medical attention are aplastic anaemia, generalised anaemia, CNS effects suggestive of MS, transverse myelitis or other demyelinating conditions, leukopenia, optic neuritis, pancytopenia, neutropenia, seizures, thrombocytopenia and TB. Adverse events that are less frequent or rare and only require medical attention if they continue or are bothersome are anorexia, asthenia, cough, cutaneous vasculitis, diarrhoea, dry eyes, dry mouth, dyspepsia, fatigue, foot abscess, joint pain, leg ulcer, ocular inflammation, generalised pain, skin rash and subcutaneous nodules.

Serious adverse events reported with etanercept include malignancies, asthma, infections, heart failure, myocardial infarction, myocardial ischaemia, chest pain, syncope, cerebral ischaemia, hypertension, hypotension, cholecystitis, pancreatitis, gastrointestinal haemorrhage, bursitis, confusion, depression, dyspnoea, abnormal healing, renal insufficiency, kidney calculus, deep vein thrombosis, pulmonary embolism, membranous glomerulonephropathy, polymyositis, thrombophlebitis, liver damage, leucopenia, paresis, paresthesia, vertigo, allergic alveolitis, angioedema, scleritis, bone fracture, lymphadenopathy, ulcerative colitis and intestinal obstruction.

Other side-effects include hypersensitivity reactions (including angioedema, bronchospasm, urticaria and anaphylaxis), worsening heart failure, fever, depression, lupus erythematosus-like syndrome and pruritus. Other effects reported for etanercept are oesophagitis, pancreatitis, gastrointestinal haemorrhage, myocardial or cerebral ischaemia, venous thromboembolism, dyspnoea, bone fracture, renal impairment, polymyositis, bursitis and lymphadenopathy

This list of adverse effects appears very comprehensive but provides only limited information on the significance and frequency of individual events.

Information from existing reviews of etanercept

In addition to the standard reference texts, there have been a large number of articles and reviews published regarding the adverse effects of etanercept.[64–73] To date the main areas of concern relate to the potential of etanercept to increase the risk of infections, malignancy, heart failure, conditions secondary to the development of autoimmune antibodies, haematological disorders and demyelinating disease.

Infections

Like other treatments for RA, psoriasis or PsA etanercept is immunosuppressant and all carry a risk of rendering the patient susceptible to infection. The most frequently occurring infections associated with etanercept and other anti-TNF are upper respiratory tract infections. These are generally not serious, that is, they do not require hospitalisation or intravenous antibiotics. The Food and Drug Administration

(FDA) review in August 2001[93] reported that of an estimated 82,000 patients treated worldwide with etanercept there had been 13,000 MedWatch reports, 2782 (21%) of which were of infections.

Mycobacterium tuberculosis infection (TB) is a major concern with anti-TNF agents. This is because TNF is important for controlling *M. tuberculosis* infection within the body. About 95% of those infected will contain the organism via an effective cell-mediated immune response. Exposure to anti-TNF agents may permit reactivation of latent infection. The number of cases with infliximab has been estimated as 24.4 cases per 100,000 compared to a rate of 6.2 cases per 100,000 in patients with RA. Data reviewed by the FDA in August 2001[93] indicated that the risk of TB with etanercept seems lower than with infliximab. However, differences in incidences may reflect different background prevalence and there may be other confounding factors; the relative risk of TB with infliximab and etanercept is difficult to quantify. The review concluded that testing for TB prior to etanercept therapy was not warranted but that caution was required and physicians need to be alert to the possibility of TB infections in patients treated with etanercept.

Other infections which may be of significance are due to *Listeria monocytogenes, Streptococcus pneumonias, Aspergillus fumigatus, Histoplasma capsulatum, Cryptococus neoformans, Pneumocystis jiroveci (carinii) and Coccidiodes immitis and opportunistic infections.*

Congestive heart failure (CHF)

The pharmacology of anti-TNFs suggested the possibility that these agents would have beneficial effects in patients with CHF. Two fairly large randomised double-blind placebo-controlled trials found no evidence of efficacy for etanercept. However, one trial found a trend towards a higher mortality with etanercept and this appeared to be dose related. These findings were not substantiated by the second trial and therefore the risk of increased mortality in patients with CHF from etanercept cannot be considered definitive.

Malignancy

There is no real indication that etanercept is associated with an increase in solid tumours over the background rate. There is some concern regarding the incidence of lymphoma, which has been reported for etanercept. Lymphomas are more common in patients with RA and there is uncertainty whether this is related to the disorder or to the treatments used for RA. Most commonly associated with anti-TNF therapy is Hodgkin's lymphoma, with an apparent time to onset of 10–21 months. It is not known if this is worse than the incidence associated with other DMARDS.

Development of antibodies

Treatment with etanercept has been associated with the development of antibodies in some patients: non-neutralising antibodies, ANA and anti-double-stranded DNA antibodies. Generally, the development of these antibodies has not been found to be clinically significant but there have been some reports of symptoms consistent with lupus-like syndrome.

Lupus-like syndromes

Reports of a lupus-like rash associated with positive antibodies appear to represent a real but very rare side-effect of etanercept therapy. None of the cases were associated with systemic features of SLE or with a definite diagnosis of SLE.

Demyelinating disease

Concerns were established after several spontaneous reports of demyelinating disease associated with etanercept: some of new cases of MS and others of exacerbations of existing MS. The pharmacology of anti-TNFs suggests a possible therapeutic role in MS, but an RCT of an anti-TNF drug (not etanercept) found an adverse effect of therapy. This finding was reflected in the experience of two patients with MS treated with infliximab. The FDA review[93] concluded that although the evidence is not conclusive, "TNF agents as a class, may worsen MS in some patients. Caution is clearly warranted in treating patients with pre-existing demyelinating syndromes or in continuing etanercept therapy in patients who develop a demyelinating syndrome."

Seizures

There have been reports of seizures or convulsions in patients treated with etanercept. However, the association with etanercept therapy is not clear: the condition of some patients with pre-existing seizures was not exacerbated by etanercept therapy.

Haematological adverse effects

There have been rare reports of aplastic anaemia and cases of pancytopenia. Although the cases of aplastic anaemia represent a rare event, the rate is higher than would have been expected. This increased rate may reflect the higher prevalence in patients with RA. All the cases

of pancytopenia were confounded by other factors and the association with etanercept is very unclear.

Intestinal perforation

Several cases of intestinal perforation have been reported for etanercept. The FDA review[93] concluded that the incidence did not appear to be in excess of the background incidence and that evidence for an association with etanercept was not strong.

Against this background information on the adverse effects profile of etanercept, we reviewed systematically all long-term (greater than 24 weeks) studies of at least 100 patients for further information on the adverse effects of etanercept.

Adverse events for etanercept: data from included studies

Ten clinical studies that provided data on the adverse events of etanercept were identified.[36,74–83] Details of all studies are presented in the data extraction tables [Appendix 4, section 'Data extraction tables: intervention efficacy – etanercept' (p. 110)]. Each of these 10 studies had included at least 100 patients and provided at least 24 weeks' data. Five of these studies were of patients treated with etanercept for RA, two were of patients with psoriasis, one was of patients with PsA, one study was of patients with ankylosing spondylitis and the last was of patients with either RA, PsA or ankylosing spondylitis.

Overall, there are data available on the adverse effects of etanercept over 24 weeks (6 months), 1 year and 2 years or more.

Adverse effects of etanercept over 24 weeks (6 months)

Six studies provided data on the adverse effects of etanercept given for a period of 24 weeks (6 months) (*Table 34*).[36,74,77,80,82,83] Two were of patients with psoriasis and there was one each of patients with PsA, RA, ankylosing spondylitis and any rheumatic disease. Four of these studies were placebo-controlled double-blind RCTs and one was also a double-blind RCT but provided no placebo data. The sixth study was an uncontrolled retrospective case series.

The total number of patients reporting an adverse event was not reported in any of the studies. In the one double-blind RCT of patients treated for PsA, non-infectious adverse events occurred in 64% of patients treated with etanercept 25 mg twice weekly compared with 66% treated with placebo.[83] Patients with psoriasis were studied in one placebo-controlled double-blind RCT[83] and one double-blind RCT but with no placebo data.[82] Individual adverse events reported by 5% or more of etanercept-treated patients in at least one of the studies are listed in *Table 35*. In the placebo-controlled RCTs, injection-site reaction was reported in 9–49% of etanercept-treated patients compared with 0–13% of placebo-treated patients. In the placebo-controlled trial of psoriasis patients, sinusitis was more common in etanercept-treated patients than placebo-treated patients.

The proportion of patients suffering an infection during treatment with etanercept 25 mg was reported in three double-blind RCTs: two placebo-controlled and one in which the control was etanercept 50 mg. Unfortunately, most of these data are commercial-in-confidence, although it can be reported that the trial of PsA found the rate of infection on active treatment and placebo to be about the same (40 and 43%).[82] Upper respiratory tract infections appeared to be more common in etanercept-treated patients than in placebo-treated patients. Of the four trials that reported placebo-controlled data, only that for PsA did not report a higher rate in the active treatment group. Individual studies reported urinary tract infection, herpes simplex infection and bronchitis.

Serious infections were reported by fewer than 1% of patients in any group in the controlled trials. The case series of 149 patients reported a rate of 3%.

Serious adverse events were uncommon and reported approximately equally on active and placebo treatments. The case series reported the highest rate (3%).

Withdrawals due to adverse events were not consistently higher in etanercept-treated patients compared with placebo; the highest rate reported was 5.6% in the uncontrolled case series.

In the one study that reported it, the proportion of patients developing anti-etanercept antibodies by 24 weeks was 2%.

The RCT comparison between etanercept 25 mg and etanercept 50 mg twice weekly found no increase in adverse events associated with the higher dose.[82]

TABLE 34 *Pooled adverse events data – etanercept, 24 weeks (6 months) follow-up*

	Davis, 2003[74] (DB-RCT, ankylosing spondylitis, 24 weeks)		**Gottlieb, 2003[83] (DB-RCT, psoriasis, 24 weeks)**		**Mease, 2004[36] (DB-RCT, psoriatic arthritis, 24 weeks)**		**Moreland, 1999[77] (DB-RCT, rheumatoid arthritis, 26 weeks)**		**Phillips, 2002[80] (uncontrolled case series, rheumatoid disease, 6 months)**	**Leonardi, 2003[82] (DB-RCT, psoriasis, 13–24 weeks)**	
	Etanercept 25 mg (*n* = 138): no. (%)	**Placebo (*n* = 139): no. (%)**	**Etanercept 25 mg (*n* = 57): no. of patients (%)**	**Placebo (*n* = 55): no. of patients (%)**	**Etanercept 25 mg (*n* = 101): no. of patients (%)**	**Placebo (*n* = 139): no. of patients (%)**	**Etanercept 25 mg (*n* = 78): no. of events/ patient-year**	**Placebo (*n* = 80):**	**Etanercept 25 mg (*n* = 180): no. of patients (%)**	**Etanercept 25 mg (*n* = 149):**	**Etanercept 50 mg (*n* = 159):**
Non-infectious adverse events (no. of patients)											
Occurring in	≥5% of patients		≥5% of patients		≥5% of patients		≥10% of patients			≥5% of patients	≥5% of patients
Any non-infectious adverse event	NR	NR	**[Confidential information removed]**	**[Confidential information removed]**	65 (64%)	69 (66%)	NR	NR	NR	**[Confidential information removed]**	**[Confidential information removed]**
Abdominal pain	8 (6%)	7 (5%)	**[Confidential information removed]**	**[Confidential information removed]**	<5%	<5%	<10%	<10%	NR	**[Confidential information removed]**	**[Confidential information removed]**
Accidental injury	17 (12%)	6 (4%)	4 (7%)	2 (4%)	8 (8%)	5 (5%)	<10%	<10%	NR	<3%	<3%
Asthenia	<5%	<5%	**[Confidential information removed]**	**[Confidential information removed]**	<5%	<5%	<10%	<10%	NR	7 (5%)	2 (1%)
Cellulitis	<5%	<5%	**[Confidential information removed]**	**[Confidential information removed]**	<5%	<5%	<10%	<10%	NR	**[Confidential information removed]**	**[Confidential information removed]**
Diarrhoea	11 (8%)	13 (9%)	**[Confidential information removed]**	**[Confidential information removed]**	1 (1%)	6 (6%)	0.18 (5%)	0.28 (6%)	NR	**[Confidential information removed]**	**[Confidential information removed]**
Dizziness	8 (6%)	3 (2%)	**[Confidential information removed]**	**[Confidential information removed]**	4 (4%)	5 (5%)	<10%	<10%	NR	**[Confidential information removed]**	**[Confidential information removed]**
Headache	19 (14%)	16 (12%)	9 (16%)	7 (13%)	8 (8%)	5 (5%)	0.46 (14%)	0.65 (10%)	NR	8 (5%)	4 (3%)
Hypertension	<5%	<5%	4 (7%)	2 (4%)	<5%	<5%	<10%	<10%	NR	**[Confidential information removed]**	**[Confidential information removed]**

continued

TABLE 34 *Pooled adverse events data – etanercept, 24 weeks (6 months) follow-up (cont'd)*

	Davis, 2003[74] (DB-RCT, ankylosing spondylitis, 24 weeks)		Gottlieb, 2003[83] (DB-RCT, psoriasis, 24 weeks)		Mease, 2004[36] (DB-RCT, psoriatic arthritis, 24 weeks)		Moreland, 1999[77] (DB-RCT, rheumatoid arthritis, 26 weeks)		Phillips, 2002[80] (uncontrolled case series, rheumatoid disease, 6 months)	Leonardi, 2003[82] (DB-RCT, psoriasis, 13–24 weeks)	
	Etanercept 25 mg (*n* = 138): no. (%)	Placebo (*n* = 139): no. (%)	Etanercept 25 mg (*n* = 57): no. of patients (%)	Placebo (*n* = 55): no. of patients (%)	Etanercept 25 mg (*n* = 101): no. of patients (%)	Placebo (*n* = 139): no. of patients (%)	Etanercept 25 mg (*n* = 78): no. of events/ patient-year	Placebo (*n* = 80):	Etanercept 25 mg (*n* = 180): no. of patients (%)	Etanercept 25 mg (*n* = 149):	Etanercept 50 mg (*n* = 159):
Injection site reaction	41 (30%)	13 (9%)	5 (9%)	0 (0%)	36 (36%)	9 (9%)	11.76 (49%)	0.79 (13%)	6 (3.6%)	<3%	<3%
Injection site bruising/ ecchymosis	29 (21%)	23 (17%)	6 (11%)	5 (9%)	12 (12%)	11 (11%)	<10%	<10%	NR	[Confidential information removed]	[Confidential information removed]
Pain	<5%	<5%	4 (7%)	4 (7%)	<5%	<5%	<10%	<10%	NR	[Confidential information removed]	[Confidential information removed]
Psoriasis	<5%	<5%	[Confidential information removed]	[Confidential information removed]	<5%	<5%	<10%	<10%	NR	[Confidential information removed]	[Confidential information removed]
Rash	11 (8%)	9 (6%)	[Confidential information removed]	[Confidential information removed]	5 (5%)	7 (7%)	<10%	<10%	14 (8.3%)	<3%	<3%
Rhinitis	8 (6%)	9 (6%)	[Confidential information removed]	[Confidential information removed]	1 (1%)	7 (7%)	0.37 (10%)	0.54 (11%)	NR	[Confidential information removed]	[Confidential information removed]
Sinusitis	<5%	<5%	8 (14%)	2 (4%)	6 (6%)	8 (8%)	0.34 (12%)	0.42 (11%)	NR	<3%	<3%
Infectious adverse events including any serious infections (no. of patients) Occurring in ≥5% patients											
Any infectious adverse event	NR	NR	[Confidential information removed]	[Confidential information removed]	40 (40%)	45 (43%)	NR	NR	NR	[Confidential information removed]	[Confidential information removed]
Upper respiratory tract infection	28 (20%)	16 (12%)	20 (35%)	11 (20%)	21 (21%)	24 (23%)	1.11 (33%)	0.93 (16%)	16 (9.5%)	9 (6%)	11 (7%)

continued

TABLE 34 *Pooled adverse events data – etanercept, 24 weeks (6 months) follow-up (cont'd)*

	Davis, 2003[74] (DB-RCT, ankylosing spondylitis, 24 weeks)		Gottlieb, 2003[83] (DB-RCT, psoriasis, 24 weeks)		Mease, 2004[36] (DB-RCT, psoriatic arthritis, 24 weeks)		Moreland, 1999[77] (DB-RCT, rheumatoid arthritis, 26 weeks)		Phillips, 2002[80] (uncontrolled case series, rheumatoid disease, 6 months)	Leonardi, 2003[82] (DB-RCT, psoriasis, 13–24 weeks)	
	Etanercept 25 mg (*n* = 138): no. (%)	**Placebo (*n* = 139): no. (%)**	**Etanercept 25 mg (*n* = 57): no. of patients (%)**	**Placebo (*n* = 55): no. of patients (%)**	**Etanercept 25 mg (*n* = 101): no. of patients (%)**	**Placebo (*n* = 139): no. of patients (%)**	**Etanercept 25 mg (*n* = 78): no. of events/ patient-year**	**Placebo (*n* = 80):**	**Etanercept 25 mg (*n* = 180): no. of patients (%)**	**Etanercept 25 mg (*n* = 149):**	**Etanercept 50 mg (*n* = 159):**
Urinary tract infection	<5%	<5%	**[Confidential information removed]**	**[Confidential information removed]**	6 (6%)	6 (6%)	<10%	<10%	NR	**[Confidential information removed]**	**[Confidential information removed]**
Herpes simplex	<5%	<5%	**[Confidential information removed]**	**[Confidential information removed]**	<5%	<5%	<10%	<10%	NR	**[Confidential information removed]**	**[Confidential information removed]**
Bronchitis	<5%	<5%	**[Confidential information removed]**	**[Confidential information removed]**	<5%	<5%	<10%	<10%	NR	**[Confidential information removed]**	**[Confidential information removed]**
Opportunistic or tuberculosis infections (no. of patients)	0	0	NR	NR	NR	NR	NR	NR	NR	<3%	<3%
Serious infections (no. of patients)	1	1	1	1	0	1	NR	NR	5 (3.0%)	**[Confidential information removed]**	**[Confidential information removed]**
Cancer	NR	NR	NR	NR	0	0	NR	NR	0	**[Confidential information removed]**	**[Confidential information removed]**
Other non-infectious serious adverse events (no. of patients)	8	4	1	2	**[Confidential information removed]**	**[Confidential information removed]**	NR	NR	5 (3.0%)	**[Confidential information removed]**	**[Confidential information removed]**
Deaths	NR	NR	0	0	0	1	NR	NR	2 (1.2%)	NR	NR
Withdrawals due to adverse events (no. of patients)	7 (5%)	1 (1%)	2 (3.5%)	6 (11%)	1 (1%)	1 (1%)	0	0	10 (5.6%)	**[Confidential information removed]**	**[Confidential information removed]**

continued

TABLE 34 *Pooled adverse events data – etanercept, 24 weeks (6 months) follow-up (cont'd)*

	Davis, 2003[74] (DB-RCT, ankylosing spondylitis, 24 weeks)		Gottlieb, 2003[83] (DB-RCT, psoriasis, 24 weeks)		Mease, 2004[36] (DB-RCT, psoriatic arthritis, 24 weeks)		Moreland, 1999[77] (DB-RCT, rheumatoid arthritis, 26 weeks)		Phillips, 2002[80] (uncontrolled case series, rheumatoid disease, 6 months)	Leonardi, 2003[82] (DB-RCT, psoriasis, 13–24 weeks)	
	Etanercept 25 mg (*n* = 138): no. (%)	**Placebo (*n* = 139): no. (%)**	**Etanercept 25 mg (*n* = 57): no. of patients (%)**	**Placebo (*n* = 55): no. of patients (%)**	**Etanercept 25 mg (*n* = 101): no. of patients (%)**	**Placebo (*n* = 139): no. of patients (%)**	**Etanercept 25 mg (*n* = 78): no. of events/ patient-year**	**Placebo (*n* = 80):**	**Etanercept 25 mg (*n* = 180): no. of patients (%)**	**Etanercept 25 mg (*n* = 149):**	**Etanercept 50 mg (*n* = 159):**
Positive test for anti-etanercept antibody	3	0	NR	NR	0	0	0	0	NR	NR	NR
Other important adverse event results	NR	NR			**[Confidential information removed]**	**[Confidential information removed]**	NR	NR	91/168 (54%) of patients experienced an adverse event; 86/168 (51%) patients experienced a minor adverse event		

DB-RCT, double-blind randomised controlled trial; NR, not reported.
Where rate is given as <3%, <5% or <10%, the data were derived from a publication that reported adverse events that had occurred at or above the given percentage rate. The listed adverse event was not specified in the report for that study and it has been assumed that it occurred at a rate below the cut off level.

TABLE 35 *Pooled adverse events data – Etanercept, 1 year follow-up*

	Klareskog, 2004[75] (RA, DB-RCT, follow-up 52 weeks) **Etanercept 25 mg (*n* = 223)**	**Bathon, 2000[78] (RA, DB-RCT, 1 year follow-up 52 weeks)** **Etanercept 25 mg (*n* = 207)**	**Elewski, 2004[81] (psoriasis, open-label, follow-up 48 weeks)** **Etanercept 25 mg (177 on placebo and 190 on 50 mg dose for first 12 weeks) (*n* = 557)** **(results expressed as exposure-adjusted rate per 100 patient-years)**	**Willis, 2001[79] (RA, open-label, follow-up approx. 1 year)** **Etanercept 25 mg (*n* = 549)**
Any adverse event	192 (86%)			
Non-infectious adverse events				
Occurring in	≥5%	in ≥10% of patients		
Any non-infectious adverse event	NR	NR	**[Confidential information removed]**	The most frequent adverse events were injection-site reactions
Abdominal pain	26 (12%)	20 (10%)		
Accidental injury	19 (9%)	<10%	**[Confidential information removed]**	
Asthenia	23 (10%)	27 (13%)		
Back pain	28 (13%)	22 (11%)		
Cough increased	14 (6%)	<10%		
Diarrhoea	23 (10%)	30 (14%)		
Dizziness	<5%	24 (12%)		
Dyspepsia	<5%	25 (12%)		
Headache	34 (15%)	46 (22%)	**[Confidential information removed]**	
Influenza-like syndrome	<5%	26 (13%)		
Injection-site reaction	46 (21%)	77 (37%)		
injection-site ecchymosis	<5%	29 (14%)	**[Confidential information removed]**	
Low peripheral lymphocyte count	<5%	NR (56% for lower dose)		
Migraine			**[Confidential information removed]**	
Nausea	22 (10%)	35 (17%)		
Neutropenia sporadic	<5%	(16%)		
Rhinitis	<5%	31 (15%)		
Rash	16 (7%)	25 (12%)		
Sinusitis	<5%	20 (10%)		
Infectious adverse events including any serious infections				
Occurring in	≥10%	≥10%		
Any infection	131 (59%)	NR	**[Confidential information removed]**	The most frequent adverse events were upper respiratory tract infections

continued

TABLE 35 *Pooled adverse events data – Etanercept, 1 year follow-up (cont'd)*

	Klareskog, 2004[75] (RA, DB-RCT, follow-up 52 weeks) **Etanercept 25 mg (*n* = 223)**	**Bathon, 2000[78] (RA, DB-RCT, 1 year follow-up 52 weeks)** **Etanercept 25 mg (*n* = 207)**	**Elewski, 2004[81] (psoriasis, open-label, follow-up 48 weeks)** **Etanercept 25 mg (177 on placebo and 190 on 50 mg dose for first 12 weeks) (*n* = 557)** **(results expressed as exposure-adjusted rate per 100 patient-years)**	**Willis, 2001[79] (RA, open-label, follow-up approx. 1 year)** **Etanercept 25 mg (*n* = 549)**
Upper respiratory tract infection		72 (35%)		
Skin infection		28 (14%)		
Serious infections	10 (4%)	< 3%	**[Confidential information removed]**	Rate of serious infections remained unchanged over the course of the study
Opportunistic infections	NR	0		NR
Cancer	4	3	**[Confidential information removed]**	Rate of malignancies have remained unchanged over the course of the study
Other non-infectious serious adverse events (no. of patients)	25 (11%)	NR	**[Confidential information removed]**	NR
Deaths (no.)	1	1	**[Confidential information removed]**	NR
Withdrawals due to adverse events	25	5	**[Confidential information removed]**	The rate of withdrawal for tolerance-related reasons was 8%
Positive test for anti-etanercept antibody	NR	<3%	**[Confidential information removed]**	NR
Other important adverse event results		All types of infection occurred at a rate of 1.5 events per patient year The rate of serious infections was similar to that in months 13–24		NR

DB-RCT, double-blind randomised controlled trial; NR, not reported.
Where rate is given as <3%, <5% or <10%, the data were derived from a publication that reported adverse events that had occurred at or above the given percentage rate.
The listed adverse event was not specified in the report for that study and it has been assumed that it occurred at a rate below the cut off level.

Adverse effects of etanercept over 12 months (1 year)

Data from two double-blind RCTs of patients suffering from RA were available for the adverse events of etanercept 25 mg over 12 months of treatment.[75,78] Unfortunately, in both of these RCTs the control was MTX and therefore comparative placebo data were not available. The most common adverse events (those reported by ≥10% of patients in at least one of these trials) are listed in *Table 35*. One study reported the proportion of patients experiencing any adverse event (86%),[75] and the same study reported a rate of 59% for any infection. Injection-site reaction was the most commonly reported adverse event in both trials. Neutropenia was reported in one of these long-term trials; this adverse effect has not been seen in trials of shorter duration. Upper respiratory tract infection was common (35% reported in one trial[78]) and skin infections were reported in 14% of patients.[78] These findings are reflected by an uncontrolled open-label follow-up study of etanercept in patients with RA.[79] Serious infections occurred in 4% of patients in one RCT[75] and in 3% in the other RCT.[78] Opportunistic infections were not reported for any of the studies. Cases of cancer were reported at rates from <1% to 2% across these studies; one of the uncontrolled open-label follow-up studies reported that the rate of malignancy had not changed over the course of the study.[79]

Other serious adverse events reported in one of the RCTs occurred at a rate of 11%. The rate of withdrawals reported by these three 1-year studies in RA varied: 11% and 2% in the two RCTs[75,78] and 8% in the uncontrolled open-label follow-up study.[79] One study reported the proportion of patients developing anti-etanercept antibodies: <3%.[78]

One-year data for etanercept in psoriasis patients were available from one uncontrolled follow-up study;[81] unfortunately, these are commercial-in-confidence and cannot be presented.

Adverse effects of etanercept over 2 years or more

Three studies provided data on the adverse effects of etanercept over a period of 2 years or more.[36,76,78] Of these, two were open-label follow-up of RCTs and one was an uncontrolled observational study. Two were of patients with RA and one was of patients with PsA. The results from these studies are summarised in *Table 36*.

The long-term data for PsA patients come from an extension of an RCT.[36] Again, these data are commercial-in-confidence and cannot be presented. Furthermore, data on serious adverse effects were not reported for this study.

Even with these long-term data, the information relating to serious adverse events, particularly serious infections and cancer, are sparse. Serious infection and opportunistic infections are not reported.

Two-year data from two studies, one of patients with RA and the other of patients with PsA,[36,78] indicate a higher rate of adverse events in patients with RA. Injection-site reaction was the most common non-infectious adverse event in both trials. Other adverse events such as headache, nausea, rash, diarrhoea and rhinitis occurred at a **[Confidential information removed]** frequency in the RA trial than in the PsA trial. These differences may reflect differences in the underlying disease or the concomitant medication taken by the two populations.

In the one study that reported it, the proportion of patients developing anti-etanercept antibodies was 3.9%.

Summary of adverse events data for etanercept

In summary, 24 weeks of treatment with etanercept 25 mg twice weekly is associated with a high rate of adverse events, but this rate is not demonstrably higher than that seen in placebo-treated patients. Only injection-site reactions (including ecchymosis, bruising or bleeding at the injection site) and possibly an increase in respiratory tract infections are clearly linked to etanercept. The overall rate of infections with etanercept is high but not necessarily higher than that on placebo. Serious infections have been reported at a rate of approximately 3% of patients and represent a concern with etanercept therapy. In clinical trials, the rate of withdrawals due to adverse events was no higher than with placebo, indicating that generally the drug was well tolerated.

Data regarding anti-etanercept antibodies are also scarce, with few studies reporting them. The rates reported indicated that up to 6% of patients might develop antibodies.

Most long-term data for 2 years or more for etanercept are from patients with RA. Furthermore, published long-term data are poorly reported and therefore of limited value. With longer term use, neurological adverse events are

TABLE 36 *Pooled adverse events data – etanercept 2 years or more follow-up*

	Bathon, 2000[78] (RA, open-label, follow-up – 2 years)	Mease, 2004[36] (PsA, open-label, follow-up 96 weeks)	Geborek, 2002[76] (RA, open-label, follow-up 2 years)
	Etanercept 25 mg (*n* = 207)	**Etanercept 25 mg [Confidential information removed]**	**Etanercept 25 mg (*n* = 166)**
Non-infectious adverse events			NR
Occurring in	≥ 10%	**[Confidential information removed]**	
Any non-infectious adverse event	NR	**[Confidential information removed]**	
Injection-site reaction	81 (39%)	**[Confidential information removed]**	
Ecchymosis (injection site)	23 (11%)	**[Confidential information removed]**	
Bleeding at injection site	32 (16%)		
Accidental injury	23 (11%)	**[Confidential information removed]**	
Headache	51 (25%)	**[Confidential information removed]**	
Back pain	25 (12%)	**[Confidential information removed]**	
Hypertension	< 10%	**[Confidential information removed]**	
Nausea	42 (20%)	**[Confidential information removed]**	
Rash	37 (18%)	**[Confidential information removed]**	
Rhinitis	37 (18%)	**[Confidential information removed]**	
Diarrhoea	35 (17%)	**[Confidential information removed]**	
Asthenia	33 (16%)	**[Confidential information removed]**	
Sporadic neutropenia	> 10%	**[Confidential information removed]**	
Dyspepsia	31 (15%)	**[Confidential information removed]**	
Dizziness	30 (15%)	**[Confidential information removed]**	
Abdominal pain	26 (13%)	**[Confidential information removed]**	
Pain	22 (11%)	**[Confidential information removed]**	
Vomiting	20 (10%)	**[Confidential information removed]**	
Low peripheral lymphocyte count	> 10%	**[Confidential information removed]**	
Infectious adverse events including any serious infections			NR
Occurring in	≥ 10%	**[Confidential information removed]**	
Any infection	NR	**[Confidential information removed]**	
Upper respiratory infection	NR	**[Confidential information removed]**	
Flu syndrome	NR	**[Confidential information removed]**	
Sinusitis	NR	**[Confidential information removed]**	
Pharyngitis	NR	**[Confidential information removed]**	
Serious infection	7 (3.4%)	**[Confidential information removed]**	3
Opportunistic infections	0		NR
Cancer (no. of patients)	4	**[Confidential information removed]**	NR (at least one)

continued

TABLE 36 *Pooled adverse events data – etanercept 2 years or more follow-up (cont'd)*

	Bathon, 2000[78] (RA, open-label, follow-up – 2 years)	**Mease, 2004[36] (PsA, open-label, follow-up 96 weeks)**	**Geborek, 2002[76] (RA, open-label, follow-up 2 years)**
	Etanercept 25 mg (*n* = 207)	**Etanercept 25 mg [Confidential information removed]**	**Etanercept 25 mg (*n* = 166)**
Other serious non-infectious adverse events	Not reported	**[Confidential information removed]**	8
Deaths (no.)	1	**[Confidential information removed]**	3
Withdrawals due to adverse events (no.)	15 (7.3%)	**[Confidential information removed]**	
Positive test for anti-etanercept antibody	8 (3.9%)	**[Confidential information removed]**	NR
Other important adverse event results		**[Confidential information removed]**	The total no. of observational years for etanercept was 232.8 Graded side-effects per 100 years (no.): Fatal 1.3 (*n* = 3) (included above) Life-threatening 0 (*n* = 0) Serious 7 (*n* = 15) Moderate 16 (*n* = 36) Mild 27 (*n* = 61) Not graded 2 (*n* = 5)

NR, not reported.
Where rate is given as <3%, <5% or <10%, the data were derived from a publication that reported adverse events that had occurred at or above the given percentage rate. The listed adverse event was not specified in the report for that study and it has been assumed that it occurred at a rate below the cut off level.

reported and haematological effects such as neutropenia appear. However, it is unclear how treatment related such affects are. As identified from earlier reviews, the main areas of concern relate to the potential of etanercept to increase the risk of serious infections, malignancy, heart failure, conditions secondary to the development of autoimmune antibodies, haematological disorders and demyelinating disease. These serious events are uncommon and not readily identified from the published reports of clinical trials.

Adverse effects of infliximab

Information from standard reference texts

The adverse effects of infliximab summarised from standard reference sources (USPDI 2004, BNF September 2004, Martindale 2002, Centocor, Remicade SPC July 2004) are listed below.

Infliximab has been associated with acute infusion-related reactions, including anaphylactic shock, and delayed hypersensitivity. Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to infliximab and a reduction in the frequency of infusion reactions.

Other common adverse events associated with infliximab are infusion-related reactions [including fever, chills, pruritus, urticaria, chest pain, dyspnoea, flushing, headache, hypotension (dizziness/fainting)], viral infection (e.g. influenza, herpes infections), serum sickness-like reactions, lupus-like syndrome, respiratory tract allergic reactions, anaphylactic reactions, headache, vertigo/dizziness, flushing, upper respiratory tract infection, lower respiratory tract infection (e.g. bronchitis, pneumonia), sinusitis, nausea, vomiting, diarrhoea, abdominal pain, dyspepsia, rash, increased sweating, dry skin, fatigue, myalgia and elevated hepatic transaminases.

Adverse events which are uncommon are abscess, cellulitis, moniliasis, sepsis, bacterial infection, TB, fungal infection, hordeolum, anaemia, leukopenia, lymphadenopathy, lymphocytosis, lymphopenia, neutropenia, thrombocytopenia, lupus-like syndrome, respiratory tract allergic reactions, pharyngitis, sinusitis, rhinitis, cough, anaphylactic reactions, depression, confusion, agitation, amnesia, apathy, nervousness, somnolence, insomnia, exacerbation of demyelinating disease suggestive of MS, conjunctivitis, endophthalmitis, keratoconjunctivitis, periorbital oedema, syncope, bradycardia, palpitation, cyanosis, arrythmia, worsening heart failure, ecchymosis/haematoma, hot flushes, hypertension, hypotension, petechia, thrombophleblitis, vasospasm, peripheral ischaemia, epistaxis, bronchospasm, pleurisy, pulmonary oedema, constipation, gastroesophageal reflux, cheilitis, diverticulitis, abnormal hepatic function, cholecystitis, fungal dermatitis/onychomycosis, eczema/seborrhoea, bullous eruption, furunculosis, hyperkeratosis, rosacea, verruca, abnormal skin pigmentation/coloration, alopecia, myalgia, arthralgia, back pain, urinary tract infection, pyelonephritis, vaginitis, injections site reactions, oedema, pain, chills/rigors, impaired healing, development of autoantibodies and complement factor abnormality.

Rare adverse events of infliximab are meningitis, tachycardia, circulatory failure, pleural effusion, intestinal perforation, intestinal stenosis, intestinal obstruction, abdominal hernia, gastrointestinal haemorrhage, hepatitis, granulomatous lesion, abscess, opportunistic infections (such as TB, atypical mycobacteria, pneumocystosis, histoplasmosis, coccidioidomycosis, cryptococcosis, aspergillosis, listeriosis and candidiasis), pancytopenia, anaphylactic shock, serum sickness, vasculitis, adult respiratory distress syndrome, falls, palpitations, lymphoma, pain in rectum, splenic infarction, tendon injury, urethral obstruction, demyelinating disorders (such as MS and optic neuritis), Guillain–Barré syndrome, neuropathies, numbness, tingling, seizure, interstitial pneumonitis/fibrosis, pancreatitis, hepatitis and vasculitis (primarily cutaneous).

Adverse effects that have been reported very rarely are salmonellosis, haemolytic anaemia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, agranulocytosis, transverse myelitis, pericardial effusion and hepatocellular damage.

Information from existing reviews of infliximab

In addition to the standard reference texts, there have been a number of articles and reviews published regarding the adverse effects of infliximab.[72,87–91] To date the main areas of concern relate to the potential of infliximab to trigger the development of autoimmune antibodies and resultant conditions, immediate and delayed infusion reactions, an increased risk of infections, malignancy and heart failure.

Development of antibodies

Infliximab is a chimeric antibody comprising a 75% human component and a 25% murine component. Treatment with infliximab has been associated with the development of anti-infliximab antibodies (human antichimeric antibodies). The development of these antibodies is associated with acute infusion reactions (anaphylactic or anaphylactoid reactions, delayed hypersensitivity-type reactions) and altered drug pharmacokinetics with diminution of clinical efficacy. In addition, some patients develop ANA and anti-double-strand DNA antibodies. The clinical significance in terms of the risk of developing lupus-like syndromes or demyelination disorders is unclear: there have been cases of demyelinating disease associated with infliximab and very rare reports of a drug-induced lupus-like syndrome associated with positive antibodies.

Infusion reactions

Infusion reactions are the most common adverse event associated with infliximab. Some reports link them with the development of antibodies, their frequency increasing with subsequent infusions, whereas others indicate that they are most frequent with a first infusion. Infusion reactions are usually mild with symptoms such as fever or chills. More serious reactions result in chest pain, hypotension and dyspnoea and there have been some cases of anaphylaxis. Delayed hypersensitivity reactions have also been reported.

Demyelinating disease

Cases of MS and demyelinating disease associated with infliximab were reported in clinical trials. Postmarketing surveillance has identified cases of central demyelination, Guillain–Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, neuropathy, transverse myelitis and optic neuritis. There have been two patients with MS treated with infliximab whose MS was exacerbated. There have been rare reports of seizures or convulsions in patients treated with infliximab. Caution is required if infliximab is used in patients with pre-existing or recent onset central nervous system demyelinating or seizure disorders.

Infections

Like other treatments for RA, psoriasis or PsA infliximab is immunosuppressant and all carry a risk of rendering the patient susceptible to infection. The most frequently occurring infections associated with infliximab and other anti-TNF agents are upper respiratory tract infections. These are generally not serious, that is, do not require hospitalisation or intravenous antibiotics. The FDA review in July 2001 reported that in clinical trials the rate of infection with infliximab has not been found to be higher than with placebo.[92] Serious infections have included pneumonia, bronchitis, peritonitis, septicaemia, pyelonephritis, cellulitis, fungal infection and herpes zoster infection.[72]

Mycobacterium tuberculosis infection is a major concern with anti-TNF agents. This is because TNF is important for controlling *M. tuberculosis* infection within the body. About 95% of those infected will contain the organism via an effective cell-mediated immune response. Exposure to anti-TNF agents may enable reactivation of latent infection. Data reviewed by the FDA in March 2003 indicated that the number of reports of TB within 6 months of treatment with infliximab was higher than expected.[93] The reporting rate for cases of TB with infliximab across the USA and the European Union (EU) was reported to be 0.5 per 1000 years of patient exposure.[93] The incidence in the USA was much lower than that in the EU (0.2 per 1000 patient years compared with 1.4 per 1000 patient-years of exposure). Testing patients for latent TB and the treatment of any TB are required prior to initiating therapy with infliximab. Programmes to educate doctors regarding this have been undertaken in the USA and the EU.

Opportunistic infections are also of concern, particularly atypical mycobacterial infections, histoplasmosis, coccidioidomycosis, *Pneumocystis jiroveci (carinii)* pneumonia, candidosis and aspergillosis.[72,93] These infections total 93 cases from a total number exposed to infliximab of 163,000 patients.[93]

Congestive heart failure

The pharmacology of anti-TNFs suggested the possibility that these agents would have beneficial effects in patients with CHF. A randomised double-blind placebo-controlled trial of 150 patients with NYHA III–IV CHF found no evidence of efficacy for infliximab 5 or 10 mg. However, the trial found a trend towards a worsening clinical status with infliximab 10 mg associated with hospitalisations for worsening CHF and one death. Therefore, infliximab is contraindicated in patients with moderate to severe CHF and should be used with caution in those with less severe CHF.[176]

Malignancy

There is concern that infliximab may increase the risk of lymphoproliferative disease. Six cases have

been reported in clinical trials. This rate is higher than that in the general US population, but it may not be higher than in the patient population being treated for RA or Crohn's disease. Data from the National Database of Rheumatoid Arthritis reveal nine cases of lymphoma for 6260 patients treated with infliximab, and data from the TREAT Registry of Crohn's disease reported one lymphoma for 1628 patients treated with infliximab. These rates were comparable to those for patients with RA or Crohn's disease not treated with infliximab.

Other malignancies have been reported in association with infliximab: in all clinical trials,[19] cases have been reported for 1687 patients treated. Compared with the Seer database, this was not significantly higher than the number expected in the general US population. Postmarketing surveillance data revealed a total of 354 malignancies in patients treated with infliximab. Gastrointestinal cancers were more frequently reported in patients with Crohn's disease than RA, but it is unclear how overall rates compare with those in the general population.

Haematological adverse effects

Haematological adverse effects were uncommon in clinical trials, and postmarketing surveillance revealed only rare cases of pancytopenia, and very rare cases of haemolytic anaemia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura and agranulocytosis.

Adverse events for infliximab: data from included studies

Against the background information on the adverse effects profile of infliximab, we reviewed systematically all long-term (greater than 24 weeks) studies of at least 100 patients for further information on the adverse effects of infliximab.

A total of 15 studies that met the review's inclusion criteria for adverse events data were identified.[61,76,94–106] Details of these studies are summarised in *Table 37* and presented in the data extraction tables in Appendix 5, section 'Data extraction tables: intervention adverse events – infliximab' (p. 150).

TABLE 37 *Studies that met the inclusion criteria for evaluation of the adverse effects of infliximab*

Study	Design	Indication	Dose of infliximab per i.v. infusion (mg/kg)	Concomitant MTX?	Concomitant DMARDs?	Duration of follow-up
Antoni, 2005[61]	DB-RCT	PsA	5	No	No	36–50 weeks
Baeten, 2003[94]	PO	Spondyloarthropathy	5			Up to approx. 2 years
Geborak, 2002[76]	PO	RA	3	Unclear	86%	2 years
Maini, 1998[105]	DB-RCT	RA	1, 3 or 10	Yes	No	26 weeks
Maini, 1999[98]	DB-RCT	RA	3 or 10	Yes	No	30 and 54 weeks
Gottlieb, 2004[106]	DB-RCT	Psoriasis	3 or 5	No	No	30 weeks
Baert, 2003[102]	PO	Crohn's disease	5	2% of patients	Yes	10 months
Cheifetz, 2003[97]	RO	Crohn's disease	Not reported	Unclear	Unclear	2.5 years
Cohen, 2000[99]	PO	Crohn's disease	Not reported	Approx 9% of patients	Approx. 40% of patients	1 year
Colombel, 2004[104]	RO	Crohn's disease	5	11% of patients	93% of patients	Median 17 months
Farrell, 2000[96]	PO	Crohn's disease	5	No	Yes	6 months
Hanauer, 2002[103]	DB-RCT	Crohn's disease	5–10	4% of patients	25% of patients	54 weeks
Hommes, 2002[101]	PO	Crohn's disease	5	31% of patients	66% of patients	Median 17 months
Sample, 2002[95]	RO	Crohn's disease	5	Unclear	68% of patients	Median 24 weeks
Sands, 2004[100]	DB-RCT	Crohn's disease	5	1% of patients	33% of patients	54 weeks

DB-RCT, double-blind randomised controlled trial; PO, prospective observational study; RO, retrospective observational study.

TABLE 38 *Adverse events of infliximab in psoriatic arthritis*

	IMPACT PsA, DB-RCT, 16 weeks follow-up		**IMPACT PsA, 20/36 weeks follow-up (36/50 weeks continuous infliximab)**	
	Placebo ***n* = 51**	**Infliximab** ***n* = 52**	**Placebo/infliximab** ***n* = 50**	**Infliximab** ***n* = 49**
Any adverse event	33 (65%)	38 (73%)	44 (88%)	41 (84%)
Non-infectious adverse events				
Occurring in ≥5% patients				
[Confidential information removed]	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**
Infusion reactions	5 (10%)	4 (8%)	7(14%)	4 (8%)
Severe infusion reactions	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**
Infectious adverse events including any serious infections				
Occurring in ≥5% patients				
[Confidential information removed]	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**
Serious Infection	0	1 (2%)	**[Confidential information removed]**	**[Confidential information removed]**
Cancer		**[Confidential information removed]**		**[Confidential information removed]**
Other non-infectious serious adverse events	1 Rectal bleeding resulting from diverticulitis	0	**[Confidential information removed]**	**[Confidential information removed]**
Withdrawals due to adverse events	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**
Deaths	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**
Positive test for antibodies	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**	**[Confidential information removed]**
Other important adverse event results	**[Confidential information removed]**	**[Confidential information removed]**	No patients had active TB. 12 severe adverse events **[Confidential information removed]**	

One of these studies is the main efficacy trial of infliximab in PsA.[61] This is the only study of exclusively PsA patients. The 16-week RCT data in this trial are supplemented by a 36-week long open-label follow-up in which all patients were treated with infliximab. For the sake of completeness, the 16-week data are presented in addition to the 36-week data. Overall in this study, up to 49 patients received 50 weeks of infliximab and up to 50 patients received 36 weeks of infliximab. The adverse event data are summarised in *Table 38*.

The placebo-controlled data up to 16 weeks demonstrated that although the incidence of adverse events with infliximab is high (73%), the same is true for placebo (65%). Infusion reactions were not more common with infliximab than with placebo (8 and 10%, respectively).

The number of patients experiencing severe infusion reactions, infection and infestations, upper respiratory tract infection (not just treatment related), serious infection and withdrawals due to adverse events were derived from

commercial-in-confidence data and so cannot be presented here.

The treatment-related adverse events that were reported by at least four patients during the first 16 weeks of treatment with infliximab were headache (four infliximab, three placebo), bronchitis (three infliximab, four placebo), upper respiratory tract infection (one infliximab, five placebo), influenza-like symptoms (one infliximab, four placebo), rhinitis (three infliximab, two placebo) and rash (three infliximab, two placebo patients). Serious adverse events reported in the first 16 weeks of the study were one case of rectal bleeding due to diverticulitis (placebo) and one case of synovitis suspected of being infectious that was culture negative (infliximab).

Data from the open-label phase of the study of PsA found that with continued use the rates of adverse events continued to be high (84%) and the rate of infusion reaction remained constant at 8%. Between 16 and 50 weeks (when all patients received infliximab), the most common adverse event was upper respiratory tract infection (23 patients), headache (seven patients), dizziness (six patients), influenza-like symptoms (five patients), non-productive cough (five patients), rhinitis (four patients), hypertension (four patients) and sinusitis (four patients). Serious adverse events that occurred during this phase of the study were surgery for inguinal hernia, angina pectoris, atrial fibrillation, urinary retention, chest pain, cerebrovascular event, fever, acute gastroenteritis, pyelonephritis and leg weakness.

No patient experienced TB infection or opportunistic infection during the study, nor were there any cases of autoimmune, cytopenic or neurological events.

Only one other included study contained patients with a diagnosis of PsA; this was a prospective observational study of patients with spondyloarthropathy.[94] This study was a pooling of the findings from three separate patient cohorts, totalling 107 patients, 32 of whom had PsA. Overall, 19/107 (18%) patients took MTX and patients were followed for up to approximately 2 years, with a total follow-up of 191.5 years. For all patients the significant adverse events included eight infections, nine serious infections, one case of cancer and no deaths, with five patients withdrawing owing to adverse events. More than 90% of all patients tested antibody positive.

Together these data provide some evidence of the tolerability and safety of infliximab in patients with PsA. However, many patients were not treated concomitantly with MTX and the data do not, therefore, reflect the situation with the use of infliximab according to its product licence.

The three studies of infliximab in patients with RA provide data on patients in most of whom infliximab was used in combination with at least one other DMARD.[76,98,105] These data are summarised in *Table 39*.

In one 2-year prospective observational study of 135 patients, treated with infliximab 3 mg/kg i.v. infusion, 86% used combination therapy,[76] but unfortunately whether all combination therapy comprised infliximab with MTX was not reported. Furthermore, only limited data were reported for this study. Over the course of this study, two serious infections, three cases of cancer, four allergic reactions and one anaphylactic reaction, two cases of lupus and two other serious adverse reactions were reported. There were no fatal reactions but three were life threatening.

Two other studies of RA were conducted by the same researchers and followed similar protocols.[98,105] Both were double-blind RCTs in which infliximab plus MTX was compared with MTX alone (MTX plus placebo). In the longer and larger of the two trials,[98] 340 patients were divided between four infliximab regimens: 3 or 10 mg/kg doses of infliximab at a frequency of every 4 or 8 weeks (*Table 39*). Across all regimens over a period of 30 weeks, infusion reactions were seen in 16–20% of patients compared with 10% of patients receiving MTX alone. Hypersensitivity-type reactions were seen in 4.1% of patients treated with infliximab plus MTX compared with 2.3% of MTX treated patients. There were no serious infusion reactions or delayed hypersensitivity reactions in any treatment group.

Infections were common on all treatments but were more common with the 10 mg/kg regimens compared with MTX (64 and 73% compared with 40%). The rate of serious infection was not higher with infliximab plus MTX than with MTX alone at 30 or 54 weeks. The same was true for all serious adverse events. There was one case of a lupus-like reaction and five cases of cancer in infliximab-treated patients. Death was reported at a rate of 1% in the infliximab/MTX-treated patients compared with 3.5% on MTX alone. Withdrawals due to adverse events occurred in 3–7% of the

TABLE 39 *Adverse events with infliximab in patients with rheumatoid arthritis*

	Maini, 1999 (DB-RCT, 30 and 54 weeks)[98]					Maini, 1998 (DB-RCT vs MTX, 26 weeks)[105]		Geborek, 2002 (prospective observational study, 2 years)[76]
	3 mg/8 weeks	3 mg/4 weeks	10 mg/8 weeks	10 mg/4 weeks	Placebo/MTX	All infliximab doses (1, 3 or 10 mg/kg) ± MTX	MTX	Infliximab 3 mg/kg
	(*n* = 86)	(*n* = 86)	(*n* = 87)	(*n* = 81)	(*n* = 86)	(*n* = 87)	(*n* = 14)	(*n* = 135)
Non-infectious adverse events								NR
Headache	22 (25%)	17 (20%)	21 (24%)	16 (20%)	9 (10%)	12.6%		
Nausea	14 (16%)	12 (14%)	12 (14%)	14 (18%)	16 (19%)			
Sinusitis	10 (11%)	6 (7%)	12 (14%)	12 (15%)	4 (5%)			
Rash	5 (6%)	7 (8%)	14 (16%)	11 (14%)	4 (5%)	6.9%		
Coughing	8 (9%)	6 (7%)	11 (13%)	12 (15%)	3 (3%)	5.7%		
Diarrhoea	7 (8%)	8 (9%)	7 (8%)	10 (13%)	10 (12%)		9.2%	
Fatigue	15 (17%)	5 (6%)	3 (3%)	9 (11%)	6 (7%)			
Dizziness	8 (9%)	5 (6%)	12 (14%)	5 (6%)	6 (7%)			
Rhinitis	7 (8%)	5 (6%)	10 (11%)	7 (9%)	5 (6%)	6.9%		
Back pain	7 (8%)	7 (8%)	6 (7%)	8 (10%)	2 (2%)			
Abdominal pain	4 (4%)	8 (9%)	7 (8%)	6 (8%)	7 (8%)			
Pain	4 (4%)	3 (3%)	7 (8%)	8 (10%)	4 (5%)			
Pharyngitis	5 (6%)	4 (5%)	6 (7%)	6 (8%)	4 (5%)	6.9%		
Arthralgia	6 (7%)	2 (2%)	5 (6%)	5 (6%)	2 (2%)			
Hypertension	5 (6%)	3 (3%)	4 (5%)	6 (8%)	3 (3%)			
Stomatitis, ulcerative	4 (4%)	3 (3%)	2 (2%)	9 (11%)	2 (2%)			
Fever	4 (4%)	7 (8%)	3 (3%)	4 (5%)	4 (5%)			
Dyspepsia	5 (6%)	5 (6%)	1 (1%)	6 (8%)	3 (3%)			
Infusion reactions	14–16 (16–20%)				9 (10%)			
Serious infusion reactions	0	0	0	0	0			
Hypersensitivity-type reactions	All doses 14 (4.1%)				2 (2.3%)			
Hypotension	All doses 8 (2.4%)				2 (2.3%)			
Urticaria	All doses 4 (1.2%)				0			
Dyspnoea	All doses 2 (0.6%),				0			
Delayed hypersensitivity reactions (after 1 hour or at 4 weeks)	0	0	0	0	0			

continued

TABLE 39 *Adverse events with infliximab in patients with rheumatoid arthritis (cont'd)*

	Maini, 1999 (DB-RCT, 30 and 54 weeks)[98]					Maini, 1998 (DB-RCT vs MTX, 26 weeks)[105]		Geborek, 2002 (prospective observational study, 2 years)[76]
	3 mg/8 weeks	**3 mg/4 weeks**	**10 mg/8 weeks**	**10 mg/4 weeks**	**Placebo/MTX**	**All infliximab doses (1, 3 or 10 mg/kg) ± MTX**	**MTX**	**Infliximab 3 mg/kg**
	(*n* = 86)	**(*n* = 86)**	**(*n* = 87)**	**(*n* = 81)**	**(*n* = 86)**	**(*n* = 87)**	**(*n* = 14)**	**(*n* = 135)**
Infectious adverse events including any serious infections								NR
Any infection	47 (53%)	40 (47%)	56 (64%)	58 (73%)	34 (40%)	NR		
Upper respiratory tract infection	29 (33%)	17 (20%)	21 (24%)	18 (23%)	14 (16%)	4.6%		
Urinary tract infection	3 (3%)	2 (2%)	6 (7%)	7 (9%)	3 (3%)	4.6%		
Infection requiring antimicrobials	20 (23%)	24 (28%)	32 (37%)	30 (38%)	18 (21%)	28/87 (32.2%)	3/14 (21.4%)	
Serious infection						2	0	2
At 30 weeks	1 (1%)	5 (6%)	5 (6%)	3 (4%)	5 (6%)			
At 54 weeks	2 (2%)	6 (7%)	7 (8%)	6 (7%)	7 (8%)			
Serious adverse events (unclear if includes infections or not)								
At 30 weeks	8 (9%)	11 (13%)	8 (9%)	10 (13%)	14 (16%)			
At 54 weeks	10 (11%)	14 (16%)	17 (20%)	16 (20%)	18 (21%)			
SLE						1		
Discoid lupus								1
Thrombocytopenia								1
Lupus-like reaction	1 infliximab-treated dose not stated							1
Pharyngitis								1
Anaphylactoid reaction								1
Allergic reactions								4
Cancer	0	0	2	3	0	0	0	3 (2 Hodgkin lymphoma, 1 mesothelioma)
Deaths	2/340 (1%) patients receiving infliximab				3 (3.5%)	1		
Withdrawals due to adverse events	Infliximab = 3–6 (3–7%);				7 (8%)	6 or 7	0	
Positive test for anti-nuclear antibody						Anti-infliximab antibodies overall incidence 17.4%		NR

continued

TABLE 39 *Adverse events with infliximab in patients with rheumatoid arthritis (cont'd)*

	Maini, 1999 (DB-RCT, 30 and 54 weeks)[98]					Maini, 1998 (DB-RCT vs MTX, 26 weeks)[105]		Geborek, 2002 (prospective observational study, 2 years)[76]
	3 mg/8 weeks	**3 mg/4 weeks**	**10 mg/8 weeks**	**10 mg/4 weeks**	**Placebo/MTX**	**All infliximab doses (1, 3 or 10 mg/kg) ± MTX**	**MTX**	**Infliximab 3 mg/kg**
	(*n* = 86)	**(*n* = 86)**	**(*n* = 87)**	**(*n* = 81)**	**(*n* = 86)**	**(*n* = 87)**	**(*n* = 14)**	**(*n* = 135)**
At 54 weeks	50/74 (68%)	40/64 (62%)	44/71 (62%)	34/64 (53%)	18/69 (26%)		7%	
Positive test for anti-dsDNA antibody						7	0	
At 30 weeks	All doses 16%				0%	NR		
At 54 weeks	9/88(10%)	9/85(11%)	9/87(10%)	6/81(7%)	0/84			
Comments/other adverse events information						Few adverse events data reported. Only adverse events 'reasonably related' to treatment listed, with all data for all doses of infliximab and infliximab plus MTX combined		Graded side-effects per 100 year: fatal 0; life-threatening 2.8 (*n* = 3); serious 10 (*n* = 11); moderate 31 (*n* = 34); mild 54 (*n* = 59); not graded 0

DB-RCT, double-blind randomised controlled trial; NR, not reported.

TABLE 40 *Adverse events of infliximab in psoriasis with no DMARDs*

	Gottlieb, 2004[106] (psoriasis, DB-RCT, 30 weeks follow-up; dosed at weeks 0, 2 and 6; 114 patients also dosed at week 26)		
	Placebo (*n* = 51)	**3 mg/kg (*n* = 98)**	**5 mg/kg (*n* = 99)**
Non-infectious adverse events			
No. of patients with ≥ 1 adverse event (%)	32 (62.7)	76 (77.6)	78 (78.8)
No. of patients with serious adverse events (%)	4 (4.1)	8 (8.1)	12 (6.1)
Infusion reactions			
No. of patients with infusion reactions (%)	1 (2.0)	18 (18.4)	22 (22.2)
No. of patients with serious infusion reactions (%)	0 (0.0)	0 (0.0)	0 (0.0)
No. of infusions with infusion reactions (%)	1 (0.7)	19 (5.6)	26 (7.6)
Mild	1 (0.7)	11 (3.2)	18 (5.2)
Moderate	0 (0.0)	8 (2.3)	6 (1.7)
Severe	0 (0.0)	0 (0.0)	2 (0.6)
Infusion reactions include headaches, chills, flushing, nausea, dyspnea, injection site infiltrations and taste perversion			
Infectious adverse events including any serious infections			
No. of patients with serious infections (%)	0 (0.0)	0 (0.0)	0 (0.0)
Cancer	0	1 (squamous cell carcinoma)	0
Other non-infectious serious adverse events (no.)		1 (cholecystitis and cholelithiasis)	2 (diverticulitis, sepsis and pyelonephritis)
Deaths	0	0	0
Withdrawals due to adverse events	None stated	None stated	None stated
Positive test for anti-etanercept antibody			
Antinuclear antibodies (%)	1/44 (2.3%)	19/83(22.9%)	20/80(25.0%)
Antibodies against double-stranded DNA	1/48(2.1%)	3/91(3.3%)	4/94(4.3%)
Antibodies to infliximab	NA	21/76(27.6%) Of those retreated at week 26, the incidence of infusion reaction was higher in those known to be antibody positive compared with those known to be antibody negative	17/87(19.5%)
Other important adverse event results	Laboratory parameters that changed significantly from baseline more often on infliximab than on placebo were alanine transferase (34 vs 16% on placebo) and aspartate transaminase (24 vs 14%).		

DB-RCT, double-blind randomised controlled trial; NA, not applicable.

infliximab/MTX-treated patients compared with 8% of MTX-treated patients.

This trial provided useful data on the proportion of patients developing antibodies on infliximab. After 54 weeks, ANA were found in 53–68% of patients treated with infliximab/MTX compared with 26% treated with MTX alone. Anti-double-stranded DNA antibodies were found in around 16% of infliximab patients at 30 weeks and around 10% at 54 weeks, but in no MTX-treated patient.

The findings of the smaller trial[105] were less well reported but generally reflect the findings from the larger trial.

One trial in patients with psoriasis[106] provided data for the use of infliximab alone compared with placebo in patients similar to a PsA population (*Table 40*). The results from this double-blind placebo-controlled trial reflect the findings of other studies: adverse events were common with infliximab, but were also common on placebo; infusion reactions occur in around 20% of patients

TABLE 41 *Summary of adverse events from studies in patients with Crohn's disease*

	Baert, 2003[102]	**Cheifetz, 2003[97]**	**Cohen, 2000[99]**	**Colombel, 2004[104]**	**Farrell, 2000[96]**	**Hanauer, 2002[103]**	**Hommes, 2002[101]**	**Sample, 2002[95]**	**Sands, 2004[100]**
No. of patients	125	165	129	500	100	385	134	109	138
Dose and regimen[a]	5 mg/kg i.v. infusion, mean no. of infusions per patients 3.9	Dose NR, mean no. of infusions per patients 2.8	Dose NR, mean no. of infusions per patients 2.7	5 mg/kg i.v. infusion, mean no. of infusions per patients NR	5 mg/kg i.v. infusion, mean no. of infusions per patients NR	5–10 mg/kg i.v. infusion, mean no. of infusions per patients NR	5 mg/kg i.v. infusion, mean no. of infusions per patients 4.4	5 mg/kg i.v. infusion, mean no. of infusions per patients NR	5 mg/kg i.v. infusion, mean no. of infusions per patients NR
Duration of follow-up	10 months	2.5 years	1 year	Median 17 months	6 months	54 weeks	Median 17 months (range 0–45 months)	Median 24 weeks (range 1–40 weeks)	54 weeks
% patients with:									
Any AE	NR		24	NR	47	NR	17	NR	NR
Infusion reaction	27	8.4	6	3.8	25	21	NR (2% serious infusion reaction	7	16
Infection	NR	NR	NR	10	14	30	0	0.9	34
Cancer	NR	NR	0	1.8	0	1.6	0	0	1.4
Other serious adverse events	NR	NR	1.5	1.6	16 (infusion reactions)	25	0	0.9	14
Deaths	0	0	0	2.0	0	0.7	0	0	1.4
Positive antibodies	45 after first infusion, 61 after 6th	NR	NR	NR	NR	Anti-double stranded DNA 22.5 ANA 45.5	NR	NR	Anti-double stranded DNA 23.3 ANA 45.9
Comparison with placebo	–	–	–	–	–	Only for infusion reaction was % higher than in placebo group			Only for development of antibodies was % higher than in placebo group

NR, not reported.
[a]In most studies infliximab administered induction dose either at week 0 only or at weeks 0, 2 and 6. Responders then retreated upon relapse of disease.

but these are almost never serious and rarely severe. The rate of infections was not reported but there were no serious infections. No deaths or withdrawals due to adverse events were reported. In these patients, as in the RA population, the proportion of patients developing antibodies was significant and of concern.

Table 41 summarises data from long-term studies of infliximab in patients with Crohn's disease.[95–97,99–104] This population is in many ways different from those with PsA and even within the trials for Crohn's disease patients are divided into those with active non-fistulising disease and those with fistulising disease. Furthermore, most patients within these trials were not treated with concomitant MTX and many are on concomitant corticosteroids. However, these data are included here because they do reflect the experience of a large number of patients (total 1785) exposed to (mostly) 5 mg/kg maintenance dose of infliximab over follow-up periods of 6 months to 2.5 years.

Overall, these data reflect those from other patient populations: infusion reactions and development of antibodies are of concern with infliximab. As with the other published long-term study data, the clinical significance of the few cases of cancer and other serious adverse events reported is impossible to discern. The analysis of those adverse effects of infliximab requires analysis of primary data.

Summary of adverse events data for infliximab

Short-term studies of 16–30 weeks in a range of indications have demonstrated that adverse events are common with infliximab, but that they are not necessarily higher than on placebo treatment. These studies have identified clearly the problem of infusion reactions with infliximab. These reactions are usually not serious but the possibility of serious infusion reactions is real. These data and longer term data indicate that infections are common in patients treated with infliximab, but it is unclear if this represents an increased rate caused by infliximab.

Infliximab therapy is associated with a risk of developing antibodies, with a higher proportion of patients testing positive after treatment.

With longer term data, one would like to answer the questions of how significant infusion reactions are: does the rate and/or severity of infusion reactions increase or decrease with increasing number of infusions? The data from the studies that met our inclusion criteria have not helped to answer these questions. Similarly, we have been unable to shed light on the clinical significance of reports of cancer, infections, heart failure and other serious adverse events.

Overall, infusion reactions and the development of antibodies and infections appear to be the most significant adverse effects of infliximab, with the possible risk of lymphomas, SLE and MS, requiring caution and further monitoring and investigation. The data indicate that the combination of infliximab and MTX is generally as well tolerated as MTX alone; however, mild infusion reactions, infections and possibly the risk of malignancy are higher with the combination therapy.

Appendix 7

Data extraction tables: comparator efficacy

Study details	Participants	Treatment	Outcomes and results
Reference Kaltwasser, 2004[46] **Study design** RCT	**Definition of PsA** Diagnosed as having at least one subtype of PsA (distal interphalangeal involvement, polyarticular involvement, arthritis mutilans, asymmetric oligoarticular arthritis or ankylosing spondylitis-like arthritis) and with joint activity involving at least 3 swollen joints and at least 3 tender joints and psoriasis affecting at least 3% BSA. Those with positive RA or rheumatoid nodules were excluded **Positive for RF excluded?** Yes **Previous therapy?** 37% (SD 38.7%) of patients had not had previous DMARD therapy Placebo: 46% (SD 50.5%) patients had not had previous DMARD therapy **Concomitant therapy?** Systemic corticosteroids: leflunomide 15% (SD 15.8%); placebo 9% (SD 9.9%) NSAIDs: leflunomide 75% (SD 78.9%); placebo 73% (SD 80.2%) Topical agents: leflunomide 23% (SD 24.2%); placebo 23% (SD 25.3%) **Adult?** Yes **Number of participants** $n = 186$	**Treatment dose regimen** Leflunomide 20 mg/day, $n = 95$ **Comparator dose regimen** Placebo equivalent, $n = 91$ **Duration of treatment** 24 weeks	**Modified ACR 20** Leflunomide: improvement/response 29/80 (36.3%, 95% CI: 25.8 to 47.8) Placebo ($n = 80$): improvement/response 16/80 (20.0%, 95% CI: 11.9 to 30.4) ($p = 0.0138$) PsARC Leflunomide: 56/95 (58.9%, 95% CI: 48.4 to 68.9) Placebo: 27/91 (29.7%, 95% CI: 20.6 to 40.2) ($p < 0.0001$) **HAQ** Leflunomide ($n = 94$): mean change from baseline –0.19 ± 0.51 SD Placebo ($n = 90$): mean change from baseline –0.05 ± 0.46 SD ($p = 0.0267$) **DLQI (dermatology life quality index)** Leflunomide ($n = 90$): mean change from baseline –1.9 ± 5.1 SD Placebo ($n = 89$): mean change from baseline –0.2 ± 5.1 SD ($p = 0.0173$) **PhGA** Leflunomide ($n = 95$): improvement/response 52.6%; deterioration 10.5% Placebo ($n = 91$): improvement/response 34.1% ($p = 0.0001$); deterioration 22.0% ($p < 0.0001$) **PtGA** Leflunomide ($n = 95$): improvement/response 31.6%; deterioration 15.8% Placebo ($n = 91$): improvement/response 30.8% ($p = 0.0036$); deterioration 24.2% ($p < 0.0001$) **Pain assessment** (NB not reported if VAS used) Leflunomide ($n = 90$): improvement/response 46.7%; deterioration 13.3% Placebo ($n = 90$): improvement/response 35.6 ($p = 0.0042$); deterioration 33.3% **Joint pain/tenderness score** 76 joints assessed Leflunomide ($n = 95$): mean change from baseline –9.1 ± 21.0 SD Placebo ($n = 91$): mean change from baseline –4.6 ± 19.6 SD ($p = 0.0022$) **Joint swelling score** 74 joints assessed

continued

Study details	Participants	Treatment	Outcomes and results
			Leflunomide (n = 95): mean change from baseline –6.8 ± 16.8 SD Placebo (n = 91): mean change from baseline –4.2 ± 13.6 SD (p = 0.0013) **TJS** 76 joints assessed Leflunomide (n = 95): mean change from baseline –5.6 ± 10.9 SD Placebo (n = 91): mean change from baseline –3.0 ± 12.3 SD (p = 0.0006) **SJS** Leflunomide (n = 95): mean change from baseline –4.4 ± 8.6 SD Placebo (n = 91): mean change from baseline –2.7 ± 9.7 SD (p = 0.0009) **CRP level (mg)** Leflunomide (n = 93): mean change from baseline –7.9 ± 20.8 SD Placebo (n = 89): mean change from baseline –0.1 ± 14.6 SD (p = 0.0182) **PASI** Leflunomide (n = 92): mean change from baseline –2.1 ± 5.9 SD Placebo (n = 90): mean change from baseline –0.6 ± 6.1 SD (p = 0.0030)

Study details	Participants	Treatment	Outcomes and results
Reference Farr, 1990[116] **Study design** RCT	**Definition of PsA** Seronegative arthritis associated with psoriasis. All patients had active joint disease uncontrolled by anti-inflammatory drugs alone. They had either ESR >30 mm/h or CRP >15 mg/l and two of the following three criteria: duration of morning stiffness >30 minutes; ≥ 3 painful or swollen joints; or tenderness or pain on movement of at least 3 joints **Positive for RF excluded?** Yes **Previous therapy?** All patients took NSAIDS and 2 in each group had taken a second-line drug **Concomitant therapy?** All patients took NSAIDS at a constant dose. 3 patients on SSZ and 6 on placebo received intra-articular steroids. **Adult?** Yes **Number of participants** $n = 30$	**Treatment dose regimen** SSZ enteric coated (Salazoprin EN) 0.5 g/day titrated up to a maximum of 2 g/day, $n = 15$ **Comparator dose regimen** Placebo equivalent, $n = 15$ **Duration of treatment** 24 weeks	**PhGA** Subjective clinical score: SSZ ($n = 9$): median at baseline 100 (98–101), at 6 months 97 (95–101) ($p < 0.05$) Placebo ($n = 9$): median at baseline 100 (100–102), at 6 months 99 (97–103) **Pain assessment (VAS)** SSZ ($n = 9$): median at baseline 67 (0–100), at 6 months 14.5 (0–45); ($p < 0.05$) Placebo ($n = 9$): median at baseline 62.5 (25–100), at 6 months 29.0 (5–50) **Mean change (SD)** SSZ ($n = 15$): –43.10 (26.00); Placebo ($n = 15$) –35.80 (21.00) (data from Cochrane review) **Joint pain/tenderness score** SSZ ($n = 9$): median at baseline 13 (2–34), at 6 months 7 (0–16) ($p < 0.05$) Placebo ($n = 9$): median at baseline 10 (1–29), at 6 months 8 (4–17) **Duration morning stiffness (minutes)** SSZ ($n = 9$): median at baseline 180 (0–720), at 6 months 10 (0–720) ($p < 0.01$) Placebo ($n = 9$): median at baseline 150 (10–720), at 6 months 120 (30–720) **ESR (mm/h)** SSZ ($n = 9$): median at baseline 31 (8–109), at 6 months 14 (5–30) ($p < 0.05$) Placebo ($n = 9$): median at baseline 22 (1–62), at 6 months 14.0 (7–25) **Mean change (SD)** SSZ ($n = 15$): –23.10 (17.00); placebo ($n = 15$): –16.40 (14.00) (data from Cochrane review) **Grip strength** SSZ ($n = 9$): median at baseline 266 (115–580), at 6 months 398 (117–600) ($p < 0.05$) Placebo ($n = 9$): median at baseline 260 (96–600), at 6 months 278.0 (127–600)

Study details	Participants	Treatment	Outcomes and results
Reference Fraser, 1993[114] **Study design** RCT	**Definition of PsA** Clinical diagnosis of PsA with asymmetric polyarthritis with psoriasis. All had inflammatory disease involving pain in three or more joints with evidence of active synovitis poorly controlled on NSAIDs **Positive for RF excluded?** Yes **Previous therapy?** NSAIDS. No DMARDs in previous 3 months **Concomitant therapy?** All patients taking NSAIDs and 2 taking low constant-dose corticosteroids **Adult?** Yes **Number of participants** *n* = 39	**Treatment dose regimen** SSZ enteric coated 500 mg/day titrating to a maximum dose of 40 mg/kg, *n* = 19 **Comparator dose regimen** Placebo equivalent, *n* = 20 **Duration of treatment** 24 weeks **Notes** No. of patients SSZ: baseline = 19, 24 weeks = 13 Placebo: baseline = 20, 24 weeks = 9	**Global index of well-being (5-point scale)** SSZ: median at baseline 3 (1-3), at 24 weeks 3 (1–3). Placebo: median at baseline 3 (0–3), at 24 weeks 2 (1–4) **VAS pain** SSZ: median at baseline 550 (5-900), at 24 weeks 150 (30–730) ($p = 0.01$). Placebo: median at baseline 585 (440-880), at 24 weeks 350 (50–630) ($p = 0.03$) **Duration morning stiffness (minutes)** SSZ: median at baseline 60 (10–720), at 24 weeks 30 (0–720) ($p = 0.008$) Placebo: median at baseline 120 (25–720), at 24 weeks 120 (0–720) **Ritchie index** SSZ: median at baseline 17 (0–43), at 24 weeks 6 (0–21) ($p = 0.002$) Placebo: median at baseline 20 (3–37), at 24 weeks 6 (2–26) ($p = 0.02$) **ESR (mm/h)** SSZ: median at baseline 35 (18–77), at 24 weeks 14 (4–55) ($p = 0.004$) Placebo: median at baseline 41 (5–38), at 24 weeks 28 (6–64) **Grip strength** SSZ: median at baseline 100 (40–300), at 24 weeks 120 (54–300) Placebo: median at baseline 108 (55–285), at 24 weeks 138 (47–255) **Haemoglobin** SSZ: median at baseline 12.2 (11.1–15), at 24 weeks 12.4 (10.4–15.2) Placebo: median at baseline 12.5 (9.5–15.9), at 24 weeks 12.9 (11–15.3)

Study details	Participants	Treatment	Outcomes and results
Reference Clegg, 1996[31] **Study design** RCT	**Definition of PsA** Diagnosed as having an established diagnosis of psoriasis and at least one of the following presentations of PsA: distal interphalangeal involvement, asymmetric peripheral arthritis or symmetric polyarthritis, and with joint activity involving at least 3 swollen and tender joints. Those with positive RA or another rheumatological disorder were excluded **Positive for RF excluded?** Yes **Previous therapy?** All patients had failed to respond to therapeutic doses of one NSAID **Concomitant therapy?** Stable doses of NSAIDs. No systemic or intra-articular steroids were permitted **Adult?** Yes **Number of participants** $n = 221$	**Treatment dose regimen** SSZ enteric coated 500 mg/day titrated up to a maximum of 2 g/day, $n = 109$ **Comparator dose regimen** Placebo equivalent, $n = 112$ **Duration of treatment** 36 weeks **Notes** Total number of patients unclear for each outcome. No. randomised: SSZ 109, placebo 112	Ref. 31 linked to ref. 112 **PsARC** SSZ: 63/109 (57.8%) Placebo: 50/112 (44.6%) ($p = 0.05$) **PhGA** SSZ: improvement 41.3%; deterioration 6.4% Placebo: improvement 38.4%; deterioration 10.7% ($p = 0.52$) **PtGA** SSZ: improvement 45.9%; deterioration 7.3% Placebo: improvement 41.1%; deterioration 9.8% ($p = 0.52$) **Joint pain/tenderness score** SSZ: improvement 58.7%; deterioration 11.9% Placebo: improvement 47.3%; deterioration 13.4% ($p = 0.22$) SSZ: mean change from baseline –10.3 ± 22.4 SD Placebo: mean change from baseline –7.8 ± 19.1 ($p = 0.38$) **Joint swelling score** SSZ: improvement 59.6%; deterioration 9.2% Placebo: improvement 51.8%; deterioration 13.4% ($p = 0.43$) SSZ: mean change from baseline –7.8 ± 12.8 SD Placebo: mean change from baseline –8.0 ± 13.7 ($p = 0.93$) **Duration morning stiffness (minutes)** SSZ: mean change from baseline –48 ± 276 SD Placebo: mean change from baseline –18 ± 252 ($p = 0.39$) **ESR (mm/h)** SSZ: mean change from baseline –6.4 ± 14.9 SD Placebo: mean change from baseline 1.1 ± 15.0 ($p < 0.01$) **CRP level (mg/ml)** SSZ: mean change from baseline –0.43 ± 2.10 SD Placebo: mean change from baseline –1.00 ± 3.03 ($p = 0.19$)

continued

Study details	Participants	Treatment	Outcomes and results
			Psoriasis (% BSA) SSZ: mean change from baseline –1.0 ± 9.9 SD Placebo: mean change from baseline 1.1 ± 6.9 ($p = 0.07$) **Responders to treatment** SSZ: 57.8% Placebo: 44.6% ($p = 0.05$) **Spondylitis functional index (no.)** SSZ: mean change from baseline –1.2 ± 4.6 SD Placebo: mean change from baseline –0.5 ± 4.9 ($p = 0.30$) **Dactylitis score (no.)** SSZ: mean change from baseline –0.5 ± 4.2 SD Placebo: mean change from baseline –0.9 ± 4.1 ($p = 0.43$) **Enthesopathy index (no.)** SSZ: mean change from baseline –1.5 ± 4.5 SD Placebo: mean change from baseline –0.9 ± 4.1 ($p = 0.25$) **Spondylitis Articular Index (no.)** SSZ: mean change from baseline –0.9 ± 2.8 SD Placebo: mean change from baseline –0.6 ± 2.9 ($p = 0.39$) **Chest expansion** SSZ: mean change from baseline 0.1 ± 1.3 SD Placebo: mean change from baseline 0.1 ± 1.8 ($p = 0.80$) **Modified Schober's test (cm)** SSZ: mean change from baseline 0.1 ± 1.0 SD Placebo: mean change from baseline 0.0 ± 1.3 ($p = 0.64$) **Occiput-to-wall (cm)** SSZ: mean change from baseline 0.3 ± 1.9 SD Placebo: mean change from baseline 0.2 ± 1.9 ($p = 0.63$) **Fingers-to-floor** SSZ: mean change from baseline –0.5 ± 7.5 SD Placebo: mean change from baseline 0.0 ± 6.5 ($p = 0.54$)

Study details	Participants	Treatment	Outcomes and results
Reference Combe, 1996[115] **Study design** RCT	**Definition of PsA** Diagnosis of PsA of at least 3 months duration including past or present psoriasis and one of the following: pain and swelling of the distal interphalangeal joints of hands or feet, peripheral asymmetric oligoarthritis, symmetrical peripheral arthritis in the absence of positive RF or nodules; or sacroiliac or spinal involvement **Positive for RF excluded?** Yes **Previous therapy?** Not stated **Concomitant therapy?** NSAIDs, analgesics and other drugs had to be kept constant during the study. Slow-acting drugs and corticosteroids were not permitted during the trial **Adult?** Yes **Number of participants** n = 120 (117 ITT)	**Treatment dose regimen** SSZ enteric coated 500 mg/day, titrated up to 2g/day, n = 53 **Comparator dose regimen** Placebo equivalent, n = 64 **Duration of treatment** 24 weeks **Notes** No. of patients: SSZ 53, placebo 64 (ITT population)	**VAS pain** SSZ (n = 53): mean change from baseline –22.9 (27.7 SD) Placebo (n = 64): mean change from baseline –12.6 (30.2 SD) (p = 0.01) **Tender joint count** SSZ (n = 53): mean change from baseline –2.8 (3.7 SD) Placebo (n = 64): mean change from baseline –2.0 (3.5 SD) (p = 0.30) SSZ: median at baseline 11.0 (0–26), at 6 months 5.0 (0–16) ($p < 0.05$) Placebo: median at baseline 8 (2–34), at 6 months 5.0 (2–14) **Joint improvement (worse, no effect, slightly better, clearly better, healed)** SSZ: worse = 7 (14%), no effect = 7 (14%), slightly better = 13 (25%), clearly better = 21 (41%), healed = 3 (6%) Placebo: worse = 14 (23%), no effect = 14 (23%), slightly better = 10 (16%), clearly better = 19 (31%), healed = 4 (7%) **Duration morning stiffness (minutes)** SSZ (n = 53): mean change from baseline –25.7 (37.8 SD) Placebo (n = 64): mean change from baseline –14.1 (77.6 SD) (p = 0.19) **Ritchie index (tender joint)** SSZ (n = 53): mean change from baseline –4.4 (4.5 SD) Placebo (n = 64): mean change from baseline –3.5 (6.6 SD) (p = 0.16) **ESR (mm/h)** SSZ (n = 53): mean change from baseline –10.7 (21.7 SD) Placebo (n = 64): mean change from baseline –4.1 (17.4 SD) (p = 0.14) **CRP level (mg)** SSZ (n = 53): mean change from baseline –11.5 (34.4 SD) Placebo (n = 64): mean change from baseline –12.2 (54.2 SD) (p = 0.97)

ITT, intention-to-treat.

Study details	Participants	Treatment	Outcomes and results
Reference Gupta, 1995[110] (Some data from Cochrane review, Jones 2000[47]) **Study design** RCT	**Definition of PsA** Patients had stable psoriasis, were seronegative and had active synovitis (at least 3 active joints) and at least one joint with radiographic abnormalities characteristic of PsA **Positive for RF excluded?** Yes **Previous therapy?** Not stated **Concomitant therapy?** Oral or intra-articular corticosteroids were not permitted during the study. NSAIDs at constant doses and propoxyphene 65 mg were permitted as needed **Adult?** Yes **Number of participants** *n* = 24	**Treatment dose regimen** SSZ (not enteric coated) 0.5 g t.d.s., titrated to 1 g t.d.s. *n* = 10 **Comparator dose regimen** Placebo equivalent, *n* = 14 **Duration of treatment** 12 weeks **Notes** No. of patients: SSZ: 10, placebo 14 No placebo data at 12 weeks	**PhGA** SSZ: mean at baseline 2.9 ± 0.3 SE, at 8 weeks 1.7 ± 0.2 SE Placebo: mean at baseline 2.2 ± 0.3 SE, at 8 weeks 2.5 ± 0.3 (p = 0.002) *Mean change (SD)* *SSZ (n = 9) –1.20 (0.81); placebo (n = 14) 0.30 (1.85)* *(Data from Cochrane review)* **PtGA** SSZ: mean at baseline 2.7 ± 0.3 SE, at 8 weeks 1.6 ± 0.4 SE Placebo: mean at baseline 2.0 ± 0.2 SE, at 8 weeks 2.3 ± 0.2 SE (p = 0.003) *Mean change on 1–5 scale (SD)* *SSZ (n = 9) –0.90 (0.99); placebo (n = 14) 0.30 (1.06)* *(Data from Cochrane review)* **Joint pain/tenderness score** SSZ: mean at baseline 27 ± 5 SE, at 8 weeks 11 ± 3 SE Placebo: mean at baseline 29 ± 7 SE, at 8 weeks 26 ± 9 SE (p = 0.066) *Mean change (SD)* *SSZ (n = 9) –13.00 (21.77); placebo (n = 14) 2.00 (29.10)* *(Data from Cochrane review)* **Joint swelling score (index)** SSZ: mean at baseline 11 ± 3 SE, at 8 weeks 4 ± 1 SE Placebo: mean at baseline 16 ± 4 SE, at 8 weeks 10 ± 2 SE (p = 0.703) *Mean change (SD)* *SSZ (n = 9) –7.00 (7.54); placebo (n = 14) –6.00 (4.40)* *(Data from Cochrane review)* **Tender joint count** SSZ: mean at baseline 23 ± 4 SE, at 8 weeks 10 ± 3 SE Placebo: mean at baseline 22 ± 5 SE, at 8 weeks 20 ± 6 SE (p = 0.061) **SJS** SSZ: mean at baseline 10 ± 3 SE, at 8 weeks 3 ± 1 SE Placebo: mean at baseline 13 ± 4 SE, at 8 weeks 7 ± 2 SE (p = 0.544)

continued

Study details	Participants	Treatment	Outcomes and results
			Duration morning stiffness (minutes) SSZ: mean at baseline 124 ± 68 SE, at 8 weeks 83 ± 11 SE Placebo: mean at baseline 55 ± 15 SE, at 8 weeks 85 ± 20 SE ($p = 0.007$) **Grip strength** *Right* SSZ: mean at baseline 92 ± 14 SE, at 8 weeks 107 ± 16 SE Placebo: mean at baseline 108 ± 10 SE, at 8 weeks 103 ± 9 SE ($p = 0.759$) *Left* SSZ: mean at baseline 94 ± 13 SE, at 8 weeks 110 ± 14 SE Placebo: mean at baseline 107 ± 8 SE, at 8 weeks 110 ± 9 SE ($p = 0.841$) **50-ft walking time (s)** SSZ: mean at baseline 10 ± 1 SE, at 8 weeks 9.7 ± 0.7 SE Placebo: mean at baseline 9 ± 1 SE, at 8 weeks 8.5 ± 0.5 SE ($p = 0.626$)

Study details	Participants	Treatment	Outcomes and results
Reference Salvarani, 2001[108] (also Salvarani, 1999[120]) **Study design** RCT	**Definition of PsA** Confirmed diagnosis of psoriasis and having at least one subtype of PsA: distal interphalangeal involvement, peripheral asymmetric oligoarthritis or symmetrical peripheral arthritis with or without axial involvement and with at least 3 tender and swollen joints of at least 6 weeks duration that did not respond to NSAIDs **Positive for RF excluded?** Yes **Previous therapy?** Disease had to have failed to respond to NSAIDs. Previous unsuccessful treatment with antimalarials, gold salts, etretinate, MTX or photochemotherapy was permitted	**Treatment dose regimen** CSA 3–5 mg/kg/day, $n = 36$ *or* SSZ enteric coated 1000 mg/day titrated to a maximum of 3000 mg/day, $n = 32$ **Comparator dose regimen** No treatment (ST), $n = 31$ **Duration of treatment** 24 weeks **Notes** No. of patients: CSA 36, SSZ 32, ST 31	*For all comparisons, CSA* n = *36, SSZ* n = *32 and ST* n = *31* **ACR 20** ACR 20 (ESR): CSA 44.4%, SSZ 43.8%, ST 35.5%. All treatment differences NS ACR 20 (CRP): CSA 44.4%, SSZ 37.5%, ST 32.3%. All treatment differences NS **ACR 50** ACR 50 (ESR): CSA 25.0%, SSZ 12.5%, ST 3.2%. All treatment differences NS ACR 50 (CRP): CSA 27.7%, SSZ 12.5%, ST 3.2%. All treatment differences NS except CSA vs ST, $p = 0.02$ **ACR 70 (CRP)** ACR 70 (ESR): CSA 13.8%, SSZ: 0.0%, ST 0.0%. CSA vs SSZ, $p = 0.05$; CSA vs ST, $p = 0.05$; SSZ vs ST, NS ACR 70 (CRP): CSA 13.8%, SSZ 0.0%, ST 0.0%. CSA vs SSZ, $p = 0.05$; CSA vs ST, $p = 0.05$; SSZ vs ST, NS

continued

Study details	Participants	Treatment	Outcomes and results
	Concomitant therapy? NSAIDS were permitted: at stable doses in the active treatment groups and at full doses in the standard therapy (ST) group. All patients were permitted systemic corticosteroids at doses of up to 5 mg/day prednisone equivalent and paracetamol **Adult?** Yes **Number of participants** *n* = 99		**VAS pain** CSA: mean change from baseline –27.2 (31.9 SD, 95% CI: –38.6 to –15.9) SSZ: mean change from baseline –17.3 (18.0 SD, 95% CI: 23.8 to 10.8) ST: mean change from baseline –12.5 (22.8 SD, 95% CI: –20.9 to –4.2) **Joint pain/tenderness score** CSA: mean change from baseline –6.9 (8.8 SD, 95% CI: –10.1 to –3.8) SSZ: mean change from baseline –4.8 (6.7 SD, 95% CI: –7.2 to –2.3) ST: mean change from baseline –1.5 (8.1 SD, 95% CI: –4.5 to 1.4) **Tender joint count** CSA: mean change from baseline –7.6 (10.4 SD, 95% CI: –11.3 to –3.9) SSZ: mean change from baseline –5.7 (6.9 SD, 95% CI: –8.2 to –3.2) ST: mean change from baseline –3.5 (8.1 SD, 95% CI: –6.5 to –0.6) **Swollen joint count** CSA: mean change from baseline –4.8 (7.5 SD, 95% CI: –7.4 to –2.1) SSZ: mean change from baseline –4.4 (5.8 SD, 95% CI: –6.5 to –2.4) ST: mean change from baseline –1.8 (5.5 SD, 95% CI: –3.8 to 0.2) **Duration morning stiffness (minutes)** CSA: mean change from baseline –41.5 (61.5 SD, 95% CI: –63.3 to 19.7) SSZ: mean change from baseline –45.9 (84.4 SD, 95% CI: –76.4 to –15.5) ST: mean change from baseline –37.1 (84.6 SD, 95% CI: –68.1 to –6.1) **Ritchie index** CSA: mean change from baseline –6.9 (95% CI: –10.1 to –3.8) SSZ: mean change from baseline –4.8 (95% CI –7.2 to –2.3) ST: mean change from baseline –1.5 (95% CI: –4.5 to 1.4) **ESR (mm/h)** CSA: mean change from baseline –12.4 (19.5 SD, 95% CI: –19.3 to 5.4) SSZ: mean change from baseline –12.9 (25.7 SD, 95% CI: –22.2, to 3.6) ST: mean change from baseline –0.9 (23.3 SD, 95% CI: –10.0 to 8.1) **CRP level (mg)** CSA: mean change from baseline –1.6 (2.3 SD, 95% CI: –2.4 to 0.8) SSZ: mean change from baseline –0.9 (3.4 SD, 95% CI: –2.2 to 0.3) ST: mean change from baseline –0.1 (2.3 SD, 95% CI: –1.0 to 0.8)

continued

Study details	Participants	Treatment	Outcomes and results
			PASI CSA: mean change from baseline –3.6 (3.7 SD, 95% CI: –4.9 to 2.3) SSZ: mean change from baseline –2.3 (3.4 SD, 95% CI: –3.5 to 1.1) ST: mean change from baseline –0.4 (3.9 SD, 95% CI: –1.8 to 1.1) **AIMS test** CSA: mean change from baseline –9.2 (9.0 SD, 95% CI: –12.4 to –6.0) SSZ: mean change from baseline –4.8 (6.3 SD, 95% CI: –7.1 to –2.5) ST: mean change from baseline –3.8 (8.3 SD, 95% CI: –6.8 to –0.7) **Spondylitis functional index (no.)** CSA: mean change from baseline –5.7 (6.8 SD, 95% CI: –8.1 to 3.3) SSZ: mean change from baseline –3.5 (3.9 SD, 95% CI: –4.9, to 2.1) ST: mean change from baseline –0.9 (5.3 SD, 95% CI: –2.9 to 1.0) **Dactylitis score (no.)** CSA 2, ST 1, SSZ 1 **Chest expansion** CSA: mean change from baseline 7.0 (14.8 SD, 95% CI: 1.4 to 12.6) SSZ: mean change from baseline 2.7 (11.0 SD, 95% CI: –1.2 to 6.7) ST: mean change from baseline 3.3 (11.7 SD, 95% CI: –1.1 to 7.8) **Modified Schober's test (cm)** CSA: mean change from baseline 1.3 (11.3 SD, 95% CI: –2.9 to 5.6) SSZ: mean change from baseline –1.8 (10.8 SD, 95% CI: –5.7 to 2.1) ST: mean change from baseline 0.0 (12.3 SD, 95% CI: –4.7 to 4.7) **Fingers-to-floor** CSA: mean change from baseline 1.0 (5.3 SD, 95% CI: –1.0 to 3.0) SSZ: mean change from baseline 0.0 (4.5 SD, 95% CI: –1.6 to 1.6) ST: mean change from baseline 2.9 (14.0 SD, 95% CI: –2.4 to 8.3) **Cervical spine flexion test (mm)** CSA: mean change from baseline –2.9 (17.0 SD, 95% CI: –9.3 to 3.6) SSZ: mean change from baseline 1.8 (9.4 SD, 95% CI: –1.6 to 5.2) ST: mean change from baseline 0.8 (8.1 SD, 95% CI: –2.3 to 3.8) **Cervical spine extension test (mm)** CSA: mean change from baseline 3.3 (16.3 SD, 95% CI: –2.9 to 9.5) SSZ: mean change from baseline –4.8 (17.9 SD, 95% CI: –11.3 to 1.6) ST: mean change from baseline –1.2 (18.6 SD, 95% CI: –8.3 to 5.8)

NS, not significant; ST, standard therapy.

Study details	Participants	Treatment	Outcomes and results
Reference Fraser, 2003[107] (with further details through contact with authors) **Study design** RCT	**Definition of PsA** Active PsA with a minimum of 3 tender joints and previous incomplete response to MTX 15 mg/week or highest tolerated dose. Stable dose of MTX to continue through study **Positive for RF excluded?** Yes **Previous therapy?** MTX **Concomitant therapy?** NSAIDs: placebo/MTX 76%; CSA/MTX 79% Prednisolone: placebo/MTX 0%; CSA/MTX 5% **Adult?** Yes **Number of participants** $n = 72$	**Treatment dose regimen** CSA (2.5 titrated to 4 mg/kg/day) + MTX (mean dose 16 g/week), $n = 38$ **Comparator dose regimen** Placebo equivalent + MTX (mean dose 16 g/week), $n = 34$ **Duration of treatment** 48 weeks	**Joint pain/tenderness score** (NB: index 0–3, not score) CSA + MTX: mean change from baseline 12.0 (SD 45.3), $p < 0.001$ Placebo + MTX: mean change from baseline 16.9 (SD 36.0), $p < 0.001$ **Tender joint count** CSA + MTX: mean change from baseline 7.3 (SD 10.2), $p < 0.001$ Placebo + MTX: mean change from baseline 8.6 (SD 9.0), $p < 0.001$ **Swollen joint count** CSA + MTX: mean change from baseline 5.0 (SD 47), $p < 0.001$ Placebo + MTX: mean change from baseline 3.8 (SD not reported), $p = NS$ **Pain (VAS)** CSA + MTX: baseline 4.7 (SD 2.2), 48 weeks 3.9 (SD 2.4); change from baseline = NS Placebo + MTX: baseline 5.1 (SD 2.3), 48 weeks 4.9 (SD 2.9); change from baseline = NS **ESR (mm/h)** CSA + MTX: baseline 24.6 (SD 21.6), 48 weeks 25.5 (SD 17.3); change from baseline = NS Placebo + MTX: baseline 24.5 (SD 19.3), 48 weeks 22.9 (SD 14.09); change from baseline = NS **CRP level (mg)** CSA + MTX: baseline 17.4 (SD 14.5), 48 weeks 12.7 (SD 14.3); change from baseline $p < 0.05$ Placebo + MTX: baseline 15.4 (SD 13.3), 48 weeks 12.6 (SD 9.0); change from baseline = NS **PASI** CSA + MTX: mean change from baseline 1.2 (SD 1.9), $p < 0.001$ Placebo + MTX: mean change from baseline 0.3 (SD not stated), $p = NS$ **PtGA** CSA + MTX: baseline 5.1 (SD 2.3), 48 weeks 4.1 (SD 2.7); change from baseline = NS Placebo + MTX: baseline 5.4 (SD 2.2), 48 weeks 4.9 (SD 2.8); change from baseline = NS

continued

Study details	Participants	Treatment	Outcomes and results
			Modified Larsen score MTX + CSA: baseline 32.9 to 12 months 34.6 compared with MTX + placebo baseline 36 to 12 months 43.4 **HAQ** CSA + MTX: baseline 1.0 (SD 0.62), 48 weeks 0.9 (SD 0.61); change from baseline = NS Placebo + MTX baseline 1.1 (SD 0.45), 48 weeks 0.9 (SD 0.52); change from baseline = NS **Synovitic joints (ultrasound)** (reduction in mean adjusted number of definite or probable synovitic joints per person) CSA + MTX: mean change from baseline –2.5 (95% CI: -4.07 to –1.01) Placebo + MTX: mean change from baseline –0.282 (95% CI: –1.67 to 1.1), $p < 0.05$)

NS, not significant.

Study details	Participants	Treatment	Outcomes and results
Reference Willkens, 1984[111] (Some data from Cochrane review, Jones, 2000[47]) **Study design** RCT	**Definition of PsA** PsA with distal interphalangeal involvement, peripheral asymmetric oligoarthritis, *or* seronegative symmetrical polyarthritis and psoriasis, *or* arthritis mutilans and psoriasis. Active arthritis with three or more active joints for 6 months was required **Positive for RF excluded?** Yes **Previous therapy?** Previous unsuccessful treatment with aspirin or NSAIDs. Previous therapy with MTX was not permitted	**Treatment dose regimen** MTX 2.5 mg every 12 h for 3 consecutive doses/week, $n = 16$ **Comparator dose regimen** Placebo equivalent, $n = 21$ **Duration of treatment** 12 weeks **Notes** No. of patients: MTX 16, placebo 21	**PhGA** Physician assessment score (1–5): MTX: median change from baseline 1 Placebo: median change from baseline 0 ($p = 0.001$) *Mean change (SD)* *MTX (n = 16) –0.72 (0.46); placebo (n = 21) 0.16 (0.62)* *(Data from Cochrane review)* **PtGA** Patient assessment score (1–5): MTX: median change from baseline 1 Placebo: median change from baseline 0 ($p = 0.087$) *Mean change (SD)* *MTX (n = 16) –0.57 (0.26); placebo (n = 21) –0.16 (0.72)* *(Data from Cochrane review)*

continued

Study details	Participants	Treatment	Outcomes and results
	Concomitant therapy? Optimal and stable doses of ibuprofen or indomethicin **Adult?** Yes **Number of participants** *n* = 37		**Joint pain/tenderness score** MTX: median change from baseline 9 Placebo: median change from baseline 10 ($p = 0.870$) *Mean change (SD)* *MTX (n = 16) –4.15 (15.40); placebo (n = 21) –5.16 (17.00)* *(Data from Cochrane review)* **Joint swelling score** MTX: median change from baseline 5 Placebo: median change from baseline 2 ($p = 0.390$) *Mean change (SD)* *MTX (n = 16) –2.57 (10.50); placebo (n = 21) –2.37 (11.50)* *(Data from Cochrane review)* **Tender joint count** MTX: median change from baseline 4 Placebo: median change from baseline 6 ($p = 0.559$) **Swollen joint count** MTX: median change from baseline 3 Placebo: median change from baseline 1 ($p = 0.635$) **Duration morning stiffness (minutes)** MTX: median change from baseline 45 Placebo: median change from baseline 30 ($p = 0.099$) **Grip strength** *Right* MTX: median change from baseline 4 Placebo: median change from baseline –1 ($p = 0.167$) *Left* MTX: mean change from baseline 9 Placebo: mean change from baseline 0 ($p = 0.149$)

Study details	Participants	Treatment	Outcomes and results
Reference Palit, 1990[117] (Some data from Cochrane review, Jones 2000[47]) **Study design** RCT	**Definition of PsA** Active PsA of at least 1 year's duration **Positive for RF excluded?** Not stated **Previous therapy?** Previous therapy with gold or suppressive antirheumatic drug therapy not permitted **Concomitant therapy?** NSAIDs in constant doses taken by all patients **Adult?** Yes **Number of participants** *n* = 82	**Treatment dose regimen** Auranofin 3 mg twice daily, *n* = 29 *or* I.m. gold (sodium thiomalate) 50 mg weekly, *n* = 27 **Comparator dose regimen** Placebo equivalent *n* = 26 **Duration of treatment** 24 weeks **Notes** No. of patients: Auranofin 20, i.m. gold 17, placebo 14	**VAS pain** Auranofin: median at baseline 4.7 (1.0–9.5), at 24 weeks 4.2 (1.3–9.2) (p = NS) I.m. gold: median at baseline 4.9 (0.5–9.9), at 24 weeks 2.7 (0.3–6.3) (p = 0.009) Placebo: median at baseline 4.3 (1.1–9.9), at 24 weeks 2.0 (0.3–6.9) (p = 0.019) *Mean change (SD)* *Auranofin (n = 24): -4.60 (23.10); i.m. gold (n = 21) –21.20 (24.30); placebo (n = 18) –26.50 (21.80)* *(Data from Cochrane review)* **Ritchie index (TJS)** Auranofin: median at baseline 13 (0–30), at 24 weeks 13 (0–24) (p = NS) I.m. gold: median at baseline 14 (1–58), at 24 weeks 9.0 (0–17) (p = 0.001) Placebo: median at baseline 11 (0–27), at 24 weeks 9 (0–26) (p = 0.041) *Mean change (SD)* *Auranofin (n = 21): 0.10 (6.80); i.m. gold (n = 21) –8.90 (9.70); placebo (n = 18) –2.30 (7.20)* *(Data from Cochrane review)* **ESR (mm/h)** Auranofin: median at baseline 24 (1–70), at 24 weeks 16 (2–46) (p = NS) I.m. gold: median at baseline 32 (1–110), at 24 weeks 15 (3–78) (p = 0.036) Placebo: median at baseline 17 (3–86), at 24 weeks 18 (6–75 (p = NS) *Mean change (SD)* *Auranofin (n = 24) –2.10 (16.50); i.m. gold (n = 21) –9.30 (22.80); placebo (n = 18): –2.20 (24.60)* *(Data from Cochrane review)* **Grip strength** Auranofin: median at baseline 173 (86–300), at 24 weeks 181 (54–300) (p = NS) I.m. gold: median at baseline 161 (51–300), at 24 weeks 192 (67–300) (p = NS) Placebo: median at baseline 123 (90–300), at 24 weeks 192 (64–300) (p = NS)

NS, not significant.

Study details	Participants	Treatment	Outcomes and results
Reference Carette, 1989[118] (Some data from Cochrane review, Jones 2000[47]) **Study design** RCT	**Definition of PsA** Psoriasis and active joint disease (swelling and/or pain/tenderness in at least 3 joints and a total joint score of at least 10 using a 3-point scale for each joint) for at least 3 months. Patients with RA were excluded **Positive for RF excluded?** Not stated **Previous therapy?** All patients had responded inadequately to anti-inflammatory drugs or NSAIDs. Patients who had taken gold previously were not excluded unless it had been taken within 2 months of the trial **Concomitant therapy?** All patients were receiving stable doses of aspirin or NSAIDs. Constant doses of corticosteroids (no more than 7.5 mg/day prednisone equivalent) were permitted. Intra-articular steroids were not permitted. Analgesics such as paracetamol and propoxyphene were permitted as required **Adult?** Yes **Number of participants** *n* = 238	**Treatment dose regimen** Auranofin 3 mg/day (increasing to 4.5 mg/day after 3 months if necessary), *n* = 120 **Comparator dose regimen** Placebo equivalent, *n* = 118 **Duration of treatment** 6 months **Notes** No. of patients: auranofin 93, placebo 95 (per protocol)	**Pain score (0 = no pain to 4 = excruciating pain)** Auranofin (*n* = 93): mean change from baseline –0.5 ± 0.10 SEM Placebo (*n* = 95): mean change from baseline –0.2 ± 0.10 SEM *Mean change (SD)* *Auranofin* (n = *93) –5.00 (0.75); placebo* (n = *95) –2.00 (0.90)* *(Data from Cochrane review)* **Joint pain/tenderness score** Auranofin (*n* = 93): mean change from baseline –7.7 ± 1.7 SEM Placebo (*n* = 95): mean change from baseline –6.1 ± 1.8 SEM *Mean change (SD)* *Auranofin* (n = *93) –12.00 (4.20); placebo* (n = *95) –11.10 (4.05)* *(Data from Cochrane review)* **Joint swelling score** Auranofin (*n* = 93): mean change at baseline –5.4 ± 1.1 SEM Placebo (*n* = 95): mean change at baseline –4.6 ± 1.6 SEM *Mean change (SD)* *Auranofin* (n = *93) –2400 (1.10); placebo* (n = *95) –2.00 (1.30)* *(Data from Cochrane review)* **Tender joint count** Auranofin (*n* = 93): mean change from baseline –4.0 ± 1.1 SEM Placebo (*n* = 95): mean change from baseline –3.7 ± 1.2 SEM **Swollen joint count** Auranofin (*n* = 93) mean change from baseline –2.5 ± 0.7 SEM Placebo (*n* = 95): mean change from baseline –2.0 ± 0.8 SEM **Duration morning stiffness (minutes)** Auranofin (*n* = 93): mean change from baseline –42.1 ± 13.6 SEM Placebo (*n* = 95): mean change from baseline –17.2 ± 8.2 SEM **Psoriasis (% BSA)** Auranofin (*n* = 93): mean change from baseline –1.6 ± 0.7 SEM Placebo (*n* = 95): mean change from baseline –0.7 ± 1.0 SEM **Functional scores for daily activities** Auranofin (*n* = 93): mean change from baseline –0.5 ± 0.09 SEM Placebo (*n* = 95): mean change from baseline –0.2 ± 0.08 SEM **Functional scores for occupational activities** Auranofin (*n* = 93): mean change from baseline –0.5 ± 0.09 SEM Placebo (*n* = 95): mean change from baseline –0.1 ± 0.09 SEM

SEM, standard error of the mean.

Study details	Participants	Treatment	Outcomes and results
Reference Levy, 1972[119] (abstract only) **Study design** RCT crossover design	**Definition of PsA** No details **Positive for RF excluded?** Not reported **Previous therapy?** Not reported **Concomitant therapy?** Not reported **Adult?** Not reported **Number of participants** $n = 6$	**Treatment dose regimen** Azathioprine 3 mg/kg/day, $n = 6$ **Comparator dose regimen** Placebo equivalent, $n = 6$ **Duration of treatment** 6 months **Notes** No. of patients not stated	**Swollen joint count** Active joint count: Azathioprine: mean at baseline 18 ± 5, at 6 months 7 ± 2 Placebo: mean at baseline 17 ± 6, at 6 months 17 ± 6 ($p < 0.01$) **Duration morning stiffness (minutes)** Azathioprine: mean at baseline 90 ± 44, at 6 months 10 ± 10 Placebo: mean at baseline 40 ± 34, at 6 months 65 ± 38 ($p < 0.05$) **Grip strength** Azathioprine: mean at baseline 140 ± 20, at 6 months 159 ± 27 Placebo: mean at baseline 140 ±32, at 6 months 134 ± 35 ($p < 0.05$)

Study details	Participants	Treatment	Outcomes and results
Reference Dougados, 1995[113] (Some data from Cochrane review, Jones, 2000[47]) **Study design** RCT	**Definition of PsA** Patients with spondylarthropathy included in the trial. The subgroup of PsA was defined as patients who had past or present psoriasis plus at least one of the following: distal interphalangeal involvement, peripheral asymmetric oligoarthritis, symmetrical polyarthritis or sacroiliac or spinal involvement. All patients had to have active disease of at least moderate severity, pain and at least one swollen joint **Positive for RF excluded?** Not stated **Previous therapy?** Not stated **Concomitant therapy?** Stable doses of NSAIDs were permitted. Corticosteroids and other disease-modifying drugs were not permitted **Adult?** Yes **Number of participants** *n* = 136 (PsA)	**Treatment dose regimen** SSZ 500 mg /day titrated up to a maximum of 3 g/day (NB: not stated if enteric coated or not), *n* = 70 **Comparator dose regimen** Placebo equivalent, *n* = 66 **Duration of treatment** 6 months	**Pain assessment (VAS)** SSZ: mean reduction from baseline –21.50 (SD 25.60) Placebo: mean reduction from baseline –7.06 (SD 22.00) *(Data from Cochrane review)* **PhGA** SSZ: mean reduction from baseline –0.64 (SD 0.66) Placebo: mean reduction from baseline –0.42 (SD 0.65) *(Data from Cochrane review)* **PtGA** SSZ: mean reduction from baseline –0.81 (SD 0.80) Placebo: mean reduction from baseline –0.32 (SD 0.70) *(Data from Cochrane review)* **Note:** Data taken from Cochrane review as original publication does not present data on PsA separately from other indications

Study details	Participants	Treatment	Outcomes and results
Reference Spadaro, 1995[109] **Study design** RCT	**Definition of PsA** Persistently negative latex test or ELISA for RF with active arthritis affecting 5 or more peripheral joints (painful and/or swollen) with or without distal interphalangeal involvement, not adequately controlled with NSAIDs; disease duration more than 6 months **Positive for RF excluded?** Yes **Previous therapy?** Not adequately controlled with NSAIDs. Also only patients who had stopped taking slow-acting antirheumatic drugs (SAARDs) (= DMARDs?) at least 3 months earlier owing to lack of efficacy or toxicity were eligible for the trial **Concomitant therapy?** Stable doses of NSAIDs **Adult?** Yes **Number of participants** $n = 35$	**Treatment dose regimen** CSA 3–5 mg/kg/day, $n = 17$ **Comparator dose regimen** MTX 7.5 mg/week, $n = 18$ **Duration of treatment** 12 months	For all outcomes CSA $n = 17$ at baseline, $n = 14$ at 6 months and $n = 10$ at 12 months For all outcomes MTX $n = 18$ at baseline, $n = 14$ at 6 months and $n = 13$ at 12 months **Painful joint count mean (SEM)** CSA: baseline 9.6 (1.2); 6 months 5.4 (1.4) ($p < 0.005$); 12 months 5.9 (1.8) ($p < 0.01$). Mean change from baseline to 12 months: 4.6 (1.2) MTX: baseline 8.4 (0.7); 6 months 3.4 (0.7) ($p < 0.005$); 12 months 2.0 (0.5) ($p < 0.005$). Mean change from baseline to 12 months: 6.6 (0.9) **SJS mean (SEM)** CSA: baseline 5.0 (0.6); 6 months 2.7 (0.7) ($p < 0.005$); 12 months 2.5 (0.8) ($p < 0.01$). Mean change from baseline to 12 months: 2.6 (0.9) MTX: baseline 4.3 (0.4); 6 months 1.7 (0.3) ($p < 0.005$); 12 months 0.8 (0.2) ($p < 0.005$). Mean change from baseline to 12 months: 3.5 (0.5) **Ritchie index mean (SEM)** CSA: baseline 8.6 (3.5); 6 months 7.4 (2.1) ($p < 0.005$); 12 months 7.6 (2.2) ($p < 0.01$). Mean change from baseline to 12 months: 14.0 (4.2) MTX: baseline 13.8 (1.4); 6 months 3.9 (0.8) ($p < 0.001$); 12 months 2.5 (0.6) ($p < 0.005$). Mean change from baseline to 12 months: 11.1 (1.7) **Morning stiffness (minutes) mean (SEM)** CSA: baseline 35.4 (8.6); 6 months 19.3 (6.6) ($p < 0.025$); 12 months 24.0 (7.9) ($p < 0.025$). Mean change from baseline to 12 months: 19.5 (5.8) MTX: baseline 63.2 (12.4); 6 months 20.0 (5.9) ($p < 0.005$); 12 months 12.3 (5.0) ($p < 0.005$). Mean change from baseline to 12 months: 55 (14.7) **Grip strength (mmHg) mean (SEM)** *Left hand* CSA: baseline 78 (22); 6 months 101 (18) ($p < 0.01$); 12 months 89 (30) ($p < 0.05$). Mean change from baseline to 12 months: –14 (5) MTX: baseline 53 (10); 6 months 101 (18) ($p < 0.025$); 12 months 102 (18) ($p < 0.005$). Mean change from baseline to 12 months: –51 (15) *Right hand* CSA: baseline 71 (24); 6 months 139 (21) ($p < 0.01$); 12 months 97 (31) ($p < 0.05$). Mean change from baseline to 12 months: –9 (5)

continued

Study details	Participants	Treatment	Outcomes and results
			MTX: baseline 91 (20); 6 months 139 (21) ($p < 0.01$); 12 months 120 (24) ($p < 0.05$). Mean change from baseline to 12 months: –17 (23) **PhGA (mm) mean (SEM)** CSA: baseline 55.7 (6.4); 6 months 37.1 (6.0) ($p < 0.01$); 12 months 41.0 (7.4) ($p < 0.01$). Mean change from baseline to 12 months: 16.0 (4.9) MTX: baseline 56.43 (4.1); 6 months 24.3 (4.9) ($p < 0.005$); 12 months 26.1 (5.0) ($p < 0.005$). Mean change from baseline to 12 months: 30.8 (4.0) **PtGA (mm) mean (SEM)** CSA: baseline 54.3 (4.9); 6 months 32.8 (5.2) ($p < 0.005$); 12 months 27.0 (6.1) ($p < 0.01$). Mean change from baseline to 12 months: 30.0 (5.6) MTX: baseline 61.0 (8.4); 6 months 40.0 (5.7) ($p < 0.05$); 12 months 30.0 (0.6) ($p < 0.025$). Mean change from baseline to 12 months: 22.7 (9.8) **PASI mean (SEM)** CSA: baseline 8.9 (2.0); 6 months 4.2 (1.1) ($p < 0.01$); 12 months 3.5 (1.3) ($p < 0.01$). Mean change from baseline to 12 months: 7.6 (2.0) MTX: baseline 5.2 (0.7); 6 months 3.1 (0.5) ($p < 0.01$); 12 months 2.9 (0.4) ($p < 0.01$). Mean change from baseline to 12 months: 2.6 (0.6) **ESR (mm/h) mean (SEM)** CSA: baseline 42.7 (6.7); 6 months 30.5 (6.2) (p = NS); 12 months 33.7 (6.0) (p = NS). Mean change from baseline to 12 months: 9.3 (6.1) MTX: baseline 41.2 (6.8); 6 months 24.4 (4.2) ($p < 0.025$); 12 months 22.4 (4.2) ($p < 0.01$). Mean change from baseline to 12 months: 19.5 (6.3) **CRP (mg/l) mean (SEM)** CSA: baseline 34.0 (7.7); 6 months 17.4 (5.4) ($p < 0.025$); 12 months 23.4 (7.5) ($p < 0.025$). Mean change from baseline to 12 months: 17.5 (7.1) MTX: baseline 24.2 (4.6); 6 months 9.9 (1.7) ($p < 0.025$); 12 months 13.0 (2.3) ($p < 0.025$). Mean change from baseline to 12 months: 13.3 (4.1) For all mean changes from baseline the difference between CSA and MTX was not statistically significant ($p > 0.05$)

ELISA, enzyme-linked immunosorbent assay; NS, not significant; SEM, standard error of the mean.

Appendix 8

Evidence synthesis model WinBUGS code

```
model
{
  # PROBABILITIES OF RESPONSE evidence synthesis model

  for (j in 1:3) { # trials
    pc[j]~dbeta(calpha,cbeta)
    rplac[j]~dbin(pc[j],nplac[j]) # control response
    # add fixed treatment effect
    logit(pt[j])<-logit(pc[j])+teffect[tresp[j]]
    rtreat[j]~dbin(pt[j],ntreat[j]) # treatment response
  }

  # PRIORS for probabilities of response
  # control probability of response
  ncontrol~dunif(0,prior.nmax)
  prespcontrol~dunif(0,1)
  calpha<-prespcontrol*ncontrol
  cbeta<-ncontrol-calpha

  # prior: treatment effects on probability of response
  for (i in 1:2) {
    teffect[i]~dnorm(0,teffect.prec) # on log-odds scale
  }

  # CHANGES IN HAQ evidence synthesis model
  # 1. data conditional on response

  for (j in 1:2) {
    # get random baseline
    dhaqbaseannual[j]~dnorm(naturalprogression.mean,naturalprogression.prec)
    dhaqbase[j]<-dhaqbaseannual[j]/4
    # calculate predicted value for each cell
    dhaqpredplac[j,1]<-dhaqbase[j]
    dhaqpredplac[j,2]<-dhaqbase[j]+idhaqplacresp
    dhaqpredtreat[j,1]<-dhaqbase[j]+idhaqtreatnoresp[tdhaq[j]]
    dhaqpredtreat[j,2]<-dhaqbase[j]+idhaqtreatresp[tdhaq[j]]
    # fit predictions to data
    for (k in 1:2) {
      dhaqplac.prec[j,k]<-1/pow(dhaqplac.se[j,k],2)
      dhaqtreat.prec[j,k]<-1/pow(dhaqtreat.se[j,k],2)
      dhaqplac[j,k]~dnorm(dhaqpredplac[j,k],dhaqplac.prec[j,k])
      dhaqtreat[j,k]~dnorm(dhaqpredtreat[j,k],dhaqtreat.prec[j,k])
      }
    }

  # 2. data not conditioned on response
  # index 3 is mease2000.
  # get random baseline
  dhaqbaseannual[3]~dnorm(naturalprogression.mean,naturalprogression.prec)
  dhaqbase[3]<-dhaqbaseannual[3]/4
```

```
# calculate predicted value for each cell
dhaqpredplac[3,1]<-dhaqbase[3]
dhaqpredplac[3,2]<-dhaqbase[3]+idhaqplacresp
dhaqpredtreat[3,1]<-dhaqbase[3]+idhaqtreatnoresp[tdhaq[3]]
dhaqpredtreat[3,2]<-dhaqbase[3]+idhaqtreatresp[tdhaq[3]]

# calculate mease2000pred and compare to data.
mease2000.predtreat<-pt[3]*dhaqpredtreat[3,2]+
  (1-pt[3])*dhaqpredtreat[3,1] # treatment arm
mease2000.predplac<-pc[3]*dhaqpredplac[3,2]+
  (1-pc[3])*dhaqpredplac[3,1]

# calculate haq change from baseline in percent.
mease2000.predtreatpc<-mease2000.predtreat/mease2000.basehaqtreat*100
mease2000.predplacpc<-mease2000.predplac/mease2000.basehaqplac*100
# calculate predicted precision using reported SE and true mean.
mease2000.dhaqpctreat.prec<-1/pow(mease2000.dhaqpctreat.se,2)
mease2000.dhaqpcplac.prec<-1/pow(mease2000.dhaqpcplac.se,2)
# compare to mease2000 data
mease2000.dhaqpctreat~
  dnorm(mease2000.predtreatpc,mease2000.dhaqpctreat.prec)
mease2000.dhaqpcplac~
  dnorm(mease2000.predplacpc,mease2000.dhaqpcplac.prec)

# PRIORS for HAQ model
# idhaq for treatment and placebo responders, and for treatment
# non-responders
for (i in 1:2) {
  idhaqtreatnoresp[i]~dnorm(0,idhaq.prec) # on haq scale
  idhaqtreatresp[i]~dnorm(0,idhaq.prec)
}
idhaqplacresp~dnorm(0,idhaq.prec)

# informative prior on natural progression
baselinedhaqprior.mean<-leeds.mean
baselinedhaqprior.prec<-1/pow(leeds.se,2)
naturalprogression.mean~dnorm(baselinedhaqprior.mean,baselinedhaqprior.prec)
# random-effects variance for natural progression
naturalprogression.prec<-1/pow(naturalprogression.sd,2)

# ######### OUTPUT #########
# what do we want to predict?

# OV[1] treatment I probability of response
# OV[2] treatment E probability of response
# OV[3] placebo probability of response
# OV[4] dhaq baseline
# OV[5] idhaq placebo response
# OV[6] idhaq treatment(I) non-response
# OV[7] idhaq treatment(I) response
# OV[8] idhaq treatment(E) non-response
# OV[9] idhaq treatment(E) response

# probabilities of response under placebo, treatments 1 and 2.
ov[3]<-prespcontrol
logit(ov[1])<-logit(ov[3])+teffect[1]
logit(ov[2])<-logit(ov[3])+teffect[2]
```

```
  # HAQ changes
  ov[4]<-naturalprogression.mean/4
  ov[5]<-idhaqplacresp
  ov[6]<-idhaqtreatnoresp[1]
  ov[7]<-idhaqtreatresp[1]
  ov[8]<-idhaqtreatnoresp[2]
  ov[9]<-idhaqtreatresp[2]
}

################ DATA ###############
list(
  # response data
  # the studies are numbered Impact=1, Mease2004=2, Mease2000=3 throughout!
  # arm 1 (treatment arm)
  rtreat=c(40,73,26),
  ntreat=c(52,101,30),
  tresp=c(1,2,2), # which treatment: 1=I, 2=E
  # arm 2 (placebo)
  rplac=c(7,32,7),
  nplac=c(52,104,30),

  # dhaqs for each trial and arm

(CiC information removed)

  tdhaq=c(1,2,2), # impact is infliximab, mease2004 is etanercept

  mease2000.basehaqtreat=1.2,
  mease2000.basehaqplac=1.2,
  mease2000.dhaqpctreat=-64.2,
  mease2000.dhaqpcplac=-9.9,
  mease2000.dhaqpctreat.se=7.2,
  mease2000.dhaqpcplac.se=7.8,

  # natural progression
  leeds.mean=0.07, leeds.se=0.03,

  # constants describing "uninformative" priors
  naturalprogression.sd=0.1,
  prior.nmax=50000,
  teffect.prec=0.0001,
  idhaq.prec=0.0001
)
```

Appendix 9

Data extraction and quality assessment tables for economic evaluations

Cost-effectiveness model (Wyeth) – data extraction

Primary source	Company submission
Author	Wyeth Pharmaceuticals UK
Date	16 July 2004
Type of economic evaluation	Cost-effectiveness analysis; health effects in terms of QALYs; NHS cost perspective (in base case)
Currency used	UK £
Year to which costs apply	Drug and monitoring costs 2000–01; Monthly Index of Medical Specialities (MIMS) 2003, 2004
	Staff costs: PSSRU; year not specified
	Direct hospital costs based on a UK study on RA; year not specified
Perspective used	NHS
Timeframe	Results presented at 6 months, 1 year, 5 years and 10 years
Comparators	The model compares two options: (i) a sequence with etanercept (monotherapy 25 mg or with MTX) and either CSA with MTX or leflunomide on initial treatment failure; (ii) a sequence of either CSA with MTX or leflunomide only. In both options, after withdrawal from DMARDs it is assumed that the disease will remain uncontrolled and progressive, and the only potential treatment is palliation (referred to as experimental therapies)
Source(s) of effectiveness data	*Etanercept*. Phase 2 study 16-0612;[60] Phase 3 study 16-0030[36] *Leflunomide*. Randomised trial[46]
	CSA. Randomised trial[107]
	Withdrawal rates for etanercept and leflunomide. Based on evidence from RA rather than PsA.[177,178]
	Annual HAQ progression. Open label extension of Mease trial for PsA patients[13,76,179]
Source(s) of resource use data	Dosage drugs: MIMS
	Monitoring and administration assumptions: BSR guidelines
	Other direct costs based on expert opinion (Leeds, Birmingham)
Source of mortality data	Assumption of no differential mortality between options. Mortality based on UK life tables together with standardised mortality ratios of 1.59 for women and 1.65 for men indicating a higher mortality rate in PsA patients
Sources of utility data	HAQ is used as the measure of disability (measured on a 0–3 scale, with a higher score being worse), the progress of which is halted in patients responding to etanercept. To obtain QALYs, an OLS regression analysis was undertaken to estimate mean EQ-5D index utilities for a given HAQ score. This was based on data collected in PsA patients in Leeds (no publication is available detailing this work). The OLS equation was
	Utility = $(-0.3 \times \text{HAQ}) + 0.81777$
Source(s) of unit cost data	PSSRU Health and Social Care Unit Costs
	MIMS
	Direct hospital costs (e.g. hospitalisations, surgical interventions, ambulatory and community care) based on results for RA reported by Kobelt *et al.* (2002)[29] at 1999 prices
Modelling approach used	The model has been developed as an individual patient-level simulation with PSA. The ability to track individuals through a number of possible clinical pathways, but in which only one individual is modelled at a time, is the key feature of the model structure

continued

Primary source	Company submission
	The model was extended beyond the trial duration to a longer term time horizon by incorporating mortality based on UK life tables, inflated by a standardised mortality ratio to indicate inflated mortality in PsA, and a number of assumptions over disease progression
	Response rate is measured by the PsARC and this determines the proportion of patients who stay on treatment at 12 weeks. Improvement in disability is measured using the HAQ index. Costs (other than the drugs being evaluated) and utilities are implemented through their relationship with HAQ. The link between HAQ and EQ-5D utility was based on an OLS regression on a cohort of PsA patients in Leeds. The annual withdrawal rate and the annual HAQ progression for responders are important parameters influencing the cost-effectiveness results
	A key assumption is that patients who are responding to etanercept are assumed to experience no progression in HAQ, an assumption not applied to comparators
	There is uncertainty regarding what happens to patients once they fail on a given therapy (who initially repond). Two scenarios are modelled: (i) that the patient's HAQ deteriorates by the same amount that it initially improved; (ii) that their HAQ returns to what it was at baseline. Given the assumption of no HAQ progression while responding, these two scenarios amount to the same thing for etanercept
	A number of factors (i.e. HAQ at baseline, disease duration, age, sex, presence of polyarthritis, use of etanercept with concomitant MTX, etc.) are considered in a multivariate regression based on the Mease trial. This is used to predict annual HAQ progression (split by 3-month periods), matched with the demographics and disease parameters of the clinical trial patients. Hence the extrapolation is not based on the characteristics of any PsA cohort but on a sample of patients with the same disease severity, duration and demographics as the Mease trial patients. Also, the covariance relationship of the parameters included in the HAQ regressions (at 4 and 12 weeks) were calculated using a Cholesky decomposition for the probabilistic analysis
Summary of effectiveness results	From a baseline HAQ of 1.1, etanercept shows a gain of 0.04 utilities at 6 months over CSA treatment. At 5 years the gain is 0.46 and at 10 years the QALY gain is 0.82
Summary of cost results	The net additional cost of etanercept compared with CSA is £2996 at 6 months. This difference increases over time up to £23,112 at 10 years, as annual fixed drug costs are building up owing to the difference in annual withdrawal rates between biologics and comparators
Summary of cost-effectiveness results	The incremental cost per QALY gained of etanercept diminishes as time goes by: at 6 months the ICER is £66,589 per QALY, whereas at 5 years this has fallen to £37,398 and at 10 years to £28,189
Sensitivity analysis	The probability of etanercept being a cost-effective strategy compared with CSA for a 10-year time horizon is 58% for a threshold of £30,000 per QALY, while the probability falls to 5% for a threshold of £20,000. CEACs are not reported at 6 months and 1–2 years but results from the cost-effectiveness plane indicate that etanercept is not cost-effective for this time horizon at a threshold of £30,000 per QALY (all base-case analysis results). A large number of univariate sensitivity analyses were generating ICERs from £35,216 per QALY if using a lower rate for HAQ progression, to £17,195 when incorporating indirect costs
Main conclusions	Subject to the assumptions made in the analysis, the base-case estimate of incremental cost per QALY gained over 10 years was £28,189, with a probability of being cost-effective of 0.58 given a £30,000 per QALY decision threshold

Cost-effectiveness model submitted by Wyeth – quality assessment

All items will be graded as either ✓ (item adequately addressed), × (item not adequately addressed), ? (unclear or not enough information), NA (not applicable) or NS (not stated)

Wyeth Pharmaceuticals submission

Study question		Comments
1. Costs and effects examined	?	Some relevant resource use and unit costs used as input parameters in the model are not properly stated in the report
2. Alternatives compared	?	The proportion of patients who are on CSA or leflunomide is not made explicit in the sequences (i.e. neither after withdrawal from etanercept nor at the start of the sequence with DMARDs). The way in which the model presents its 'structural options' (i.e. three comparator options) seems to contradict the narrative description of the sequences and the results stated in the report
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	×	Etanercept is indicated for the treatment of active and progressive PsA in adults when the response to previous DMARD therapy has been inadequate. The licence indication per se would seem to justify the exclusion of MTX and SSZ as comparators. However, this would also seem to exclude CSA and leflunomide as relevant alternatives. The licence would suggest comparison against other licensed drugs in the class (i.e. infliximab) and palliative care
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	×	The description of the sequences in the report and the results obtained from the model do not match. The results section (7.9) only describes results for CSA, with the leflunomide option only analysed in the univariate sensitivity analysis
6. The rationale for choosing the alternative programmes or interventions compared is stated	?	The rationale is provided but it would seem unreasonable
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	Cost-effectiveness/utility analysis; effects in terms of QALYs
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	×	When data from PsA studies are not available, it is not always clear when estimates for RA are being used. Regarding the multivariate regression on the Mease trial, the assumption that the placebo arm in the etanercept trial is equal to effectiveness of CSA/leflunomide does not seem to be justified based on the limited evidence provided (Table 7.4)
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	

continued

Study question		Comments
Costs		
13. All the important and relevant resource use included	?	Direct costs estimated as a function of HAQ level based on a UK RA study.[29] The list of resource use included is not stated
14. All the important and relevant resource use measured accurately (with methodology)	?	Costs of high maintenance patient (i.e. after withdrawal from DMARDs) derived from expert opinion and direct hospital costs from a single UK study on RA
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	×	Direct costs as a function of HAQ
17. Productivity costs treated separately from other costs	✓	Indirect costs (productivity costs) as a function of HAQ based on one UK study on RA[29]
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	×	Year to which unit costs apply is not always clearly stated (e.g. PSSRU costs, direct hospital costs)
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	✓	QALYs
20. Methods to value health states and other benefits are stated (e.g. time trade-off)	NA	Based on EQ-5D index
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals etc.)	NA	Based on EQ-5D index
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	Patient-level simulation model (discrete event simulation)
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately	×	The results section does not explore all the potential scenarios build up in the model (e.g. rebound assumptions)
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?	×	Discounting was applied at 3.5% for both costs and benefits
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	NA	Probabilistic sensitivity analysis of decision model using 2nd-order Monte Carlo simulation
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	NA	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	NA	
Probabilistic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	✓	

continued

Study question		Comments
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	✓	Both are assessed
32. Are the probability distributions adequately detailed and appropriate?	✓	See above
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✓	See above
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	✓	
35. The choice of variables for sensitivity analysis is justified	✓	
36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	
39. Applicable to the NHS setting	✓	

Cost-effectiveness model (Schering-Plough) – data extraction

Primary source	Company submission
Author	Schering-Plough Ltd
Date	9 November 2004
Type of economic evaluation	Cost-effectiveness analysis
Currency used	UK £
Year to which costs apply	2003
Perspective used	NHS
Timeframe	Results for the Active Joint Model presented at 2, 5 (base case) 10 and 30 years. Results for the Chronic Active Joint model based on a 5-, 10-, 30- (base case) and 45-year time horizons
Comparators	Standard supportive therapy, mainly physiotherapy and NSAIDs
Source(s) of effectiveness data	IMPACT 1 trial[61] used for weeks 0–50
	Toronto Psoriatic Arthritis Research Programme (observational study). The natural history of the disease beyond 50 weeks for the placebo arm was assessed from morbidity and mortality data collected from this database.
Source(s) of resource use data	Subsample (n = 100) of the Toronto Psoriatic Arthritis Research Programme database was used to estimate the past 3 months direct health resource utilisations (i.e. health professional costs, ambulatory care, hospitalisation, aids, drug costs and laboratory and radiological tests) through a questionnaire
	Drug administration and monitoring resource use is not stated. Apparently, only a chest X-ray and a PPD (purified protein derivative) skin test for tuberculosis are included as baseline cost
Source(s) of unit cost data	Canadian health resource utilisation was assigned UK based costs based on MIMS and Charing Cross Hospital, London
	Any other costs not covered by the above were converted to UK £ based on OECD purchasing power parity table (2003)

continued

Primary source	Company submission
Modelling approach used	Both the Chronic and the Active Joint models were developed as a Markov model using individual patient-level simulation with PSA. The model was extended beyond the trial duration using the Toronto PsA Research Programme database (in particular, beyond 50 weeks for the placebo arm). A subsample of 100 random patients from that database was used to collect data on resource utilisation and EQ-5D through a questionnaire. Response rates are not incorporated in the model, as treatment is assumed to be continuous unless during the individual patient simulation 3 consecutive cycles (16 weeks) were experienced at the highest active joint count (≥10). Annual withdrawal rates based on adverse effects or lack of efficacy are also disregarded
Summary of effectiveness results	For the Active Joint model, infliximab shows a gain of 1.47 QALYs at 5 years over standard supportive therapy. Base-case results for the Chronic Joint model (30-year time horizon) show a 6.2 QALY gain
Summary of cost results	For the Active Joint model, the cost difference of infliximab compared with standard supportive therapy is £54,049 at 5 years. The Chronic Joint model shows a £210,039 cost difference at 30 years (base case)
Summary of cost-effectiveness results	The ratio between incremental costs and QALYs diminishes as time goes by: at 2 years the ICER is £58,612 per QALY, whereas at 10 years this has fallen to £33,282 and at 30 years to £31,071 (all results for the Active Joint Model). At the 45-year time horizon, the chronic model shows an ICER of £35,327
Sensitivity analysis	Apart from the sensitivity analysis of varying time horizons, only a sensitivity analysis on discount rates is reported, with a minimal effect on cost-effectiveness
Main conclusions	The model does not include either of the two main instruments that have been used for measuring clinical response in PsA: the PsARC and the ACR. It does not consider the inclusion of patient disability measures, such as the HAQ. Although the number of active joints has been shown to be a good predictor for short-term outcomes, other outcome measures should have been considered in order to capture the effect of disability in the long term. Results need to be explored further in the light of different rebound scenarios; the model does not make explicit what happens after patients withdraw from infliximab. It is not made clear whether results are applicable to a UK setting given that direct costs are based on resource use estimates from Canada rather than from the UK NHS

Cost-effectiveness model (Schering-Plough) – quality assessment

All items will be graded as either ✓ (item adequately addressed), × (item not adequately addressed), ? (unclear or not enough information), NA (not applicable) or NS (not stated)

Schering-Plough submission

Study question		Comments
1. Costs and effects examined	×	The treatment effect of infliximab which is implemented is not clear. Some relevant resource use (monitoring tests) and unit costs (UK infusion costs) used as input parameters in the model are not clear. A detailed description of the parameters used to populate the model is not provided
2. Alternatives compared	?	It seems like the comparator is 'standard supportive therapy', defined as mainly physiotherapy and NSAIDs (Section 4.4). However, in Section 4.5.2, the decision model is said to compare infliximab with 'standard therapy', defined as continued usual PsA management. No further details of the parameters used for the comparator arm are provided
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	×	The exclusion of productivity losses from the main analysis implicitly indicates a healthcare system perspective

continued

Study question		Comments
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	?	According to the summary of product characteristics (SPC) indications, infliximab is indicated for the treatment of active and progressive PsA in adults when the response to previous DMARD therapy has been inadequate. If the comparator used was the equivalent to 'palliative care' this would be the main alternative to infliximab. However, as already mentioned, the nature of the comparator is not clear from the text
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	×	
6. The rationale for choosing the alternative programmes or interventions compared is stated	×	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	×	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	Supplemented by an observational study
11. Potential biases identified (especially if data not from RCTs)	×	There are remarkable differences between the baseline characteristics of the patients from the IMPACT trial and the Toronto observational study regarding the number of active joints (i.e. 95% of patients from the IMPACT trial have ≥ 10 vs only 19% in the Toronto database) and number of swollen joints. This point is noted but its consequences are not explored
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	
Costs		
13. All the important and relevant resource use included	?	Direct costs were stratified by active joint states, but no breakdown of such costs is provided. Monitoring costs for infliximab seem not to be included in the analysis
14. All the important and relevant resource use measured accurately (with methodology)	×	Not reported
15. Appropriate unit costs estimated (with methodology)	?	Not clearly reported
16. Unit costs reported separately from resource use data	×	
17. Productivity costs treated separately from other costs	NA	
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	×	The year to which unit costs apply is not stated. We understand it is 2003 as they use the OECD PPP 2003 to convert Canadian currency to UK £
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life-years, QALYs, etc.)	✓	QALYs

continued

Study question		Comments
20. Methods to value health states and other benefits are stated (e.g. time trade-off)	✓	Based on the administration of the EQ-5D to a sample of patients in the Toronto PsA database. This facilitates utility estimates for the various Markov states used in the model
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals, etc.)	✓	EQ-5D – UK public values
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	Markov model
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	×	No justification for the choice of modelling approach is reported. Key input parameters (direct costs, utilities) are reported but not in full detail
24. All model outputs described adequately	✓	
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?	×	3.5% on costs and benefits (therefore not consistent with NICE's current recommendation)
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	NA	Probabilistic analysis of decision models
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs)	NA	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	NA	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	?	We have to assume so; not clearly reported. No full description or list of input parameters is provided
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	?	Overall variability between patients (first order uncertainty) is explored through the patient simulation. A probabilistic sensitivity analysis seems to have been undertaken in order to explore parameter uncertainty, but the methods used are not reported
32. Are the probability distributions adequately detailed and appropriate?	?	Not reported
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	×	Very limited sensitivity analysis. Only conducted on the discount rates of 0, 5 and 7%
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis)	NA	
35. The choice of variables for sensitivity analysis is justified	NA	
36. The ranges over which the variables are varied are stated	NA	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as aggregated form	×	Costs are not disaggregated
39. Applicable to the NHS setting	×	It is not clear whether results are applicable to a UK setting given that direct costs are based on resource use estimates from Canada rather than from the UK NHS

Appendix 10

Details of adjustment for placebo response in the York Model

The PsA long-term model uses two results from the evidence synthesis in evaluating how the effects of the two treatments compare: the response rates to either treatment and the changes in HAQ score resulting from each treatment.

From the evidence synthesis, we also know the response rates and changes in HAQ due to placebo. However, placebo is not a long-term treatment option and, therefore, we adjust the effects of both treatments for the placebo effect. The effects of both treatments are summarised in terms of changes in HAQ score. The average change in HAQ score resulting from each treatment can be calculated using response rates and the estimated HAQ changes conditional on response. At each cycle, the changes in HAQ score due to each treatment [etanercept, infliximab or placebo (which is considered equivalent to palliative care)] are shown in the *Figure 9*. The HAQ change obtained under each possible path is given on the right, with N denoting the natural progression; $i\Delta$ denoting the incremental HAQ change due to treatment response, treatment non-response or placebo response and p denoting the probability of response to either treatment or placebo.

However, in our long-term model, whereas both the treatment responders and the placebo group continue to receive the HAQ change indicated above throughout several cycles, the group of treatment non-responders is taken off treatment immediately after a single cycle. We therefore simplify the long-term model to that shown in *Figure 10* and add the HAQ increment for treatment non-responders ($i\Delta_{noresp} - p_{plac}i\Delta_{plac}$) separately whenever they are taken off treatment.

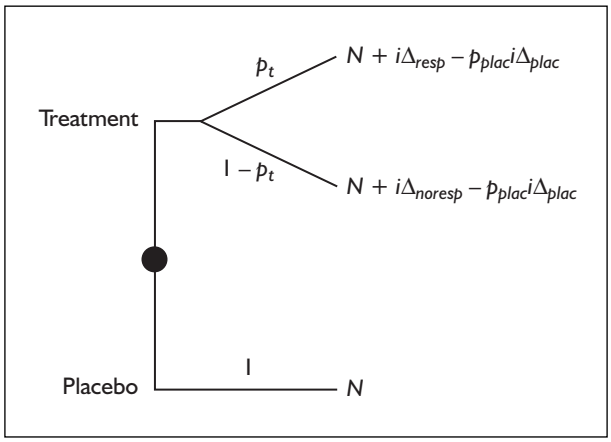


FIGURE 9 *Placebo effect adjustment at 12 weeks*

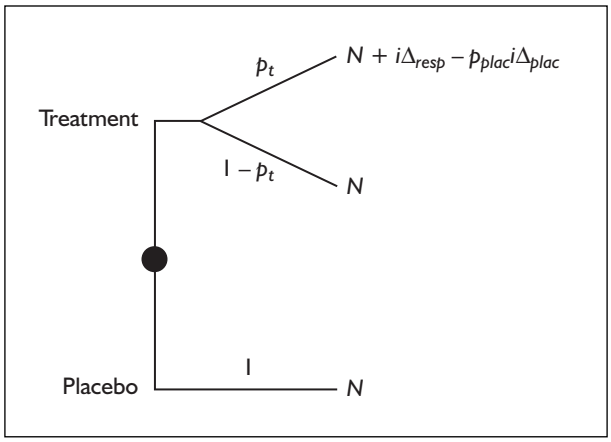


FIGURE 10 *Placebo effect adjustment after 12 weeks*

By calculating the HAQ change as above, we have 'netted out' the placebo effect from the treatment effect.

Appendix 11

Evidence on annual HAQ progression while on anti-TNF drugs

Treatment	Mean	SE	Source	Notes
Infliximab	**[Confidential information removed]**	**[Confidential information removed]**	IMPACT open-label results[127]	**[Confidential information removed]**
Etanercept	**[Confidential information removed]**	**[Confidential information removed]**	Wyeth open-label study[150]	**[Confidential information removed]**
Infliximab	0.11	NA	Antoni *et al.*, 2002[180]	54-week open-label PsA study, 10 patients. 50% discontinuation after week 10, 4 because of clinical remission. A total of 8 patients attained ACR 70 responses by week 10, with 6 out of 8 maintaining it at week 54. HAQ progression reported here is the difference between HAQ at week 6 (i.e. initial 3 doses) and week 54. Single-centre, Germany
Infliximab	NA	NA	Feletar *et al.*, 2004[181]	12-month observational study of 16 patients. Treatment of refractory PsA. Six patient (38%) discontinued treatment (mean time to treatment discontinuation 24.5 weeks). Single-centre, Canada
Etanercept	NA	NA	Mease *et al.*, 2004[182]	1-year open-label extension. After 145 patients received 48 weeks of etanercept, 39% had an HAQ disability score of zero
Etanercept	NA	NA	Mease *et al.*, 2004[182]	2-year open-label extension, 71 patients on etanercept during 88 weeks. Only radiographic progression measures reported
Infliximab	NA	NA	Settas *et al.*, 2004[183]	Retrospective 1-year open-label study, 26 patients. At week 52, 40% had an HAQ disability of zero

NA, not applicable; SE, standard error.

Appendix 12

Details of costs used in the York Model

Unit costs[a]

Unit costs	£ (2004–05)	Source
Drug costs		
Etanercept cost per vial (25 mg)	89.38	BNF No. 48, September 2004 version
Infliximab cost per vial (100 mg)	419.62	BNF No. 48, September 2004 version (7% price reduction applied based on sales volume)
Hospital visit costs		
Day-case rheumatology	515.00	NHS Reference Costs 2003 (HRG H26)
Outpatient rheumatology, first attendance	110.00	NHS Reference Costs 2003, Outpatients
Outpatient rheumatology, follow-up attendance	79.00	NHS Reference Costs 2003, Outpatients
Staff nurse, cost per patient-related hour	34.00	PSSRU Unit Costs of Health and Social Care 2004
Laboratory tests[b]		
Full blood count (FBC)	2.42	York NHS Trust
ESR	2.39	York NHS Trust
LFT	0.61	York NHS Trust
U&E	1.12	York NHS Trust
Chest X-ray	21.20	York NHS Trust
TB Heaf test	7.09	NHS Reference Costs 2003
Antinuclear antibodies (ANA)	3.77	York NHS Trust
DNA binding (double-stranded DNA)	3.77	York NHS Trust

[a] We include costs of tests undertaken to determine eligibility (i.e. TB Heaf test and chest X-ray) for all patients. We cannot predict the proportion of patients developing 'lupus like' symptoms so we include costs of antibodies tests as a one-off. VAT not included in laboratory tests and drug acquisition drugs.
[b] Price year 2004–05, hospital costs.

Drug acquisition costs

Treatment	Schedule	No. of treatments at 12 weeks	No. of subsequent annual treatments	Average weight (kg)	Required dose	Vial size (mg)	Wastage on?	Vials per dose	No. of vials at 12 weeks	Yearly no. of subsequent vials	1st 3 months drug costs (£)	Subsequent annual drug costs (£)
Etanercept	Twice weekly	24	104	–	25 mg	25	No	1	24	104	2,145.12	9,295.52
Infliximab	0, 2, 6 weeks; 8 weeks thereafter	3	6.5	60	5 mg/kg	100	No	3	9	19.5	3,776.58	8,182.59
Infliximab	0, 2, 6 weeks; 8 weeks thereafter	3	6.5	80	5 mg/kg	100	No	4	12	26	5,035.44	10,910.12

Drug administration costs[a]

Treatment	Administration costs (initial trial period)				Subsequent annual administration costs				
	Outpatient rheumatology (first attendance)	Outpatient rheumatology (follow-up attendance)	Day-case rheumatology	Visit staff nurse	1st 3 months administration costs (£)	Outpatient rheumatology (follow-up attendance)	Day-case rheumatology	Visit staff nurse	Subsequent annual administration costs (£)
Etanercept	1	–	–	4	246.00	–	–	–	0.00
Infliximab	–	–	3	–	772.50	–	6.5	–	1,673,75

[a] Cost of infliximab administration estimated as half day-case based on expert opinion. During initial 12 weeks, after first educational visit for etanercept self-injection, monthly visits to staff nurse in order to check progress (expert opinion).
Source: expert opinion and SPC posology indications.

Drug monitoring costs

	Etanercept				Infliximab			
	Resource use weeks 0–12	Subsequent annual resource use	Costs weeks 0–12 (£)	Subsequent annual costs (£)	Resource use weeks 0–12	Subsequent annual resource use	Costs weeks 0–12 (£)	Subsequent annual costs (£)
Hospital visit costs								
Outpatient rheumatology follow-up	1	2	79.00	158.00	1	–	79.00	0.00
Staff nurse, patient/hour	0	1	0.00	34.00	–	–	0.00	0.00
Laboratory tests								
Chest X-ray	1	–	21.20	0.00	1	–	21.20	0.00
TB HEAF test	1	–	7.09	0.00	1	–	7.09	0.00
ANA	1	–	3.77	0.00	1	–	3.77	0.00
Double-stranded DNA	1	–	3.77	0.00	1	–	3.77	0.00
Full blood count (FBC)	2	2	4.84	4.84	2	2	4.84	4.84
ESR	2	2	4.78	4.78	2	2	4.78	4.78
LFT	2	2	1.22	1.22	2	2	1.22	1.22
U&E	2	2	2.24	2.24	2	2	2.24	2.24
Total monitoring costs			127.91	205.08	1	–	127.91	13.08

In order to avoid double-counting, clinician and nurse time for clinical examinations and tests is assumed to be covered by usual outpatient visits for administration of infliximab.
In the case of etanercept, only the costs of the first 3 months are excluded (I.e. during initial administration costs of the drug). Monitoring visits take place every 3 months after the patient is stable, with alternate visits between nurse and consultant (expert opinion). Previous outpatient visit for administration of TB tests for eligibility counted in for both anti-TNF drugs.
Source: BSR guidelines use of anti-TNF drugs.

Appendix 13

Evidence synthesis – specification of the prior distribution

	Sensitivity analysis	**Base-case version**
Response rates modelled as random baselines	pco[j]~dnorm(baseMean,baseTau)	pc[j]~dbeta(calpha,cbeta)
	Normal distribution (log-odds ratio scale)	Uniform distribution (0 – 1 interval)
Baseline priors	baseMean~dnorm(0,0.0001) baseTau~dgamma(3,1)	ncontrol~dunif(0,prior.nmax) prespcontrol~dunif(0,1) calpha<-prespcontrol*ncontrol cbeta<-ncontrol-calpha

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

HTA Commissioning Board

Members

Current and past membership details of all HTA 'committees' are available from the HTA website (www.hta.ac.uk)

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern, Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Ms Norma Armston, Lay Member, Bolton

Professor Max Bachmann Professor of Health Care Interfaces, Department of Health Policy and Practice, University of East Anglia

Professor Rudy Bilous Professor of Clinical Medicine & Consultant Physician, The Academic Centre, South Tees Hospitals NHS Trust

Dr Paul Cockcroft, Consultant Medical Microbiologist and Clinical Director of Pathology, Department of Clinical Microbiology, St Mary's Hospital, Portsmouth

Professor Adrian K Dixon, Professor of Radiology, University Department of Radiology, University of Cambridge Clinical School

Dr David Elliman, Consultant Paediatrician/ Hon. Senior Lecturer, Population Health Unit, Great Ormond St. Hospital, London

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales Swansea

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medicines & Healthcare Products Regulatory Agency, London

Professor William Rosenberg, Professor of Hepatology, Liver Research Group, University of Southampton

Dr Susan Schonfield, Consultant in Public Health, Specialised Services Commissioning North West London, Hillingdon Primary Care Trust

Dr Phil Shackley, Senior Lecturer in Health Economics, School of Population and Health Sciences, University of Newcastle upon Tyne

Dr Margaret Somerville, PMS Public Health Lead, Peninsula Medical School, University of Plymouth

Dr Graham Taylor, Scientific Director & Senior Lecturer, Regional DNA Laboratory, The Leeds Teaching Hospitals

Professor Lindsay Wilson Turnbull, Scientific Director, Centre for MR Investigations & YCR Professor of Radiology, University of Hull

Professor Martin J Whittle, Associate Dean for Education, Head of Department of Obstetrics and Gynaecology, University of Birmingham

Dr Dennis Wright, Consultant Biochemist & Clinical Director, Pathology & The Kennedy Galton Centre, Northwick Park & St Mark's Hospitals, Harrow

Pharmaceuticals Panel

Members

Chair,
Dr John Reynolds, Chair Division A, The John Radcliffe Hospital, Oxford Radcliffe Hospitals NHS Trust

Professor Tony Avery, Head of Division of Primary Care, School of Community Health Services, Division of General Practice, University of Nottingham

Ms Anne Baileff, Consultant Nurse in First Contact Care, Southampton City Primary Care Trust, University of Southampton

Professor Stirling Bryan, Professor of Health Economics, Health Services Management Centre, University of Birmingham

Mr Peter Cardy, Chief Executive, Macmillan Cancer Relief, London

Professor Imti Choonara, Professor in Child Health, Academic Division of Child Health, University of Nottingham

Dr Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Dr Karen A Fitzgerald, Consultant in Pharmaceutical Public Health, National Public Health Service for Wales, Cardiff

Mrs Sharon Hart, Head of DTB Publications, *Drug & Therapeutics Bulletin*, London

Dr Christine Hine, Consultant in Public Health Medicine, South Gloucestershire Primary Care Trust

Professor Stan Kaye, Cancer Research UK Professor of Medical Oncology, Section of Medicine, The Royal Marsden Hospital, Sutton

Ms Barbara Meredith, Lay Member, Epsom

Dr Andrew Prentice, Senior Lecturer and Consultant Obstetrician & Gynaecologist, Department of Obstetrics & Gynaecology, University of Cambridge

Dr Frances Rotblat, CPMP Delegate, Medicines & Healthcare Products Regulatory Agency, London

Professor Jan Scott, Professor of Psychological Treatments, Institute of Psychiatry, University of London

Mrs Katrina Simister, Assistant Director New Medicines, National Prescribing Centre, Liverpool

Dr Richard Tiner, Medical Director, Medical Department, Association of the British Pharmaceutical Industry, London

Dr Helen Williams, Consultant Microbiologist, Norfolk & Norwich University Hospital NHS Trust

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell,
Consultant Vascular and General Surgeon, Department of Surgery, Royal Devon & Exeter Hospital

Dr Aileen Clarke,
Reader in Health Services Research, Public Health & Policy Research Unit, Barts & the London School of Medicine & Dentistry, London

Dr Matthew Cooke, Reader in A&E/Department of Health Advisor in A&E, Warwick Emergency Care and Rehabilitation, University of Warwick

Dr Carl E Counsell, Clinical Senior Lecturer in Neurology, Department of Medicine and Therapeutics, University of Aberdeen

Ms Amelia Curwen, Executive Director of Policy, Services and Research, Asthma UK, London

Professor Gene Feder, Professor of Primary Care R&D, Department of General Practice and Primary Care, Barts & the London, Queen Mary's School of Medicine and Dentistry, London

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, Department of General Practice and Primary Care, South Tees Hospital NHS Trust, Middlesbrough

Ms Bec Hanley, Co-Director, TwoCan Associates, Hurstpierpoint

Ms Maryann L Hardy, Lecturer, Division of Radiography, University of Bradford

Professor Alan Horwich, Director of Clinical R&D, Academic Department of Radiology, The Institute of Cancer Research, London

Dr Simon de Lusignan, Senior Lecturer, Primary Care Informatics, Department of Community Health Sciences, St George's Hospital Medical School, London

Professor Neil McIntosh, Edward Clark Professor of Child Life & Health, Department of Child Life & Health, University of Edinburgh

Professor James Neilson, Professor of Obstetrics and Gynaecology, Department of Obstetrics and Gynaecology, University of Liverpool

Dr John C Pounsford, Consultant Physician, Directorate of Medical Services, North Bristol NHS Trust

Karen Roberts, Nurse Consultant, Queen Elizabeth Hospital, Gateshead

Dr Vimal Sharma, Consultant Psychiatrist/Hon. Senior Lecturer, Mental Health Resource Centre, Cheshire and Wirral Partnership NHS Trust, Wallasey

Dr L David Smith, Consultant Cardiologist, Royal Devon & Exeter Hospital

Professor Norman Waugh, Professor of Public Health, Department of Public Health, University of Aberdeen

Expert Advisory Network

Members

Professor Douglas Altman,
Director of CSM & Cancer Research UK Med Stat Gp, Centre for Statistics in Medicine, University of Oxford, Institute of Health Sciences, Headington, Oxford

Professor John Bond,
Director, Centre for Health Services Research, University of Newcastle upon Tyne, School of Population & Health Sciences, Newcastle upon Tyne

Mr Shaun Brogan,
Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE,
Chief Executive, Office of the Chief Executive. Trust Headquarters, Altnagelvin Hospitals Health & Social Services Trust, Altnagelvin Area Hospital, Londonderry

Ms Tracy Bury,
Project Manager, World Confederation for Physical Therapy, London

Professor Iain T Cameron,
Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark,
Medical Writer & Consultant Pharmacist, Rossendale

Professor Collette Clifford,
Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham, Edgbaston, Birmingham

Professor Barry Cookson,
Director, Laboratory of Healthcare Associated Infection, Health Protection Agency, London

Professor Howard Cuckle,
Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Dr Katherine Darton,
Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux,
Professor of Paediatric Epidemiology, London

Mr John Dunning,
Consultant Cardiothoracic Surgeon, Cardiothoracic Surgical Unit, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw,
Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles,
Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby,
Professor of Community Rehabilitation, Institute of General Practice and Primary Care, University of Sheffield

Mr Leonard R Fenwick,
Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Professor David Field,
Professor of Neonatal Medicine, Child Health, The Leicester Royal Infirmary NHS Trust

Mrs Gillian Fletcher,
Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn,
Professor of Medicine, Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham

Ms Grace Gibbs,
Deputy Chief Executive, Director for Nursing, Midwifery & Clinical Support Services, West Middlesex University Hospital, Isleworth

Dr Neville Goodman,
Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Alastair Gray,
Professor of Health Economics, Department of Public Health, University of Oxford

Professor Robert E Hawkins,
CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor Allen Hutchinson,
Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Dr Duncan Keeley,
General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping,
Research Degrees Programme Director & Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy,
Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay,
Professor of Psychiatry for the Elderly, University of Leicester, Leicester General Hospital

Professor Julian Little,
Professor of Human Genome Epidemiology, Department of Epidemiology & Community Medicine, University of Ottawa

Professor Rajan Madhok,
Medical Director & Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor David Mant,
Professor of General Practice, Department of Primary Care, University of Oxford

Professor Alexander Markham,
Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Chris McCall,
General Practitioner, The Hadleigh Practice, Castle Mullen

Professor Alistair McGuire,
Professor of Health Economics, London School of Economics

Dr Peter Moore,
Freelance Science Writer, Ashtead

Dr Sue Moss, Associate Director,
Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Mrs Julietta Patnick,
Director, NHS Cancer Screening Programmes, Sheffield

Professor Tim Peters,
Professor of Primary Care Health Services Research, Academic Unit of Primary Health Care, University of Bristol

Professor Chris Price,
Visiting Chair – Oxford, Clinical Research, Bayer Diagnostics Europe, Cirencester

Professor Peter Sandercock,
Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, Genetics Department, St James's University Hospital, Leeds

Dr Ken Stein,
Senior Clinical Lecturer in Public Health, Director, Peninsula Technology Assessment Group, University of Exeter

Professor Sarah Stewart-Brown,
Professor of Public Health, University of Warwick, Division of Health in the Community Warwick Medical School, LWMS, Coventry

Professor Ala Szczepura,
Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor,
Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster,
Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@hta.ac.uk
http://www.hta.ac.uk

ISSN 1366-5278