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Abstract

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

M Rodgers,[1]* D Epstein,[2] L Bojke,[2] H Yang,[1] D Craig,[1] T Fonseca,[1] L Myers,[1] I Bruce,[3] R Chalmers,[4] S Bujkiewicz,[5] M Lai,[5] N Cooper,[5] K Abrams,[5] D Spiegelhalter,[6] A Sutton,[5] M Sculpher[2] and N Woolacott[1]

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Background: Etanercept, infliximab and adalimumab are licensed in the UK for the treatment of active and progressive psoriatic arthritis (PsA) in adults who have an inadequate response to standard treatment.
Objective: To determine the clinical effectiveness, safety and cost-effectiveness of these biologic agents in the treatment of active and progressive PsA.
Data sources: Systematic reviews were performed, with data sought from 10 electronic databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Science Citation Index, Conference Proceedings Citation Index – Science, ClinicalTrials.gov, metaRegister of Current Controlled Trials, NHS Economic Evaluation Database, Health Economic Evaluations Database and EconLit) up to June 2009.
Review methods: Full paper manuscripts of titles/abstracts considered relevant were obtained and assessed for inclusion by two reviewers according to criteria on study design, interventions, participants and outcomes. Data on study and participant characteristics, efficacy outcomes, adverse effects, costs to the health service and cost-effectiveness were extracted, along with baseline data where reported. The primary efficacy outcomes were measures of anti-inflammatory response, skin lesion response and functional status, and the safety outcome was the incidence of serious adverse events. The primary measure of cost-effectiveness was incremental cost per additional quality-adjusted life-year (QALY). Standard meta-analytic techniques were applied to efficacy data. Published cost-effectiveness studies and the economic analyses submitted to the National Institute for Health and Clinical Excellence (NICE) by the biologic manufacturers were reviewed. An economic model was developed by updating the model produced by the York Assessment Group for the previous NICE appraisal of biologics in PsA.
Results: Pooled estimates of effect demonstrated a significant improvement in patients with PsA for all joint disease and functional status outcomes at 12–14 weeks' follow-up. The biologic treatment significantly reduced joint symptoms for etanercept [relative risk

(RR) 2.60, 95% confidence interval (CI) 1.96 to 3.45], infliximab (RR 3.44, 95% CI 2.53 to 4.69) and adalimumab (RR 2.24, 95% CI 1.74 to 2.88), with 24-week data demonstrating maintained treatment effects. Trial data demonstrated a significant effect of all three biologics on skin disease at 12 or 24 weeks. Evidence synthesis found that infliximab appeared to be most effective across all outcomes of joint and skin disease. The response in joint disease was greater with etanercept than with adalimumab, whereas the response in skin disease was greater with adalimumab than with etanercept, although these differences are not statistically significant. Under base-case assumptions, etanercept was the most likely cost-effective strategy for patients with PsA and mild-to-moderate psoriasis if the threshold for cost-effectiveness was £20,000 or £30,000 per QALY. All biologics had a similar probability of being cost-effective for patients with PsA and moderate-to-severe psoriasis at a threshold of £20,000 per QALY.

Limitations: Limited available efficacy data and difficulty in assessing PsA activity and its response to biologic therapy.

Conclusions: The data indicated that etanercept, infliximab and adalimumab were efficacious in the treatment of PsA compared with placebo, with beneficial effects on joint symptoms, functional status and skin. Short-term data suggested that these biologic agents can delay joint disease progression and evidence to support their use in the treatment of PsA is convincing. Future research would benefit from long-term observational studies with large sample sizes of patients with PsA to demonstrate that beneficial effects are maintained, along with further monitoring of the safety profiles of the biologic agents.

Funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

Glossary

Acitretin A synthetic derivative of vitamin A, which 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 or 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.

American College of Rheumatology 20% improvement criteria (ACR 20) ACR 20 is a response measure that requires a 20% reduction in the tender joint count, a 20% reduction in the swollen joint count, and a 20% reduction in at least three out of five additional measures, including patient and physician global assessment, pain, disability and an acute-phase reactant.

American College of Rheumatology 50% improvement criteria (ACR 50) ACR 50 is a response measure that requires a 50% reduction in the tender joint count, a 50% reduction in the swollen joint count, and a 50% reduction in at least three out of five additional measures, including patient and physician global assessment, pain, disability and an acute-phase reactant.

American College of Rheumatology 70% improvement criteria (ACR 70) ACR 70 is a response measure that requires a 70% reduction in the tender joint count, a 70% reduction in the swollen joint count, and a 70% reduction in at least three out of five additional measures, including patient and physician global assessment, pain, disability and an acute-phase reactant.

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, for example, lupus (systemic lupus erythematosus).

Biologic (biological) therapies Medical preparations derived from living organisms. Includes biologic drug and other new drugs that target the pathologically active T cells involved in psoriasis and psoriatic arthritis.

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

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, which 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).

Credible interval In Bayesian statistics, a credible interval is a posterior probability interval estimation that incorporates problem-specific contextual information from the prior distribution. Credible intervals are used for the purposes similar to those of confidence intervals in frequentist statistics.

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.

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

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, as well as azathioprine, cyclophosphamide, antimalarial drugs, 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-effects 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-effects model.

Health Assessment Questionnaire (HAQ) HAQ is a validated, self-administered questionnaire that measures two dimensions of health status, including physical disability and pain. The physical disability comprises eight subscales: dressing, grooming, arising, hygiene, reach, eating, walking, and grip and activities. HAQ is scored from 0 (able to function without difficulty) to 3 (unable to function).

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 (ITT) An ITT analysis is one in which all of the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not.

Methotrexate (MTX) One of the oldest chemotherapy drugs that is used to treat cancer. Used in the treatment of psoriasis.

Mixed-treatment comparison (MTC) 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 vs B and B vs C trials) and indirect comparisons (A vs 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, which recognises only one antigen.

Non-steroidal anti-inflammatory drugs (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.

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 s/he is 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 patients with psoriasis have this type.

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.

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

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.

Psoriatic Arthritis Response Criteria (PsARC) PsARC is a composite response measure that incorporates patient global self-assessment, physician global assessment, and tender and swollen joint scores.

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 (QoL) A concept incorporating all the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity, as well as other factors that 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 RR 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 (RA) 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.

Squamous cell carcinoma A form of skin cancer that is more aggressive than basal cell carcinoma. People who have received psoralen combined with ultraviolet A may be at risk of this type of skin cancer.

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.

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.

Tumor 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.

Visual analogue scale (VAS) 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 (WMD) (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
ADEPT	Adalimumab Effectiveness in Psoriatic Arthritis Trial
ANA	antinuclear antibody
ANOVA	analysis of variance
BAD	British Association of Dermatologists
BNF	*British National Formulary*
BSA	body surface area
BSC	best supportive care
BSR	British Society for Rheumatology
BSRBR	British Society for Rheumatology Biologics Register
CEAC	cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CiC	commercial-in-confidence
CPCI-S	Conference Proceedings Citation Index – Science
CRD	Centre for Reviews and Dissemination
CRP	C-reactive protein
DARE	Database of Abstracts of Reviews of Effects
df	degrees of freedom
DIC	deviation information criterion
DIP	distal interphalangeal
DLQI	Dermatology Life Quality Index
DMARD	disease-modifying antirheumatic drug
dsDNA	double-stranded DNA
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
ESR	erythrocyte sedimentation rate
FBC	full blood count
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire-Disability Index
HEED	Health Economic Evaluations Databases
HLA	human leucocyte antigen
HODaR	Health Outcomes Data Repository
HR	hazard ratio
HRQoL	health-related quality of life
HTA	Health Technology Assessment
IQR	interquartile range
i.v.	intravenous
ICER	incremental cost-effectiveness ratio (e.g. incremental cost per QALY gained)
IMPACT	Infliximab Multinational Psoriatic Arthritis Controlled Trial
IPD	individual patient data
ITT	intention to treat
LFT	liver function test
LOCF	last observation carried forward
MeSH	medical subject heading
MIMS	online and print prescribing database for health professionals
*m*RCT	metaRegister of Current Controlled Trials
MTC	mixed-treatment comparison

MTX	methotrexate
NH	natural history
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NOAR	Norfolk Arthritis Register
NRR	National Research Register
NSAID	non-steroidal anti-inflammatory drug
OMERACT	Outcome Measures in Rheumatoid Arthritis (Rheumatology) Clinical Trials
OR	odds ratio
PASI	Psoriasis Area and Severity Index
pdf	probability density function
PRESTA	Psoriasis Randomized Etanercept STudy in Subjects with Psoriatic Arthritis
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
QALY	quality-adjusted life-year
QoL	quality of life
RA	rheumatoid arthritis
RCT	randomised controlled trial
RF	rheumatoid factor
RR	relative risk
SCI	Science Citation Index
SD	standard deviation
SE	standard error
SF-36	Short Form questionnaire-36 items
SJC	swollen joint count
STA	single technology appraisal
TB	tuberculosis (infection)
THIN	The Health Improvement Network
TIDI	Transparent Interactive Decision Interrogator
TNF	tumour necrosis factor
TJC	tender joint count
TSS	Total Sharp Score
U&E	urea and electrolytes
URTI	upper respiratory tract infection
UVB	ultraviolet light, type B
VAS	visual analogue scale

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 in the notes 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 was deemed *commercial-in-confidence* and *academic-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* and *academic-in-confidence* data removed and replaced by the statement 'commercial-in-confidence and academic-in-confidence information (or data) 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, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Executive summary

Background

Psoriatic arthritis (PsA) is defined as a unique inflammatory arthritis affecting the joints and connective tissue, and is associated with psoriasis of the skin or nails, which, because it involves both skin and joints, can result in significant impairment of quality of life (QoL) and psychosocial disability. Owing to the lack of a precise definition and diagnostic marker for PsA, it is difficult to gauge its exact prevalence. The UK-adjusted prevalence of PsA in the primary care setting has been estimated to be 0.3%. Etanercept (Enbrel®), infliximab (Remicade®) and adalimumab (Humira®) are biologic agents that target tumour necrosis factor (TNF) activity in the treatment of PsA. All three agents are licensed in the UK for the treatment of active and progressive PsA in adults when the response to previous disease-modifying antirheumatic drugs (DMARDs) has been inadequate.

Objective

To determine the clinical effectiveness, safety and cost-effectiveness of etanercept, infliximab and adalimumab for the treatment of active and progressive PsA in patients who have an inadequate response to standard treatment (including DMARD therapy).

Methods

Systematic reviews of the evidence on clinical efficacy, safety and cost-effectiveness of etanercept, infliximab and adalimumab in the treatment of PsA were performed. Data for the review were sought systematically from 10 electronic databases [including MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL)] up to June 2009. Industry submissions were searched for additional unpublished data. Randomised controlled trials (RCTs) (including open-label extensions) were included in the evaluation of efficacy. Safety data were sought from RCTs and observational studies reporting serious adverse events [serious infections, malignancies and activation of tuberculosis (TB)] for a minimum of 500 patients in any indication receiving one or more of the biologic agents of interest. The primary efficacy outcomes were measures of anti-inflammatory response [Psoriatic Arthritis Response Criteria (PsARC), American College of Rheumatology 20% Improvement Criteria (ACR 20)], skin lesion response [Psoriasis Area and Severity Index (PASI)] and functional status [Health Assessment Questionnaire (HAQ)]. The safety outcome was the incidence of serious adverse events. The primary measure of cost-effectiveness was incremental cost per additional quality-adjusted life-year (QALY).

Standard meta-analytic techniques were applied to efficacy data. In addition, in the absence of head-to-head comparison on the relative efficacy between the alternative biologics, an indirect comparison was undertaken using Bayesian methods. A narrative synthesis was used for adverse event data. Published cost-effectiveness studies and the economic analyses submitted to the National Institute for Health and Clinical Excellence (NICE) by the biologic manufacturers were reviewed. An economic model was developed by updating the model produced by the York Assessment Group for the previous NICE appraisal of biologics in PsA. This model was revised to

evaluate the impact of biologics on both skin and joint disease and to include new evidence from the clinical review and evidence synthesis.

Results

Efficacy

Six RCTs were identified for the evaluation of clinical efficacy (43 publications). The six RCTs comprised two RCTs in patients with PsA for each of the three agents. All trials were double-blind and placebo-controlled RCTs. All trials were rated 'good' by the quality assessment.

Pooled estimates of effect demonstrated a significant improvement in patients with PsA for all joint disease and functional status outcomes at 12–14 weeks' follow-up. The biologic treatment significantly reduced joint symptoms assessed by PsARC for etanercept [relative risk (RR) 2.60, 95% confidence interval (CI) 1.96 to 3.45], infliximab (RR 3.44, 95% CI 2.53 to 4.69) and adalimumab (RR 2.24, 95% CI 1.74 to 2.88). This was consistent with the results from the pooled estimates of ACR 20. Furthermore, the statistically significant reduction in HAQ score also indicated a beneficial effect of these biologic therapies on patients' functional status. Significant heterogeneity was observed only in the outcome of PsARC in infliximab. The 24-week data for all three biologics demonstrated that the treatment effects are maintained. Trial data demonstrate a significant effect of all three biologics on skin disease in terms of PASI response, at 12 or 24 weeks.

The results of evidence synthesis found that infliximab appears to be the most effective of the three biologics. Across all outcomes of joint and skin disease at 12 weeks, infliximab is associated with the highest probabilities of response. The response in joint disease (PsARC and ACR) is greater with etanercept than with adalimumab, whereas the response in skin disease (PASI) is greater with adalimumab than with etanercept, although these differences are not statistically significant. In those patients who achieve a PsARC response to treatment the highest mean reductions in the functional and psychological impact of the disease, measured by HAQ, are seen with infliximab and etanercept (–0.657 for infliximab and –0.630 for etanercept). For all three biologics the changes in HAQ for those patients who did not respond to treatment were below the minimum clinically significant threshold (–0.3).

Short-term radiographic measures indicate that these agents can slow disease progression in the short term (< 24 weeks). The available follow-up data, although promising, are inadequate to determine if these effects persist in the longer term.

Safety

Thirty-two relevant studies were identified for the evaluation of safety of these biologics. The rates of serious infection were etanercept 0.6%–13.2%, infliximab 0.8%–13.8% and adalimumab 0.4%–5.1%. The rates of malignancy were etanercept 1%–5.7%, infliximab 0.16%–5.1% and adalimumab 0.1%–1.1%. The rates of activation of TB for the treatment were etanercept 0%–1.4%, infliximab 0.06%–4.6% and adalimumab 0%–0.4%.

Cost-effectiveness

Six cost-effectiveness studies were identified in the literature review: three published models and three submissions from manufacturers. The published models estimated that the incremental cost-effectiveness ratio (ICER) for etanercept versus palliative care was between £26,000 and £38,000 per QALY, but did not consider the impact of biologics on the skin component of PsA. Abbott [Abbott Laboratories Ltd. Adalimumab (HUMIRA): *Multiple technology appraisal of adalimumab, etanercept and infliximab for psoriatic arthritis National Institute for Health and*

Clinical Excellence (NICE) Health Technology Appraisal. Maidenhead: Abbott Laboratories Ltd; 2009] estimated an ICER for adalimumab of £30,000, with etanercept dominated by adalimumab, and an ICER for infliximab versus adalimumab of £199,000. Schering-Plough [Schering-Plough. *REMICADE (infliximab): Remicade in the treatment of Psoriatic Arthritis (PsA) in the United Kingdom.* A submission to the National Institute of Clinical Excellence: Welwyn Garden City: Schering-Plough Ltd; 2009] concluded that the most cost-effective strategy depended on patient weight. (Since the production of this report, Schering-Plough has merged with Merck.) Wyeth [Wyeth Pharmaceuticals. *Etanercept (ENBREL): Appraisal of the clinical and cost-effectiveness of etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. An appraisal submission for the National Institute of Health and Clinical Excellence*. Maidenhead: Wyeth; 2009] estimated an ICER for etanercept of £12,000 compared with DMARDs.

The de novo York Assessment Group model evaluated the cost-effectiveness of the three biologic therapies and palliative care only. Under base-case assumptions, for patients with PsA and mild-to-moderate skin disease, the ICER etanercept versus palliative care is about £18,000 per QALY, and the ICER of infliximab versus etanercept is about £44,000 per QALY. Adalimumab is extendedly dominated. The probability that etanercept is cost-effective is 0.436 at a threshold of £20,000 per QALY and 0.475 at a threshold of £30,000 per QALY. The expected lifetime prescription costs of biologic therapies is considerably greater than offset cost savings elsewhere in the NHS.

For patients with PsA and moderate-to-severe skin disease who continue on biologics after 3 months if they respond for skin or joints, the ICER of adalimumab versus palliative care is about £16,000 per QALY, the ICER of etanercept versus adalimumab is about £21,000 per QALY and the ICER for infliximab versus etanercept is about £26,000 per QALY. If the cost-effectiveness threshold were £20,000 per QALY then all biologics have a similar probability of being cost-effective.

For patients with PsA with negligible skin involvement, the ICER of etanercept versus palliative care is about £18,000 per QALY, and the ICER of infliximab versus etanercept is about £65,000 per QALY. Adalimumab is extendedly dominated in this group.

The second-line use of biologics was explored in a sensitivity analysis. As these results are based on non-randomised comparisons they should be considered with caution. For patients with PsA and mild-to-moderate psoriasis who have failed adalimumab or infliximab as first-line therapy for either adverse events or inefficacy, the ICER for etanercept is < £20,000 per QALY. For patients who have failed etanercept as first-line therapy for either adverse events or inefficacy, the ICER for adalimumab is < £20,000 per QALY and the ICER for infliximab is < £30,000 per QALY.

These results are sensitive to several model assumptions and alternative sources of data.

Discussion

Despite the limited data, there was clear evidence of a significant improvement for all the biologic therapies on the joint disease condition and functional status of patients with PsA at short-term follow-up. There was also some evidence of beneficial effects for these agents on the skin disease response, although data on this outcome is sparse in PsA. There was a paucity of long-term data on joint disease progression. An indirect comparison of the three agents indicates that infliximab is associated with the highest probability of response on joint and skin outcomes. The range of serious adverse events did not differ considerably between agents, although there was considerable uncertainty around these estimates.

The Assessment Group found that under base-case assumptions, etanercept is most likely to be the cost-effective strategy for patients with PsA and mild-to-moderate psoriasis if the threshold for cost-effectiveness was £20,000 or £30,000 per QALY. All biologics have a similar probability of being cost-effective for patients with PsA and moderate-to-severe psoriasis at a threshold of £20,000 per QALY.

A number of outstanding uncertainties include:

- Bayesian indirect comparison analyses provide evidence of the relative efficacy of these biologics; however, those findings may be considered more uncertain than would be provided in head-to head RCTs.
- The patients in most trials are not precisely representative of the population recommended for biologics in current guidelines. It is unclear whether the beneficial effects are similar in those treated in routine clinical practice.
- The adverse event data are derived primarily from patients with rheumatoid arthritis (RA) or other indications. The generalisability of these findings to patients with PsA remains unclear.
- The progression of HAQ on and off treatment, and the length of time over which biologics are assumed to be effective.
- The long-term progression of PsA with and without biologics.
- The prescription cost of biologics.
- The relationship between utility and severity of arthritis and psoriasis.
- Alternative rules about continuing therapy beyond 3 months depending on response.
- The health-care costs of treating psoriasis and arthritis of varying severity.

Conclusions

Implication for service provision

- The limited data indicate that etanercept, infliximab or adalimumab is efficacious in the treatment of PsA compared with placebo, with beneficial effects on joint symptoms, functional status and skin. Short-term data suggest that these three biologic agents can delay joint disease progression.
- Despite such limited data from PsA trials in the evaluation of efficacy of these biologics, the evidence to support their use in the treatment of PsA is convincing, given the size of treatment effect and quality of data.
- An indirect analysis found that across all outcomes at 12 weeks (PsARC, ACR and PASI) infliximab is associated with the highest probability of response. In those patients who achieve a PsARC response to treatment, the highest mean reductions in HAQ are seen with infliximab and etanercept.
- This review cannot rule out concerns about an increased risk of serious adverse events (serious infection, malignancy and activation of latent TB) of the biologics investigated.
- The Assessment Group found that, under base-case assumptions, etanercept would be considered the most cost-effective strategy for patients with PsA and minimal or mild-to-moderate psoriasis if the threshold for cost-effectiveness were £20,000–30,000 per QALY.
- All biologics have a similar probability of being cost-effective at a threshold of £20,000 per QALY for patients with PsA and moderate-to-severe psoriasis, if patients who respond at 3 months for either skin disease or joint disease continue with biologic therapy.
- In a secondary analysis, etanercept appeared most likely to be cost-effective at a threshold of £20,000 or £30,000 per QALY for patients with PsA and mild-to-moderate psoriasis who have failed adalimumab or infliximab as first-line therapy for either adverse events or inefficacy.

- For patients with PsA and mild-to-moderate psoriasis who have failed etanercept as first-line therapy for either adverse events or inefficacy, adalimumab seems most likely to be cost-effective at a threshold of £20,000 per QALY, although infliximab is most likely to be cost-effective if the threshold is £30,000 per QALY.

Recommendations for research

- Long-term observational studies with large sample sizes of patients with PsA are required to demonstrate that beneficial effects for joint and skin disease and improvement of function are maintained. In particular, data on the effects of joint disease progression (e.g. radiographic assessment), and long-term HAQ progression while responding to biologic agents and health-related quality of life are required. Withdrawal rates due to lack of efficacy and adverse events should also be reported.
- Further monitoring of the safety profiles of the biologic agents [e.g. through the British Society for Rheumatology Biologics Register (BSRBR)] is required. Future research should also establish whether long-term patterns of adverse events of these biologic agents in PsA are similar to those in RA.
- Further investigation is required to reduce uncertainties around the following parameters identified in the economic model:
  - The length of time over which biologics are assumed to be effective.
  - The change in HAQ following withdrawal from biologic drugs.
  - Evidence from general practice about the prescribing, administration and monitoring costs of biologic therapy.
  - The NHS costs of treating psoriasis and arthritis of varying severity.
  - The progression of HAQ on and off biologic treatment.
  - The effectiveness and withdrawal rates of biologics used as second-line therapy.
- Future studies should assess how the biologic treatment of both arthritis and psoriasis affects patients' QoL, using generic preference-based utility instruments.
- The cost-effectiveness of sequential use of biologic therapies should be evaluated further.
- Although indirect analysis is useful, future trials comparing one biologic agent with another in the treatment of PsA are warranted.
- The effectiveness and cost-effectiveness of biologics in patients who might not quite reach the current BSR/British Association of Dermatologists criteria for either psoriasis or arthritis, but might nevertheless benefit from biologic therapy, should also be examined.

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Chapter 1

Background

Description of health problem

Epidemiology

Psoriatic arthritis (PsA) is defined as a unique inflammatory arthritis affecting the joints and connective tissue, and is associated with psoriasis of the skin or nails.[1] There are difficulties in estimating its prevalence due to the lack of a precise definition and diagnostic criteria for PsA.[2] The prevalence of psoriasis in the general population has been estimated at between 2% and 3%,[1] and the prevalence of inflammatory arthritis in patients with psoriasis has been estimated to be up to 30%.[3] PsA affects males and females equally, with a worldwide distribution. Figures for the UK have estimated the adjusted prevalence of PsA in the primary care setting to be 0.3%, based on data from north-east England involving six general practices, covering a population of 26,348.[4] Another study reported PsA prevalence rates per 100,000 of 3.5 for males and 3.4 for females, based on data from 77 general practices in the Norwich Health Authority, with a population of 413,421.[5] Severe PsA with progressive joint lesions can be found in at least 20% of patients with psoriasis.[6]

Aetiology, pathology and prognosis

Psoriatic arthritis is a hyperproliferative and inflammatory arthritis that is distinct from rheumatoid arthritis (RA).[7,8] The aetiology of PsA is not fully known; genetic susceptibility and exogenous influences might play roles in the cause of disease.[9] The expression of major histocompatibility complex antigens [e.g. human leucocyte antigen (HLA)-B27] might also predispose certain patients to develop PsA, as well as a number of environmental factors, such as trauma, repetitive motion, human immunodeficiency virus infection, and bacterial infection.[9] PsA is diagnosed when a patient with psoriasis has a distinctive pattern of peripheral and/or spinal arthropathy.[10] The rheumatic characteristics of PsA include stiffness, pain, swelling, and tenderness of the joints and surrounding ligaments and tendons.[11]

Several clinical features distinguish PsA from RA. In PsA, the absolute number of affected joints is less and the pattern of joint lesion involvement tends to be asymmetric.[12] The joint distribution tends to occur in a ray pattern in PsA, with the common involvement of distal interphalangeal (DIP) joint and nail lesions. All joints of a single digit are thus more likely to be affected in PsA, whereas in RA the same joints on both sides tend to be affected.[1] Dactylitis, spondylitis and sacroiliitis are common in PsA, whereas they are not in RA.[12] In PsA the affected joints are tighter, contain less fluid, and are less tender than those in RA, with a propensity for inflammation of the entheseal sites. PsA and RA also show differences in the inflammatory reaction that accompanies each form of arthritis.[12] Extra-articular manifestations of PsA are also different from those of RA; rheumatoid nodules are particularly absent in patients with PsA.[1] Most patients with PsA develop psoriasis first, while joint involvement appears first only in 19% of patients, and concurrently with psoriasis in 16% of cases.[10] For those who develop psoriasis first, the onset time of PsA is around 10 years after the first signs of psoriasis.[1] In addition, rheumatoid factor (RF) (an antibody produced by plasma cells) may be detected in about 13% of patients with PsA, whereas it can be detected in more than 80% of patients with RA.[1]

Psoriatic arthritis is a progressive disorder, ranging from mild synovitis to severe progressive erosive arthropathy.[11,13] Research has found that patients PsA presenting with oligoarticular disease progress to polyarticular disease; a large percentage of patients develop joint lesions and deformities, which progress over time.[9] Despite clinical improvement with current disease-modifying antirheumatic drug (DMARD) treatment, radiological joint damage has been shown in up to 47% of patients with PsA at a median interval of 2 years.[14] Untreated patients with PsA may have persistent inflammation and progressive joint damage.[11] The deformities resulting from PsA can lead to shortening of digits due to severe joints or bone lysis.[1] Remission can occur in PsA, especially in patients with Health Assessment Questionnaire (HAQ) levels of < 1 score.[15] Of those who can sustain clinical remission, only a small fraction of patients can discontinue medication with no evidence of damage.[16] Research has reported that the frequency of remission was 17.6% in patients with PsA, and the average duration of remission was 2.6 years, from data of 391 patients with peripheral arthritis.[16] Joint damage can occur early in the disease often prior to functional limitation.[9,17] This appears to be associated with the development of inflamed entheses close to peripheral joints, although the link still remains largely unclear.[13] It has been shown that there is an association between polyarthritis and functional disability, with higher mean HAQ scores than those in oligoarthritic patients.[18,19]

A number of risk factors have been found to be predictive of the progression of PsA. A polyarticular onset (five or more swollen joints) of PsA is an important risk factor in predicting the progressive joint deformity.[20] Each actively inflamed joint in PsA is associated with a 4% risk of increased damage within 6 months.[1] HLA antigens have also been found to be predictive of the progression of joint damage. It has been shown that HLA-B27, HLA-B39 and HLA-DQW3 were associated with disease progression.[21] Other risk factors for a more progressive course of PsA include the presence of an elevated erythrocyte sedimentation rate (ESR) and being female.[1,22]

A classification scheme for PsA on the basis of joint manifestations describes five patterns of disease:[9,23]

1. *Distal interphalangeal arthritis* This condition is considered as the classic form of PsA. It can occur as the sole presentation or in combination with other symptoms. It can be symmetrical or asymmetrical and can involve a few or many joints. Adjacent nails may demonstrate psoriatic changes and progressive joint erosions are common.
2. *Arthritis mutilans* It is a severe presentation of the disease with osteolysis of the phalanges, metatarsals and metacarpals.
3. *Symmetric polyarthritis* The clinical feature of symmetric polyarthritis is similar to RA, with inflammation of the metacarpals and the proximal interphalangeal joints being prominent. However, it is usually milder than RA and patients are often RF-negative.
4. *Oligoarthritis* This is the most common condition of PsA, which is characterised by asymmetric involvement of a small number of joints (fewer than four). Arthritis in a single knee might be the first symptom of oligoarthritis.
5. *Spondylitis and/or sacroiliitis* It resembles ankylosing spondylitis, but is generally less severe and less disabling. The axial skeleton tends to be involved in an atypical fashion, with the lumbar spine as the most common site of involvement.

Despite this classification, these patterns of PsA often overlap and evolve from one pattern to another as the disease progresses and diagnostic investigations become more thorough.[13] A common feature of PsA is dactylitis (or 'sausage digit') in which the whole digit appears swollen due to inflammation of the tendons and periosteum as well as the joints.[9,11] Radiographic features of PsA involve the distinctive asymmetric pattern of joint involvement, sacroiliitis and spondylitis, 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. PsA is a lifelong disorder and its impact on patients' functional status and quality of life (QoL) fluctuates over time.[24] As it involves both skin and joints, PsA can result in significant impairment of QoL and psychosocial disability[7,10] compared with a healthy population. Patients with PsA score significantly worse in health-related quality of life (HRQoL) assessment on physical mobility, pain, energy, sleep, social isolation and emotional reaction.[25] A comparison of HRQoL between patients with PsA and patients with RA found that both patient populations had lower physical health than healthy control patients.[26] Patients with PsA reported more role limitations due to emotional problems and more bodily pain after the adjustment of the difference in vitality and other covariates. These findings were also reflected in another comparison of disability and QoL between patients with RA and patients with PsA; this study reported that despite greater peripheral joint damage in patients with RA the function and QoL scores were similar for both groups.[27,28] These reveal that there might be unique psychological disabilities associated with the psoriasis dimension (i.e. skin lesion) of PsA. Due to the skin involvement, patients with PsA may also suffer from other psychological consequences, such as embarrassment, self-consciousness and even depression. Because of a significant reduction in a patient's HRQoL, ideally PsA should be diagnosed early and treated aggressively in order to minimise joint damage and skin disease.[17]

The severity of PsA is also reflected in increased mortality. Patients with PsA have a 60% higher risk of mortality relative to the general population.[24,29,30] The causes of premature death are similar to those noted in the general population, with cardiovascular causes being the most common.[1] The estimated reduction in life expectancy for patients with PsA is approximately 3 years.[31]

The economic costs of PsA have not been well quantified. In the USA, the mean annual direct (health and social care) cost per patient with PsA is estimated as US$3638 according to data from Medstat MarketScan in 1999–2000.[32] In Germany, the mean annual direct cost per patient with PsA is estimated as €3162, with a mean indirect cost (time lost from work and normal activities) per patient of €11,075.[33] Studies of RA[34–36] and psoriasis[37] have shown that costs increase with the severity of both diseases, and productivity losses are significant,[38,39] largely as a consequence of extensive work disability.[35] These findings are likely to be generalisable to PsA.

Studies of the economic impact of RA in the UK before the introduction of biologic therapies found that direct health-care costs represented about one-quarter of all costs, and these were dominated by inpatient and community day care,[40] with DMARDs representing a minor proportion: 3%–4% of total costs and 13%–15% of direct costs.[41] Evidence from the USA suggests that expenditure on biologic therapies might represent 35% of direct cost,[42] but similar data are not yet available for the UK. Increasing expenditure on biologic therapies might be at least partly offset by cost savings elsewhere,[43] although, as yet, the evidence for this is only suggestive.

Assessment of treatment response in psoriatic arthritis

The assessment of 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 being developed by an international collaboration on outcome measures in rheumatology (OMERACT – Outcome Measures in Rheumatoid Arthritis Clinical Trials). There are a number of 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'.[44] In recent years the compound response criterion, the American College of Rheumatology 20% improvement criteria (ACR 20), has gained general acceptance for the assessment of treatments for PsA, and this has been adopted for many PsA trials. Another compound measure, Psoriatic Arthritis Response Criteria (PsARC), was developed specifically for a trial in PsA and has been adopted by the BSR.[45]

American College of Rheumatology 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 (TJC), a 20% reduction in the swollen joint count (SJC), and a 20% reduction in three out of five additional measures, including patient and physician global assessment, pain, disability and an acute-phase reactant. In patients with RA, ACR 20 has been confirmed as being able to discriminate between a clinically significant improvement and a clinically insignificant one.[46,47] It is unclear whether the ACR 20 has the same discriminatory validity in PsA.[48] 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 the patient's disease status that may 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. Because of the differences between PsA and RA, it is imperative that, when the ACR response criteria are used in the trials of treatment for PsA, the DIP joints are included. Rather than changes from bad to moderate synovitis in any individual joint, these criteria detect improvement from swollen to not swollen or from tender to not tender joints. Therefore, patients with oligoarthritis in a few large joints may not appear to respond as well on this outcome as patients with polyarthritis involving many smaller joints.

Psoriatic Arthritis Response Criteria

The Psoriatic Arthritis Response Criteria were developed for a trial of sulfasalazine in PsA,[49] and incorporate four assessment measures (patient self-assessment, physician assessment, joint pain/tenderness score and joint swelling score). Treatment response was 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 these 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 it was 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 biologics in PsA[50] elected to use PsARC as the primary joint response to biologic treatment, although it advocates some extra data collection, such as a patient self-assessed disability (HAQ), and a biochemical marker of disease activity, such as ESR or C-reactive protein (CRP).

Radiological assessments

In all arthropathies progression of the disease can only be truly measured by assessment of the joint damage. The 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 Total Sharp Score (TSS), modified to include the DIP and metatarsophalangeal joints of the feet and interphalangeal joint of the first toe, has been used in the trials of etanercept and adalimumab.[51,52] None of these methods that were developed for RA score additional radiographic changes that are specific to PsA. A new score has been tested by Wassenberg *et al.*,[53] but this scoring method has not yet been validated in clinical trials. Whichever method is selected it is important that trials should be stratified by baseline radiographic findings.

Health Assessment Questionnaire

The HAQ score is a well-validated tool in the assessment of patients with RA.[48] 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). A modification of the HAQ for spondylarthropathies (HAQ-S) and for psoriasis (HAQ-SK) have been developed, but when tested against HAQ their scores were almost identical,[54] suggesting either can be used in PsA.[48] The HAQ is one component of the ACR 20 (50 or 70) response criteria.

The 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).[55] Although the HAQ has been used as a disability measure and is a common outcome measure in PsA trials, it may not sufficiently incorporate all aspects of disease activity (i.e. deformity or damage resulting from disease process, especially in late PsA), therefore, clinical assessment of disease activity and both clinical and radiological assessments of joint damage remain important outcome measures in PsA.[56]

Overall, the advantage of the HAQ as an instrument is that it can measure the functional and psychological impact of the disease. HAQ is conventionally used as a driver of QoL scores and costs in main economic evaluations on the use of biologics and DMARDs in RA.[57–59]

Psoriasis Area and Severity Index

When evaluating the efficacy of interventions in the treatment of PsA, the outcome measures used must assess disease activity in both the joint and the skin.[48] In clinical trials of patients with psoriasis, assessment of the response to treatment is usually based on the Psoriasis Area and Severity Index (PASI). The PASI is also used in trials of PsA; given the various degrees of severity of psoriasis in these patients, not all patients are evaluable for the 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.[48] Although it is widely used, the PASI measure also has a number of 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 errors. It combines an extent and a severity score for each of the four body areas (head, trunk, upper extremities and lower extremities). The extent score of 0–6 is allocated according to the percentage of skin involvement (e.g. 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 of 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 that the 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 (> 36) are not common even in severe psoriasis. Furthermore, it fails to capture the disability that commonly arises from involvement of functionally or psychosocially important areas (hands, feet, face, scalp and genitalia), which together represent only a small proportion of total BSA.

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 primary outcome variable of arthritis in 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. PASI has been chosen as the primary outcome variable of psoriasis in the economic evaluation because it is recommended to assess severity and response in the British Association of Dermatologists (BAD) guidelines and used in the majority of randomised controlled trials (RCTs).

Current service provision

The effective treatment for PsA needs to consider both skin and joint conditions, especially if both are significantly affected. In current services it is rheumatologists who manage the majority of patients with PsA. Although dermatologists focus principally on the cutaneous expression of psoriasis, they frequently use drugs, such as methotrexate (MTX) or biological agents, which may benefit both skin and joints. Patients with severe manifestations of PsA in joints and skin will tend to be managed jointly by rheumatologists and dermatologists, whereas many patients with less severe joint disease may remain under the care of dermatologists alone.

Most treatments for PsA have been borrowed from those used for RA and non-steroidal anti-inflammatory drugs (NSAIDs) are widely used.[10] 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.[13] Local corticosteroid injections are also frequently used,[10] although there is a significant risk of a serious flare in psoriasis when corticosteroids are withdrawn. Disease that is unresponsive to NSAIDs, and in particular polyarticular disease, should be treated with DMARDs in order to reduce the joint damage and prevent disability.[13] It is also suggested that aggressive treatment of early-stage progressive PsA should be used in order to improve prognosis.[13] Again, the treatments used are based on the experience in RA rather than knowledge of the pathophysiology of PsA or trial-based efficacy. Currently, MTX and sulfasalazine are considered the DMARDs of choice, despite the largely empirical evidence for MTX and the modest effects of sulfasalazine.[13] A review of the experience of 100 patients with PsA treated with DMARDs[60] reported that of those treated with sulfasalazine, gold, MTX or hydroxychloroquine over 70% of patients had discontinued due to a lack of efficacy or adverse events (range 35% with MTX to 94% with hydroxychloroquine).

Another DMARD (leflunomide) has, in addition to being licensed for RA, also been licensed for use in PsA. This 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. Clinical trials have demonstrated the efficacy in RA[61] and PsA.[62] Evidence also suggests that clinical responses in patients with RA receiving leflunomide treatment are equivalent to those receiving MTX treatment.[63] Unlike MTX, however, leflunomide has little effect on the skin. Other drugs investigated for the treatment of PsA are auranofin, etretinate, fumaric acid, intramuscular gold, azathioprine, and Efamol Marine.[54] Ciclosporin and penicillamine are also sometimes used in clinical practice.[64]

Costs of current service

Based on prices from the *British National Formulary* (*BNF*),[65] weekly treatment costs with the most commonly used DMARDs in PsA, sulfasalazine and MTX are approximately £2 and < £0.50, respectively. The cost of ciclosporin is approximately £40–80 per week.

Prescriptions for DMARDs for all indications have been rising rapidly in general practice in England from 300,000 per quarter year in December 2003 to over 500,000 in December 2008, with expenditure increasing from £2M per quarter year to nearly £4.5M during this period. In addition to the cost of DMARDs, the cost of NSAIDs was almost £4M per quarter year in

December 2008, although the number of prescriptions and expenditure on NSAIDS has fallen sharply in recent years.[66]

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 of patients with confirmed PsA in the Netherlands found considerable variations among rheumatologists in the delivery of care; 29% failed to diagnose PsA, mainly due to their failure to enquire about skin lesions.[67] 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 for those patients who were correctly diagnosed with PsA than for the remaining patients who were incorrectly diagnosed.

Description of technology under assessment

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, resulting in the migration and activation of T cells, which then release tumour necrosis factor-alpha (TNF-α). TNF-α is one of several proinflammatory cytokines that have been implicated in the pathogenesis of both psoriasis and PsA.[68,69] Newer strategies for the treatment of PsA focus 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.[70] Etanercept, infliximab and adalimumab are among a number of these new biological 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.[10] Infliximab is a murine/human chimeric anti-TNF monoclonal gamma immunoglobulin that inhibits the binding of TNF to its receptor.[10] Adalimumab is a fully humanised monoclonal IgG1 antibody and TNF antagonist.[71] All three biologics are licensed in the UK for the treatment of active and progressive PsA in adults when the response to previous DMARD therapy has been inadequate.

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 £2324, and the annual cost thereafter is £9296. The acquisition costs of adalimumab are the same, based on the recommended dose regimen (40-mg subcutaneous injections administered every other week). The recommended dose for infliximab is 5 mg/kg is given as an intravenous (i.v.) 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, four or five vials of infliximab depending upon the patient's body weight. The initial 3-month acquisition cost of infliximab is estimated to be £5035, assuming four vials, and the annual cost thereafter is £10,912.

Current expenditure on biologic therapies in England is considerable. For all indications, the cost of prescribing in 2008 was £152.2M for etanercept, £102.7M for adalimumab and £77.1M for infliximab, with > 95% of these prescriptions dispensed by hospitals.[72] Expenditure for biologic drugs increased during 2008 by 15% for etanercept, 55% for adalimumab and 25% for infliximab. Among the drugs appraised by the National Institute for Health and Clinical Excellence (NICE), etanercept and adalimumab are now ranked in the top five by estimated cost of prescribing in England.

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Chapter 2

Definition of decision problem

Decision problem

The use of biologics in inflammatory disease is a rapidly evolving area. Etanercept and infliximab were previously evaluated together for their efficacy and safety in PsA in 2006[73] and adalimumab was separately evaluated more recently.[74] There is a need for an up-to-date evaluation of all three biological agents that are licensed for use in the treatment of PsA.

It is important to establish how well these three licensed biologics work in patients with PsA, in terms of both joint and skin response, as well as disease progression. In addition to determining the absolute efficacy of the biologics relative to placebo, it is important to determine their relative clinical effectiveness and cost-effectiveness.

Overall aims and objectives of assessment

To determine the clinical effectiveness, safety and cost-effectiveness of etanercept, infliximab and adalimumab for the treatment of active and progressive PsA in patients who have an inadequate response to standard treatment (including DMARD therapy).

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing clinical effectiveness

A systematic review of the evidence for the clinical effectiveness and safety of etanercept, infliximab and adalimumab for the treatment of active and progressive PsA in patients who have an inadequate response to standard treatment (including DMARD therapy) was conducted following the general principles recommended in the guidance of the Centre for Reviews and Dissemination (CRD) guidance[75] and the quality of reporting of meta-analyses (QUOROM) statement.[76]

Search strategy

The following databases were searched for relevant clinical effectiveness and cost-effectiveness research:

- MEDLINE
- EMBASE
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Science Citation Index (SCI)
- Conference Proceedings Citation Index – Science (CPCI-S)
- ClinicalTrials.gov
- metaRegister of Current Controlled Trials (*m*RCT)
- NHS Economic Evaluation Database (NHS EED)
- Health Economic Evaluations Database (HEED)
- EconLit.

Searches of major bibliographic databases were undertaken in three tranches – for RCTs, for economic evaluations and for studies of serious adverse effects. In the RCT and economic evaluation searches, the etanercept and infliximab search was limited by date (1 April 2004 to date), updating the searches undertaken for the 2006 Health Technology Assessment (HTA) report.[73] The search for adalimumab had no date limits. The searches for studies of adverse effects of all three drugs were not date limited. Internet resources were also searched for information on adverse effects. At the time of receiving the company submission (August 2009), update searches were conducted to ensure that the review remained up to date and covered all relevant evidence at the time of submission. No language or other restrictions were applied. In addition, reference lists of all included studies and industry submissions made to NICE were hand-searched to identify further relevant studies.

The terms for search strategies were identified through discussion between an information specialist and the research team, by scanning the background literature and browsing the MEDLINE medical subject headings (MeSH). As several databases were searched, some degree of duplication resulted. To manage this issue, the titles and abstracts of bibliographic records were imported into ENDNOTE bibliographic management software to remove duplicate records.

Inclusion and exclusion criteria

Two reviewers independently screened all titles and abstracts. Full paper manuscripts of any titles/abstracts that may be relevant were obtained where possible and the relevance of each study was assessed by two reviewers according to the criteria below. Studies were included in the review according to the inclusion criteria, described as follows. Studies that did not meet all of the criteria were excluded and their bibliographic details listed with reasons for exclusion. Any discrepancies were resolved by consensus or consulting a third reviewer if necessary.

Study design

Randomised controlled trials (including any open-label extensions of these RCTs) were included in the evaluation of efficacy. Information on the rate of serious adverse events was sought from regulatory sources [the US Food and Drug Administration (FDA), European Medicines Agency (EMEA)]. If these failed to report the necessary data to calculate event rates then non-randomised studies that provided these data for etanercept, infliximab and adalimumab were included in the review. If multiple non-randomised studies were identified, inclusion was limited to those studies reporting outcomes for a minimum of 500 patients receiving biologic therapy.

Interventions

Etanercept, infliximab and adalimumab were the interventions of interest. Comparators were placebo, another of the three listed agents, or conventional management strategies for active and progressive PsA that have responded inadequately to previous DMARD therapy, excluding TNF inhibitors.

Participants

For the evaluation of the effectiveness of etanercept, infliximab and adalimumab, included studies were of adults with active and progressive PsA with an inadequate response to previous standard therapy (including at least one DMARD). Trials of effectiveness had to specify that the patients had PsA, with the definition and/or the inclusion criteria for PsA stated. For the assessment of adverse effects, studies of patients with other conditions were eligible for inclusion in the review.

Outcomes

The eligible outcomes of effectiveness were measures of the anti-inflammatory response (PsARC, ACR 20/50/70), response of psoriatic skin lesions (PASI), functional measures (HAQ), radiological assessments of disease progression or remission, QoL assessments [e.g. Dermatology Life Quality Index (DLQI)] and overall global assessments.

In terms of the outcomes of adverse events of biologics, we provided an initial overview of previous systematic reviews of biologic safety (see *Results of review of clinical effectiveness*) before conducting our systematic review of adverse events of these agents. Our systematic review specifically focused on the known serious adverse events of these agents: malignancies, severe infections (i.e. those that require i.v. antibiotic therapy and/or hospitalisation or cause death) and reactivation of latent tuberculosis (TB). If additional serious adverse events have been reported to regulatory bodies then the incidence of these were also assessed. In addition, data relating to serious adverse events in indications other than PsA were also considered in our systematic review, provided it was clinically appropriate to do so.

Data extraction strategy

Data on study and participant characteristics, efficacy outcomes, adverse effects, costs to the health service and cost-effectiveness were extracted. Baseline data were extracted where

reported. Data were extracted by one reviewer using a standardised data extraction form and independently checked for accuracy by a second reviewer. The results of data extraction were presented in the structured tables (see *Appendix 3*, *Efficacy data extraction: etanercept/infliximab/adalimumab*). Disagreements were resolved through consensus, or consulting a third reviewer if necessary. Attempts were made, where possible, to contact authors for missing data. Data from studies with multiple publications were extracted and reported as a single study. In the rare case of minor discrepancies for the same data between published and unpublished data, data from published sources were used.

Quality assessment strategy

The quality of RCTs and other study designs were assessed using standard checklists.[75] Regarding the additional studies reviewed for data on serious adverse events: as all observational studies are prone to confounding and bias to some extent, non-randomised studies including < 500 patients receiving biologics were excluded from the review. The assessment was performed by one reviewer and checked independently by a second. Disagreements were resolved through consensus or by consulting a third reviewer if necessary.

Data analysis

Where sufficient clinically and statistically homogeneous data were available, data were pooled using standard meta-analytic methods. The levels of clinical and methodological heterogeneity were investigated, and statistical heterogeneity was assessed using Q- and I^2-statistics. Given the small number of trials available, a fixed-effects model was used to pool outcomes where pooling was appropriate. Sensitivity analyses were undertaken when permitted by sufficient data (e.g. exclusion of concomitant MTX treatment). The potential short- and long-term benefits of etanercept, infliximab and adalimumab on both the psoriasis and arthritis components of PsA were investigated. The rates of serious adverse effects of these biologic agents were synthesised narratively.

As trials conducting head-to-head comparisons of etanercept, infliximab and adalimumab were not available the possibility of conducting some form of indirect comparison was investigated. Indirect comparisons are useful analytic tools when direct evidence on comparisons of interest is absent or sparse.[77] Meta-analysis using indirect comparisons enables data from several sources to be combined, while taking into account differences between the different sources, in a similar way to, but distinct from, how a random-effects model takes into account between-trial heterogeneity. As with a mixed-treatment comparison (MTC), Bayesian indirect comparisons need a 'network of evidence' to be established between all of the interventions of interest. The three drugs being evaluated all have a common comparator: placebo. It is this common comparator that allows the network between etanercept, infliximab and adalimumab to be established and provide information on the benefits of these agents relative to placebo and each other.

To help inform both the clinical review and the economic modelling four separate outcomes were considered. These outcomes were: PsARC response, HAQ score conditional on PsARC response, ACR 20/50/70 responses and PASI 50/75/90 responses. All outcomes were evaluated at 12 weeks. The evidence synthesis was undertaken using WINBUGS (version 1.4.2). WINBUGS is a Bayesian analysis software tool that, through the use of Markov chain Monte Carlo, calculates posterior distributions for the parameters of interest given likelihood functions derived from data and prior probabilities. Full details of the Bayesian indirect comparison methods and the WINBUGS codes along for the four different analyses are presented in *Appendix 5*.

Results of review of clinical effectiveness

Quantity and quality of research available

A total of 1320 records were identified from both the clinical effectiveness and adverse event searches (*Figure 1*). Details of studies excluded at the full publication stage are provided in *Appendix 4*.

Randomised controlled trials and extensions in psoriatic arthritis

Of the 701 studies identified from the search for RCTs, a total of 43 publications, representing multiple publications of six RCTs and their extensions met the inclusion criteria for the review of efficacy.[51,52,78–118] Two placebo-controlled RCTs in patients with PsA were found for each of the three agents: etanercept,[52,78,97,99,105,107,110] infliximab[79–82,89–91,95,96,98,106,109,111–118] and adalimumab.[51,83,88,92,93,100–104] Baseline characteristics from all six RCTs are presented in *Table 1*.

Additional adverse event studies

In total, 742 records were identified from the separate search for larger studies reporting adverse event rates for biologic agents in any indication. Of these records, 32 publications reported treatment with etanercept, infliximab or adalimumab in 500 or more patients, and reported either adverse event rates directly or provided sufficient information to calculate these rates (*Figure 1*).[89,97,99,119–148]

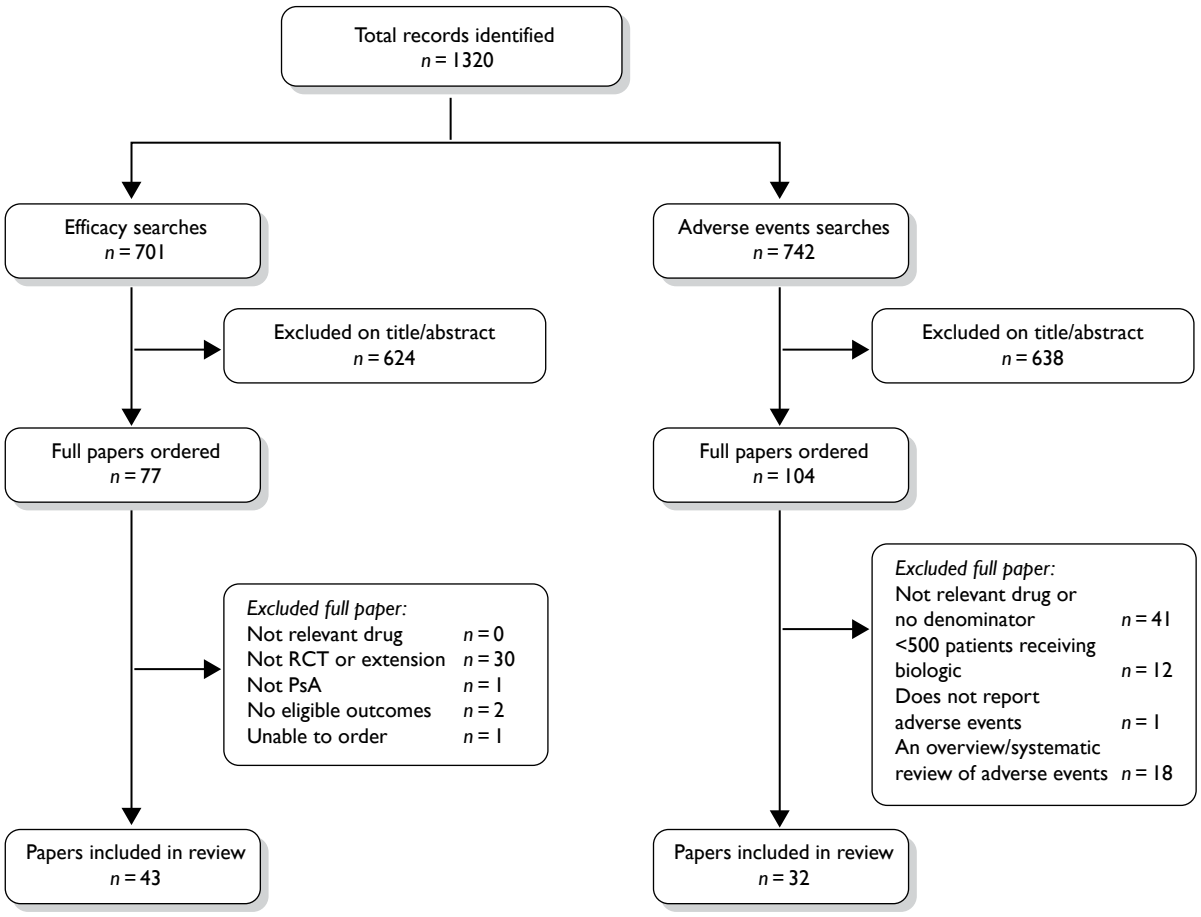

FIGURE 1 Flow chart showing the number of studies identified and included.

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TABLE 1 Summary of trial population characteristics

	Etanercept				Infliximab				Adalimumab			
	Mease 2000[78]		Mease 2004[52,97,99,105,107,110]		IMPACT[79–81,89,96,109,111,113–115,117,118]		IMPACT 2 [82,90,91,95,98,106,112,116]		ADEPT[51,88,92,93,100–104]		Genovese 2007[83]	
	Etanercept (*n* = 30)	Placebo (*n* = 30)	Etanercept (*n* = 101)	Placebo (*n* = 104)	Infliximab (*n* = 52)	Placebo (*n* = 52)	Infliximab (*n* = 100)	Placebo (*n* = 100)	Adalimumab (*n* = 151)	Placebo (*n* = 162)	Adalimumab (*n* = 51)	Placebo (*n* = 49)
Age (years): mean (SD)	46.0 (30.0–70.0)[a]	43.5 (24.0–63.0)[a]	47.6 (18–76)[a]	47.3 (21–73)[a]	45.7 (11.1)	45.2 (9.7)	47.1 (12.8)	46.5 (11.3)	48.6 (12.5)	49.2 (11.1)	50.4 (11.1)	47.7 (11.3)
Male (%)	53	60	57	45	58	58	71	51	56	55	57	51
Duration of PsA (years): mean (SD)	9.0 (1–31)[a]	9.5 (1–30)[a]	9.0 (–)[a]	9.2 (–)[a]	8.7 (8.0)	8.5 (6.4)	8.4 (7.2)	7.5 (7.8)	9.8 (8.3)	9.2 (8.7)	7.5 (7.0)	7.2 (7.0)
Duration of psoriasis (years): mean (SD)	19.0 (4–53)[a]	17.5 (2–43)[a]	18.3 (–)[a]	19.7 (–)[a]	16.9 (10.9)	19.4 (11.6)	16.2 (11.0)	16.8 (12.0)	17.2 (12.0)	17.1 (12.6)	18.0 (13.2)	13.8 (10.7)
Number of prior DMARDs: mean (SD)	1.5	2.0	1.6	1.7	–	–	–	–	1.5	1.5	1.7	2.1
Proportion of patients with numbers of previous DMARDs[b]	–	–	27% = 0 40% = 1 20% = 2	21% = 0 50% = 1 19% = 2	0% = 0 52% = 1 37% = 2–3 12% = 3+	2% = 0 38% = 1 48% = 2–3 12% = 3+	71% = 1–2 12% = 2+	67% = 1–2 9% = 2+	–	–	–	
Concomitant therapies during study (%)												
Corticosteroids	20	40	19	15	17	29	15	10	–	–	–	–
NSAIDs	67	77	88	83	89	79	71	73	–	–	73	86
MTX	47	47	45	49	46	65	47	45	51	50	47	47
Hydroxychloroquine	–	–	–	–	–	–	–	–	–	–	16	16
Sulfasalazine	–	–	–	–	–	–	–	–	–	–	8	14
Leflunomide	–	–	–	–	–	–	–	–	–	–	6	4
Other DMARDs	–	–	–	–	–	–	–	–	–	–	2	6
Type of PsA (%)												
DIP joints in hand and feet	–	–	51	50	–	–	–	–	–	–	–	–
Arthritis mutilans	–	–	1	2	–	–	–	–	1	0	0	0

continued

TABLE 1 Summary of trial population characteristics *(continued)*

	Etanercept				Infliximab				Adalimumab			
	Mease 2000[78]		Mease 2004[52,97,99,105,107,110]		IMPACT[79–81,89,96,109,111,113–115,117,118]		IMPACT 2 [82,90,91,95,98,106,112,116]		ADEPT[51,88,92,93,100–104]		Genovese 2007[83]	
	Etanercept (*n*=30)	Placebo (*n*=30)	Etanercept (*n*=101)	Placebo (*n*=104)	Infliximab (*n*=52)	Placebo (*n*=52)	Infliximab (*n*=100)	Placebo (*n*=100)	Adalimumab (*n*=151)	Placebo (*n*=162)	Adalimumab (*n*=51)	Placebo (*n*=49)
Polyarticular arthritis	–	–	86	83	100	100	–	–	64	70	82	84
Asymmetric peripheral arthritis	–	–	41	38	–	–	–	–	25	25	10	14
Ankylosing arthritis	–	–	3	4	–	–	–	–	1	0	2	2
TJC: mean (SD)	22.5 (11, 32)[b]	19.0 (10, 39)[b]	20.4 (–)[b]	22.1 (–)[b]	23.7 (13.7)	20.4 (12.1)	24.6 (14.1)	25.1 (13.3)	23.9 (17.3)	25.8 (18.0)	25.3 (18.3)	29.3 (18.1)
SJC: mean (SD)	14.0 (8, 23)[b]	14.7 (7, 24)[b]	15.9 (–)[b]	15.3 (–)[b]	14.6 (7.5)	14.7 (8.2)	13.9 (7.9)	14.4 (8.9)	14.3 (12.2)	14.3 (11.1)	18.2 (10.9)	18.4 (12.1)
HAQ (0–3): mean (SD)	1.3 (0.9, 1.6)[b]	1.2 (0.8, 1.6)[b]	1.1 (–)[b]	1.1 (–)[b]	1.2 (0.7)	1.2 (0.7)	1.1 (0.6)	1.1 (0.6)	1.0 (0.6)	1.0 (0.7)	0.9 (0.5)	1.0 (0.7)
Patients evaluable for PASI at baseline: no. (%)	19 (63%)[c]	19 (63%)[c]	CiC	CiC	22 (42%)[d]	17 (33%)[d]	83 (83%)[c]	87 (87%)[c]	70 (46%)[c]	70 (43%)[c]	–	–
PASI (0–72) at baseline among patients evaluable for PASI: mean (SD)	10.1 (2.3–30.0)[a]	6.0 (1.5–17.7)[a]	CiC	CiC	8.6 (6.6)	8.1 (6.6)	11.4 (12.7)	10.2 (9.0)	7.4 (6.0)	8.3 (7.2)	–	–

ADEPT, Adalimumab Effectiveness in Psoriatic Arthritis Trial; CiC, commercial-in-confidence data removed; IMPACT, Infliximab Multinational Psoriatic Arthritis Controlled Trial; SD, standard deviation.

a Median (range).

b Median (25th, 75th percentile).

c Patients with ≥3% BSA psoriasis at baseline.

d Patients with a baseline PASI score of ≥2.5.

Assessment of effectiveness

Efficacy of etanercept

Both trials evaluating etanercept for PsA were double-blind and placebo-controlled, and both were rated as 'good' on the quality assessment rating (*Table 2*).[52,78,97,99,105,107,110] Both trials were available as industry trial reports and journal publications.

The baseline characteristics of the trial population are summarised in *Table 1*. Both trials were of adults (aged 18–70 years), with active PsA (defined in both trials as at least three swollen joints and at least three tender or painful joints, although only the more recent trial[52,97,99,105,107,110] specified stable plaque psoriasis). Patients in both trials had demonstrated an inadequate response to NSAIDs. Over 70% of the patients in the larger trial[52,97,99,105,107,110] had previously used at least one DMARD. Over 80% of patients in the Mease *et al.*[52,97,99,105,107,110] trial had polyarticular disease, indicating that, overall, the disease was severe. Patients were not required to have active psoriasis at baseline, but 77% of etanercept patients and 73% of placebo patients did have. The proportion of patients with spine involvement and arthritis mutilans at baseline was reported only for the larger trial, 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 disease activity (TJC, SJC, HAQ at baseline, plus baseline and previous medication), significant differences between the populations in terms of overall disease severity are unlikely. Patients taking stable doses of MTX or corticosteroids were permitted to continue with that dose and randomisation was stratified for MTX use at baseline. 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

TABLE 2 Results of quality assessment for trials of etanercept

	Study	
Quality assessment criteria	**Mease 2000[78]**	**Mease 2004[52,97,99,105,107,110]**
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?	NR	NR
Adequate baseline details presented?	Y	Y
Baseline comparability?	Y	Y
Similar cointerventions?	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; NR, not reported; Y, yes.

patients for whom etanercept is recommended for use: these patients, according to the BSR, would have demonstrated a lack of response to at least two DMARDs.[149]

In both trials, etanercept was administered by subcutaneous (s.c.) injection twice weekly at a dose of 25 mg. Treatment with active drug or placebo was administered for 12 weeks in the smaller trial[78] and for 24 weeks in the larger trial.[52,97,99,105,107,110] 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, ACR 20/50/70 and HAQ at week 12. The primary outcome variable in the Mease 2000 trial[78] was PsARC, whereas in the Mease *et al.* [52,97,99,105,107,110] trial it was ACR 20. Data on PASI at week 12 are available from the small[78] trial only. RCT outcome data for PsARC, ACR 20/50/70, HAQ, PASI and radiographic assessment of progression at week 24 are available from the larger trial[52,97,99,105,107,110] ($n = 205$). In addition, a subgroup analyses by concomitant MTX use provided additional PsARC, ACR 20/50/70 data at weeks 12 and 24. As subgroup analyses in already fairly small trials, the findings generated must be interpreted with some caution. They are useful, however, to explore the influence concomitant MTX has on the main treatment effect. All outcome data are summarised in *Table 3*, with pooled 12-week data shown 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 4*.

Efficacy after 12 weeks' treatment

The individual trial results (*Table 3*) and 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 response, 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 response, demonstrating a basic degree of efficacy in terms of arthritis-related symptoms. Around 45% of patients treated with etanercept achieved an ACR 50 response, and around 12% achieved an ACR 70 response, demonstrating a good level of efficacy. The subgroup analyses conducted on the Mease *et al.* [52,97,99,105,107,110] data revealed that the effect of etanercept was not dependent on patients' concomitant use, or not, of MTX. The PASI results from Mease *et al.*[78] indicate some beneficial effect on psoriasis at 12 weeks; however, the data were too sparse (38 patients in total) to establish statistical significance. The statistically significant reduction in HAQ score with etanercept compared with placebo indicates 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, although these data were available only for one trial (see *Table 3*). As at 12 weeks, the subgroup analyses conducted on the Mease *et al.* [52,97,99,105,107,110] data revealed that the effect of etanercept was not dependent upon patients' concomitant use, or not, of MTX. The size of treatment effect did not appear greater at 24 weeks than at 12 weeks.

At 24 weeks, the TSS annualised rate of progression was statistically significantly lower in patients treated with etanercept than in patients receiving placebo. This treatment difference did not vary with or without concomitant MTX use. However, this duration of follow-up is to be considered short and barely adequate for this outcome.

TABLE 3 Etanercept efficacy outcomes: RCT data

Outcomes		Etanercept: *n* (%)	Placebo: *n* (%)	RR or mean difference (95% CI)
Mease 2000,[78] 12 weeks				
PsARC[a]		26/30 (87)	7/30 (23)	3.71 (1.91 to 7.21)
ACR 20		22/30 (73.0)	4/30 (13)	5.50 (2.15 to 14.04)
ACR 50		15/30 (50.0)	1/30 (3)	15.00 (2.11 to 106.49)
ACR 70		4/30 (13)	0/30 (0)	9.00 (0.51 to 160.17)
HAQ% change from baseline: mean (SD)		*n* = 29 (64.2–38.7)	*n* = 30 (9.9–42.9)	CiC
PASI 50		8/19 (42)	4/19 (21)	2.00 (0.72 to 5.53), *p* = 0.295
PASI 75		5/19 (26)	0/19 (0)	11.00 (0.65 to 186.02), *p* = 0.0154
Mease 2004,[52,97,99,105,107,110] 12 weeks				
PsARC	All pts	73/101 (72)	32/104 (31)	2.35 (1.72 to 3.21), *p* < 0.001
	+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)
ACR 20[a]	All pts	60/101 (59)	16/104 (15)	3.86 (2.39 to 6.23), *p* < 0.001
	+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)
ACR 50	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)
ACR 70	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% change from baseline: mean (SD)		(*n* = 96) 53.5, (43.4)	(*n* = 99) 6.3, (42.7)	CiC
Mease 2004,[52,97,99,105,107,110] 24 weeks				
PsARC	All pts	71/101 (70)	24/104 (23)	3.05 (2.10 to 4.42), *p* < 0.001
	+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)
ACR 20	All pts	50/101 (50)	14/104 (13)	3.68 (2.17 to 6.22), *p* < 0.001
	+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)
ACR 50	All pts	37/101 (37)	4/104 (4)	9.52 (3.52 to 25.75), *p* < 0.001
	+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)
ACR 70	All pts	9/101 (9)	1/104 (1)	9.27 (1.20 to 71.83), *p* = 0.009
	+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% change from baseline: mean (SD)		(*n* = 96) 53.6 (55.1)	(*n* = 99) 6.4 (49.6)	47.20 (32.47 to 61.93), *p* < 0.001
PASI 50		31/66 (47)	11/62 (18);	2.65 (1.46 to 4.80), *p* < 0.001
PASI 75		15/66 (23)	2/62 (3)	7.05 (1.68 to 29.56), *p* = 0.001
PASI 90		4/66 (6)	2/62 (3)	1.88 (0.36 to 9.90), *p* = 0.681
TSS mean (SD) annualised rate of progression	All pts	(*n* = 101) –0.03 (0.73)	(*n* = 104) 0.53 (1.39)	–0.56 (–0.86 to –0.26), *p* = 0.0006
	+MTX	(*n* = 42) 0.06 (0.76)	(*n* = 43) 0.48 (1.00)	–0.42 (–0.80 to –0.04), *p* = 0.12345
	–MTX	(*n* = 59) –0.09 (0.71)	(*n* = 61) 0.57 (1.62)	–0.66 (–1.11 to –0.21), *p* = 0.0014

CI, confidence interval; CiC, commercial-in-confidence data removed; pts, patients; SD, standard deviation.
a Primary outcome variable in the respective trials.

TABLE 4 Meta-analysis of etanercept efficacy data: outcomes at 12 weeks

Trial	Etanercept	Placebo	RR or mean difference (95% CI)
PsARC			
Mease 2000[78]	26/30 (87%)	7/30 (23%)	3.71 (1.91 to 7.21)
Mease 2004[52,97,99,105,107,110]	73/101 (72%)	32/104 (31%)	2.35 (1.72 to 3.21), $p<0.001$
			Pooled RR (95% CI), p-value, I^2: 2.60 (1.96 to 3.45), $p<0.00001$, $I^2=34\%$
ACR 20			
Mease 2000[78]	22/30 (73%)	4/30 (13%)	5.50 (2.15 to 14.04)
Mease 2004[52,97,99,105,107,110]	60/101 (59%)	16/104 (15%)	3.86 (2.39 to 6.23), $p<0.001$
			Pooled RR (95% CI), p-value, I^2: 4.19 (2.74 to 6.42), $p<0.00001$, $I^2=0\%$
ACR 50			
Mease 2000[78]	15/30 (50%)	1/30 (3%)	15.00 (2.11 to 106.49)
Mease 2004[52,97,99,105,107,110]	38/101 (38%)	4/104 (4%)	9.78 (3.62 to 26.41), $p<0.001$
			Pooled RR (95% CI), p-value, I^2: 10.84 (4.47 to 26.28), $p<0.00001$, $I^2=0\%$
ACR 70			
Mease 2000[78]	4/30 (13%)	0/30 (0%)	9.00 (0.51 to 160.17)
Mease 2004[52,97,99,105,107,110]	11/101 (11%)	0/104 (0%)	23.68 (1.41 to 396,53), $p<0.001$
			Pooled RR (95% CI), p-value, I^2: 16.28 (2.20 to 120.54), $p=0.006$, $I^2=0\%$
HAQ% change from baseline: mean (SD)			
Mease 2000[78]	($n=29$) –64.2 (CiC)	($n=30$) –9.9 (CiC)	–54.3 (33.47 to 75.13)
Mease 2004[52,97,99,105,107,110]	($n=96$) –53.5 (CiC)	($n=99$) –6.3 (CiC)	–47.20 (35.11 to 59.29)
			Pooled RR (95% CI), p-value, I^2: –48.99 (38.53 to 59.44), $p<0.00001$, $I^2=0\%$

CiC, commercial-in-confidence data removed.

At 24 weeks, the treatment effect on psoriasis favoured etanercept with relative risks (RRs) for PASI 75 of 7.05 [95% confidence interval (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 result for PASI 75 and PASI 50 was statistically significant despite there being only 66 patients on etanercept evaluable for psoriasis.[52,97,99,105,107,110]

Longer-term follow-up

The results for long-term follow-up are summarised in *Table 5*. The data 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 annualised rate of progression TSS for all patients was –0.03 [standard deviation (SD 0.87)] indicating that on average no clinically significant progression of joint erosion had occurred. Limited 2-year data indicated little change in mean TSS, although data on patient numbers or variability were not reported.

TABLE 5 Etanercept efficacy outcomes: uncontrolled follow-up data

Trial	Type of data	Duration	Outcomes		Etanercept/placebo
Mease 2000[78]	Uncontrolled	36 weeks	PsARC		26/30 (87%)
			ACR 20		26/30 (87%)
			ACR 50		19/30 (63%)
			ACR 70		10/30 (33%)
			HAQ% change from baseline: mean (median)		CiC
			PASI 75		7/19 (37%)
			PASI 50		11/19 (58%)
Mease 2004[52,97,99,105,107,110]	Uncontrolled	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 (0.87)
				+MTX	(*n* = 42) 0.01 (0.81)
				–MTX	(*n* = 59) –0.13 (0.91)
		24 months	TSS mean change from baseline		Etanercept/etanercept –0.38
					Placebo/etanercept 0.50

CiC, commercial-in-confidence data removed; pts, patients.

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 efficacy for etanercept in the treatment of PsA. Conclusions to be drawn from these data are limited by the small sample size and the short duration of one of the trials.
- There is evidence from two RCTs that etanercept treatment improves patients' functional status as assessed using the HAQ score.
- There is limited evidence from the two RCTs that etanercept treatment has a beneficial effect on the psoriasis component of the disease.
- Uncontrolled follow-up of patients indicate 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. Data from uncontrolled follow-up indicate that, on average, disease progression may be halted for at least 1 year; however, these data may not be reliable.

Efficacy of infliximab

The literature search identified two RCTs of infliximab for the treatment of PsA.[79–82,89–91,95,96,98,106,109,111–118] Both were rated as 'good' by the quality assessment (*Table 6*). The trials were reported in published papers and abstracts, and the industry trial report was made available.

Both were double-blind, placebo-controlled trials of adult patients with active PsA, randomising a total of 304 patients. All patients had been diagnosed with PsA for at least 6 months, with a negative RF and active disease including 5+ swollen/tender joints. All patients must have had an inadequate response to at least one DMARD.[79–82,89–91,95,96,98,106,109,111–118] One trial required patients to have active plaque psoriasis with at least one qualifying target lesion (≥2-cm diameter).[82,90,91,95,98,106,112,116] The earlier of the two trials did not require patients to have active psoriasis at baseline, but 42% of infliximab patients and 33% of placebo patients did have (defined as PASI score of at least 2.5).[79–81,89,96,109,111,113–115,117,118] The proportion of patients with spine involvement, arthritis mutilans and erosions at baseline was not reported for either trial, so the severity of disease across the populations is unknown. The baseline characteristics of the trial populations are summarised in *Table 1*. These demonstrate that the trial populations are

TABLE 6 Results of quality assessment for trials of infliximab

	Study	
Quality assessment criteria	**IMPACT**[79–81,89,96,109,111,113–115,117,118]	**IMPACT 2**[82,90,91,95,98,106,112,116]
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?	NR	NR
Adequate baseline details presented?	Y	Y
Baseline comparability?	Y	Y
Similar cointerventions?	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

IMPACT, Infliximab Multinational Psoriatic Arthritis Controlled Trial; ITT, intention to treat; NR, not reported; Y, yes.

broadly similar, are likely to be representative of a population with quite severe PsA requiring further DMARD or biologic therapy, and that the treatment and placebo groups were well balanced. Relative to the patients for whom infliximab treatment is recommended in practice, these trial populations may be less severely affected, with only around one-half in the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT)[79–81,89,96,109,111,113–115,117,118] and possibly even fewer in IMPACT 2,[82,90,90,95,98,106,112,116] having failed to respond to two or more DMARDs (failure to respond to DMARDs as defined by the BSR).[149]

In the RCT phase of the IMPACT trial,[79–81,89,96,109,111,113–115,117,118] 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. Patients in the IMPACT 2 trial[82,90,91,95,98,106,112,116] 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. Further infusions of infliximab were administered to all patients in an open-label fashion (timing dependent upon whether they were originally randomised to infliximab, or crossed over from placebo either at week 16 or 24) with further follow-up at week 54.

The primary outcome variable in these trials was ACR 20 at 14 or 16 weeks. The two trials also reported 14-week and/or 16-week outcome data for ACR 50, ACR 70, PsARC, HAQ, PASI 50, PASI 75 and PASI 90 (RCT data). IMPACT 2[82,90,91,95,98,106,112,116] also maintained randomisation and reported these outcomes at week 24. Both studies reported longer-term open-label follow-up of patients after 50 and 54 weeks (IMPACT[79–81,89,96,109,111,113–115,117,118] and IMPACT 2,[82,90,91,95,98,105,112,115] respectively). All data are summarised in *Table 7*, with pooled data presented in *Table 8*.

TABLE 7 Infliximab efficacy outcomes: RCT data

Trial	Duration (weeks)	Outcomes		Infliximab	Placebo	RR or mean difference (95% CI)
IMPACT (randomised period)[79–81,89,96,109,111,113–115,117,118]	14	PsARC		40/52 (76.9%)	7/52 (13.5%)	5.71 (2.82 to 11.57)
		ACR 20	All pts	35/52 (67.3%)	6/52 (11.5%)	5.83 (2.68 to 12.68)
			+MTX	NR	NR	–
			–MTX	NR	NR	–
		ACR 50		19/52 (36.5%)	1/52 (1.9%)	19.00 (2.64 to 136.76)
		ACR 70		11/52 (21.2%)	0/52 (0%)	23.00 (1.39 to 380.39)
	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) $p<0.01$
			+MTX	15/24 (62.5%)	4/34 (11.8%)	5.31 (2.01 to 14.03), $p<0.01$
			–MTX	19/28 (67.9%)	1/18 (5.6%)	12.21 (1.79 to 83.46), $p<0.01$
		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)% change from baseline		($n=48$) –49.8 (56.8)	($n=47$) 1.6 (56.9)	–51.4 (–74.5 to –28.3), $p<0.01$
		PASI 50[a]		22/22 (100%)	0/16 (0%)	33.26 (2.17 to 510.71)
		PASI 75[a]		15/22 (68.2%)	0/16 (0%)	22.91 (1.47 to 356.81)
		PASI 90[a]		8/22 (36.4%)	0/16 (0%)	12.57 (0.78 to 203.03)
		PASI mean (SD) change from baseline[b]		($n=42$) –4.1 (3.9)	($n=38$) 0.9 (3.7)	–5 (–6.8 to –3.3), $p<0.01$
IMPACT 2 (randomised)[82,90,91,95,98,106,112,116]	14	PsARC		77/100 (77%)	27/100 (27%)	2.85 (2.03 to 4.01)
		ACR 20	All pts	58/100 (58%)	11/100 (11%)	5.27 (2.95 to 9.44)
			+MTX	NR	NR	–
			–MTX	NR	NR	–
		ACR 50		36/100 (36%)	3/100 (3)%	12.00 (3.82 to 37.70)
		ACR 70		15/100 (15%)	1/100 (1%)	15.00 (2.02 to 111.41)
		HAQ mean (SD)% change from baseline		($n=100$) –48.6 (43.3)	($n=100$) 18.4 (90.5)	–67.00 (–86.66 to –47.33)
		PASI 50[b]		CiC	CiC	CiC
		PASI 75[b]		CiC	CiC	CiC
		PASI 90[b]		CiC	CiC	CiC
		PASI mean (SD)% change from baseline		NR	NR	–
	24	PsARC		70/100 (70%)	32/100 (32%)	2.19 (1.60 to 3.00)
		ACR 20	All pts	54/100 (54%)	16/100 (16%)	3.38 (2.08 to 5.48)
			+MTX	NR	NR	–
			–MTX	NR	NR	–
		ACR 50		41/100 (41%)	4/100 (4%)	10.25 (3.81 to 27.55)
		ACR 70		27/100 (27%)	2/100 (2%)	13.5 (3.30 to 55.26)
		PASI 50[b]		CiC	CiC	CiC
		PASI 75[b]		CiC	CiC	CiC
		PASI 90[b]		CiC	CiC	CiC
		HAQ mean (SD)% change from baseline		($n=100$) –46.0 (42.5)	($n=100$) 19.4 (102.8)	–65.40 (–87.20 to –43.60)
		PASI mean (SD)% change from baseline		NR	NR	–
		Total modified van der Heijde–Sharp score: mean (SD) change from baseline		–0.70 (2.53)	0.82 (2.62)	–

CiC, commercial-in-confidence data removed; NR, not reported; pts, patients.

a PASI 50/75/90 outcomes are for subgroup of patients with PASI scores ≥2.5 at baseline.

b Two sites did not perform baseline PASI measurements.

Efficacy after 14–16 weeks' treatment

At 14 weeks, both trials reported a significant improvement in the PsA-specific PsARC measure for patients receiving infliximab, relative to those receiving placebo (pooled RR 3.44, 95% CI 2.53 to 4.69 – *Table 8*). There was evidence of statistical heterogeneity ($I^2 = 68\%$) between the two study estimates, due to the different placebo response rates (13.5% vs 27%). PsARC response on infliximab was around 77% in both trials.

The pooled RR for ACR 20 at 14 weeks was 5.47 (95% CI 3.43 to 8.71), with an overall response of 61% in infliximab-treated patients, demonstrating a clear degree of efficacy of infliximab in

TABLE 8 Meta-analysis of infliximab efficacy data: outcomes at 14 weeks

Trial	Outcomes	Infliximab	Placebo	RR or mean difference (95% CI)
	PsARC			
IMPACT[79–81,89,96,109,111,113–115,117,118]		40/52 (76.9%)	7/52 (13.5%)	5.71 (2.82 to 11.57)
IMPACT 2[82,90,91,95,98,106,112,116]		77/100 (77%)	27/100 (27%)	2.85 (2.03 to 4.01)
	Pooled RR (95% CI) to *p*-value			3.44 (2.53 to 4.69), $p<0.0001$
	I^2			$I^2 = 68\%$
	ACR 20			
IMPACT[79–81,89,96,109,111,113–115,117,118]		35/52 (67.3%)	6/52 (11.5%)	5.83 (2.68 to 12.68)
IMPACT 2[82,90,91,95,98,106,112,116]		58/100 (58%)	11/100 (11%)	5.27 (2.95 to 9.44)
	Pooled RR (95% CI), *p*-value			5.47 (3.43 to 8.71)
	I^2			$I^2 = 0\%$
	ACR 50			
IMPACT[79–81,89,96,109,111,113–115,117,118]		19/52 (36.5%)	1/52 (1.9%)	19.00 (2.64 to 136.76)
IMPACT 2[82,90,91,95,98,106,112,116]		36/100 (36%)	3/100 (3%)	12.00 (3.82 to 37.70)
	Pooled RR (95% CI), *p*-value			13.75 (5.11 to 37.00), $p<0.0001$
	I^2			$I^2 = 0\%$
	ACR 70			
IMPACT[79–81,89,96,109,111,113–115,117,118]		11/52 (21.2%)	0/52 (0%)	23.00 (1.39 to 380.39)
IMPACT 2[82,90,91,95,98,106,112,116]		15/100 (15%)	1/100 (1%)	15.00 (2.02 to 111.41)
	Pooled RR (95% CI), *p*-value			17.67 (3.46 to 90.14), $p=0.001$
	I^2			$I^2 = 0\%$
	PASI 50			
IMPACT[79–81,89,96,109,111,113–115,117,118]		22/22 (100%)	0/16 (0%)	33.26 (2.17 to 510.71)
IMPACT 2[82,90,91,95,98,106,112,116]		CiC	CiC	CiC
	Pooled RR (95% CI), *p*-value			10.58 (5.47 to 20.48), $p<0.0001$[a]
	I^2			$I^2 = 0\%$
	PASI 75			
IMPACT[79–81,89,96,109,111,113–115,117,118]		15/22 (68.2%)	0/16 (0%)	22.91 (1.47 to 356.81)
IMPACT 2[82,90,91,95,98,106,112,116]		CiC	CiC	CiC
	Pooled RR (95% CI), *p*-value			26.68 (7.79 to 91.44), $p<0.0001$[a]
	I^2			$I^2 = 0\%$

CiC, commercial-in-confidence data removed.

TABLE 8 Meta-analysis of infliximab efficacy data: outcomes at 14 weeks *(continued)*

Trial	Outcomes	Infliximab	Placebo	RR or mean difference (95% CI)
	PASI 90			
IMPACT[79–81,89,96,109,111,113–115,117,118]		8/22 (36.4%)	0/16 (0%)	12.57 (0.78 to 203.03)
IMPACT 2[82,90,91,95,98,106,112,116]		CiC	CiC	CiC
	Pooled RR (95% CI), *p*-value			40.01 (5.93 to 270.15), $p<0.0001$[a]
	I^2			$I^2=0\%$
	HAQ% change from baseline: mean (SD)			
IMPACT[79–81,89,96,109,111,113–115,117,118]		(*n*=48) –49.8 (56.8)	(*n*=47) 1.6 (56.9)	–51.4 (–74.27 to –28.54)
IMPACT 2[82,90,91,95,98,106,112,116]		(*n*=100) –48.6 (43.3)	(*n*=100) 18.4 (90.5)	–67.00 (–86.66 to –47.33)
	Pooled WMD (95% CI), *p*-value			–60.37 (–75.28 to –45.46)
	I^2			$I^2=3\%$

CiC, commercial-in-confidence data removed.
a Combined 14- and 16-week data.

terms of arthritis-related symptoms. As very few patients receiving placebo achieved an ACR 50 or ACR 70 response, the pooled RRs clearly favoured infliximab in terms of these outcomes, although the limited number of observations mean that there is considerable uncertainty around these pooled estimates, as reflected by their CIs (see *Table 8*). Despite the potentially large relative effects, it should also be noted that only the minority of infliximab-treated patients achieved an ACR 50 or ACR 70 response at 14 weeks (36% and 17%, respectively). Data from the IMPACT trial[79–81,89,96,109,111,113–115,117,118] indicated no significant difference in ACR 20 response at 16 weeks between patients with and without concomitant MTX, although the number of patients in each of these groups was small.

As with the ACR outcomes, few patients receiving placebo demonstrated skin improvements over 14–16 weeks in terms of a PASI response; the pooled RR for PASI 50 was 10.58 (95% CI 5.47 to 20.48), demonstrating a clear degree of efficacy of infliximab in terms of skin-related symptoms. PASI 75 and PASI 90 response measures favoured infliximab even more strongly, although it should be noted that PASI outcomes were recorded only for those patients with a score of at least 2.5 at baseline. Forty-two per cent of patients receiving infliximab achieved the highest level of skin response (PASI 90), although again there is considerable uncertainty around the estimates (see *Table 7*).

The statistically significant pooled percentage change from baseline in HAQ score with infliximab compared with placebo [mean difference –60.37 (–75.28 to –45.46)] indicates a beneficial effect of infliximab on functional status.

Efficacy after 24 weeks

The IMPACT 2 trial[82,90,91,95,98,106,112,116] maintained randomisation for 24 weeks. The data for all measures of joint disease, psoriasis and HAQ are similar to those observed at the earlier 14-week follow-up, suggesting that the benefits of infliximab are maintained up to 24 weeks of treatment (see *Table 7*). Change from baseline in modified van der Heijde–Sharp score significantly differed between infliximab and placebo groups, indicating that infliximab may inhibit progression of joint damage at 24 weeks (see *Table 7*).

Longer-term follow-up

The data for longer-term follow-up (50 or 54 weeks) from the two IMPACT trials are summarised in *Table 9*. These data are uncontrolled and may therefore be unreliable. Also, the duration of treatment varied between participants, as some will have crossed over from placebo treatment. However, the data broadly indicate that the levels of efficacy achieved with infliximab in terms of joint disease, psoriasis and HAQ after 14–24 weeks' treatment might be maintained in the medium term.

In terms of radiographic assessment, there was no significant change from baseline in the total modified van der Heijde–Sharp score for those infliximab-treated patients followed up at 50 or 54 weeks in the two studies, suggesting infliximab may inhibit progression of joint damage. However, as with other post-24-week outcomes, there was no placebo group for comparison.

Summary of the efficacy of infliximab in the treatment of PsA

- There is evidence from two double-blind placebo controlled trials of a good level of efficacy for infliximab 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 short duration of the controlled trials; 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.
- Radiographic data from uncontrolled follow-up of infliximab trials suggest that the drug may delay the progression of joint disease in PsA, although these data are not of high quality.

TABLE 9 Infliximab efficacy outcomes: uncontrolled follow-up data

Trial	Duration (weeks)	Outcomes		Infliximab/placebo
IMPACT[79–81,89,96,109,111,113–115,117,118]	50	ACR 20	All pts	34/49 (69.4%)
			+MTX	16/22 (72.7%)
			–MTX	18/27 (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		(*n*=45) –42.5 (59.0)
		PASI 50[a]		19/22 (86.3%)
		PASI 75[a]		13/22 (59%)
		PASI 90[a]		9/22 (40.9%)
		PASI: mean (SD) change from baseline[a]		(*n*=35) –4.8 (5.9)
		Total modified van der Heijde–Sharp score: mean (SD) change from baseline		(*n*=70) –1.72 (5.82)
IMPACT 2[82,90,91,95,98,106,112,116]	54	PsARC		67/90 (74.4%)
		PASI 50[a]		57/82 (69.5%)
		PASI 75[a]		40/82 (48.8%)
		PASI 90[a]		32/82 (39%)
		Total modified van der Heijde–Sharp score: mean (SD) change from baseline		Infliximab/infliximab –0.94 (3.4) Placebo/infliximab 0.53 (2.6)

pts, patients.
a PASI 50/75/90 outcomes are for subgroup of patients with ≥3% BSA psoriasis.

Efficacy of adalimumab

Both trials evaluating adalimumab for PsA were double blind and placebo controlled, and both were rated as 'good' on the quality assessment rating (*Table 10*).[51,83,88,92,93,100–104]

Both trials were of adults (aged 18–70 years), with active PsA (defined in both trials as three or more swollen joints and three or more tender or painful joints, with active psoriatic skin lesions or a documented history of psoriasis). Patients in the larger trial had demonstrated an inadequate response to NSAIDs and received no concomitant DMARDs other than MTX.[51,88,92,93,100–104] All patients in the smaller trial received concomitant DMARDs or had a history of DMARD therapy with inadequate response.[83]

The baseline characteristics of the trial populations are summarised in *Table 1*. In both trials, around one-half of the randomised patients received concomitant MTX. Other DMARDs and NSAIDs were used concomitantly by patients in the smaller trial,[83] but not by those in the larger trial.[51,88,92,93,100–104] The mean number of prior DMARDs used was similar between the trials, although as seen in trials of the other biologics, the trials clearly included patients who had not yet demonstrated a lack of response to at least two DMARDs. The proportion of patients with polyarticular disease between the two trials indicated that overall the disease was moderate to severe. The proportion of patients with spine involvement, and arthritis mutilans at baseline made up only a small proportion of the trial population. The similarity of the trials on other measures of disease activity (TJC, SJC and HAQ at baseline) suggests that significant differences between the populations in terms of overall disease severity are unlikely. 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.

TABLE 10 Results of quality assessment for trials of adalimumab

	Study	
Quality assessment criteria	**ADEPT[51,88,92,93,100–104]**	**Genovese 2007[83]**
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?	NR	Y
Treatment administered blind?	Y	Y
Outcome assessment blind?	Y	Y
Patients blind?	Y	Y
Blinding successful?	NR	NR
Adequate baseline details presented?	Y	Y
Baseline comparability?	Y	Y
Similar cointerventions?	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

ADEPT, Adalimumab Effectiveness in Psoriatic Arthritis Trial; ITT, intention to treat; NR, not reported; Y, yes.

In both trials adalimumab was administered by subcutaneous injection every other week at a dose of 40 mg. Treatment with active drug or placebo was administered for 12 weeks in the smaller trial (Genovese *et al.*)[83] and for 24 weeks in the larger trial (Adalimumab Effectiveness in Psoriatic Arthritis Trial – ADEPT).[51,88,92,93,100–104] In both trials the controlled phase was followed by a follow-up period, during which adalimumab was administered in an open-label fashion to all patients.

Outcome data derived under RCT conditions are available from both trials for PsARC, ACR 20, ACR 50 and ACR 70 and HAQ at week 12. The larger of the two trials also reported these outcomes at 24 weeks. In addition, this trial reported PASI 50/70/90 outcomes at 12 and 24 weeks, as well as data on progression of joint disease at 24 weeks expressed in terms of the mean TSS.[51,88,92,93,100–104] All randomised outcome data are summarised in *Table 11*, with pooled data presented in *Table 12*.

ADEPT[51,88,92,93,100–104] reported longer-term open-label follow-up of patients at 48, 104, and 144 weeks. These data are summarised in *Table 13*.

Efficacy after 12 weeks' treatment

At 12 weeks, both trials reported a significant improvement in the PsA-specific PsARC measure for adalimumab relative to placebo (pooled RR 2.24; 95% CI 1.74 to 2.88), with an overall response rate of around 59% for adalimumab. The pooled RR for ACR 20 at 12 weeks was 3.65 (95% CI 2.57 to 5.17), demonstrating a clear degree of efficacy of adalimumab in terms of arthritis-related symptoms. There was no statistically significant heterogeneity between any of the pooled outcomes. The pooled RRs for ACR 50 and ACR 70 also clearly favoured adalimumab, although as with other estimates of these outcomes their related CIs were wide (*Table 12*). Again, the large relative differences on these higher-response thresholds reflect some response with biologic therapy versus virtually none with placebo (e.g. 18% vs 0.5% for ACR 70). Data from the larger trial indicated little evidence of any differential ACR response at 12 weeks between patients with and without concomitant MTX.[51,88,92,93,100–104]

Only one trial reported 12-week PASI response measures: in patients with psoriasis of at least 3% BSA at baseline.[51,88,92,93,100–104] Response was significantly greater for adalimumab than placebo at all three PASI thresholds (PASI 50/75/90 – see *Table 11*). As with the ACR outcomes, there was little evidence of any differential PASI response between patients receiving and not receiving concomitant MTX, although the number of patients in each subgroup was small.

The statistically significant pooled absolute mean change from baseline in HAQ score with adalimumab compared with placebo (mean difference –0.27; 95% CI –0.36 to –0.18) indicates a beneficial effect of adalimumab on functional status.

Efficacy after 24 weeks' treatment

The ADEPT trial[51,88,92,93,100–104] maintained randomisation for 24 weeks. The data for all measures of joint disease, psoriasis and HAQ were all similar to those observed at the earlier 14-week follow-up, suggesting that the benefits of adalimumab are maintained for up to 24 weeks of treatment (see *Table 12*).

In addition, this trial[51,88,92,93,100–104] reported a statistically significant difference in mean change in TSS score from baseline (–0.2 vs 0.1, $p < 0.001$), favouring adalimumab over placebo in terms of delayed progression of joint disease. However, this duration of follow-up is to be considered short and barely adequate for this outcome.

TABLE 11 Adalimumab efficacy outcomes: RCT data

Trial	Duration (weeks)	Outcomes		Adalimumab	Placebo	RR or mean difference (95% CI)
ADEPT[51,88,92,93,100–104]	12	PsARC		94/151 (62%)	42/162 (26%)	2.40 (1.80 to 3.20), $p<0.05$
		ACR 20	All pts	88/151 (58%)	23/162 (14%)	4.10 (2.75 to 6.14), $p<0.05$
			+MTX	43/77 (55%)		
			–MTX	45/74 (61%)		
		ACR 50	All pts	54/151 (36%)	6/162 (4%)	9.66 (4.28 to 21.79), $p<0.05$
			+MTX	27/77 (36%)		
			–MTX	27/74 (36%)		
		ACR 70	All pts	30/151 (20%)	1/162 (1%)	32.19 (4.44 to 233.11), $p<0.05$
			+MTX	13/77 (17%)		
			–MTX	17/74 (23%)		
		HAQ change from baseline: mean (SD)		–0.4(0.5)	–0.1(0.5)	–0.3 (–0.41 to –0.19), $p<0.001$
		PASI 50[a]	All pts	50/69 (72%)	10/69 (14%)	5.00 (2.77 to 9.03), $p<0.05$
			+MTX	17/29 (76%)		
			–MTX	28/40 (70%)		
		PASI 75[a]	All pts	34/69 (49%)	3/69 (4%)	11.33 (3.65 to 35.17), $p<0.05$
			+MTX	17/29 (59%)		
			–MTX	17/40 (43%)		
		PASI 90[a]	All pts	21/69 (30%)	0/69 (0%)	43.00 (2.66 to 696.04), $p<0.05$
			+MTX	11/29 (38%)		
			–MTX	10/40 (25%)		
	24	PsARC		91/151 (60%)	37/162 (23%)	2.64 (1.93 to 3.60), $p<0.05$
		ACR 20	All pts	86/151 (57%)	24/162 (15%)	3.84 (2.59 to 5.70), $p<0.05$
			+MTX	42/77 (55%)		
			–MTX	44/74 (59%)		
		ACR 50	All pts	59/151 (39%)	10/162 (6%)	6.33 (3.34 to 12.64), $p<0.05$
			+MTX	28/77 (36%)		
			–MTX	31/74 (42%)		
		ACR 70	All pts	35/151 (23%)	1/162 (1%)	37.55 (5.21 to 270.70), $p<0.05$
			+MTX	17/77 (22%)		
			–MTX	17/74 (23%)		
		HAQ change from baseline: mean (SD)		–0.4(0.5)	–0.1 (0.4)	–0.3 (–0.40 to –0.20), $p<0.001$
		PASI 50[a]	All pts	52/69 (75%)	8/69 (12%)	6.50 (3.34 to 12.64), $p<0.05$
			+MTX	25/29 (86%)		
			–MTX	27/40 (68%)		
		PASI 75[a]	All pts	41/69 (59%)	1/69 (1%)	41.00 (5.80 to 289.75), $p<0.05$
			+MTX	21/29 (72%)		
			–MTX	20/40 (50%)		
		PASI 90[a]	All pts	29/69 (42%)	0/69 (0%)	59.00 (3.68 to 946.75), $p<0.05$
			+MTX	15/29 (52%)		
			–MTX	14/40 (35%)		
		TSS mean change from baseline		–0.2 ($n=144$)	0.1 ($n=152$)	$p<0.001$

continued

TABLE 11 Adalimumab efficacy outcomes: RCT data *(continued)*

Trial	Duration (weeks)	Outcomes	Adalimumab	Placebo	RR or mean difference (95% CI)
Genovese 2007[83]	12	PsARC	26/51 (51%)	14/49 (24%)	1.78 (1.06 to 3.00), $p<0.05$
		ACR 20	20/51 (39%)	8/49 (16%)	2.40 (1.17 to 4.94), $p<0.05$
		ACR 50	13/51 (25%)	1/49 (2%)	12.49 (1.70 to 91.90), $p<0.05$
		ACR 70	7/51 (14%)	0/49 (0%)	14.42 (0.85 to 5.26), $p=$n.s.
		HAQ change from baseline: mean (SD)	–0.3 (0.5)	–0.1 (0.3)	–0.2 (–0.36 to –0.04), $p=0.015$
	24 (open-label extension)	PsARC	38/51 (75%)	32/46 (70%)	–
		ACR 20	33/51 (65%)	26/46 (57%)	–
		ACR 50	22/51 (43%)	17/46 (37%)	–
		ACR 70	13/51 (27%)	10/46 (22%)	–
		HAQ change from baseline: mean (SD)	–0.3 (0.5)	–0.4 (0.4)	–

n.s., not significant; pts, patients.
a Reported for patients with at least 3% BSA psoriasis.

The smaller of the two trials allowed patients to enter an open-label follow-up period from weeks 12–24.[83] The pattern of reported joint disease outcomes appears similar to those reported at the end of the 12-week randomised period; however, estimates based on these non-randomised data cannot be considered reliable.

Longer-term follow-up

The larger adalimumab trial followed patients in an open-label fashion, measuring several outcomes at 48 weeks and at 2 years (*Table 13*).[51,88,92,93,100–104] Both ACR response rates and mean HAQ scores at weeks 48 and 104 appeared to have remained stable relative to the randomised observations of these outcomes at weeks 12 and 24. Similarly, rates of PASI response reported at 48 weeks appeared largely consistent with the earlier randomised observations. Disease progression as measured by TSS was reported at weeks 48 and 144, with higher mean values than observed at 24 weeks, although the open-label observational nature of these open-label data makes it difficult to reliably determine any clear changes in TSS over time.

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

- There is evidence from two double-blind placebo-controlled trials of a good level efficacy for adalimumab in the treatment of PsA, with beneficial effects on joint disease and functional status as assessed by HAQ.
- There is limited evidence from a single RCT that adalimumab treatment has a beneficial effect on the psoriasis component of the disease in patients with PsA, as measured by PASI.
- Conclusions to be drawn from these data are limited by the short duration the controlled trials; large-scale controlled data to evaluate long-term effects are not available.
- Uncontrolled follow-up of patients indicate that treatment benefits in terms of joint disease and HAQ measures may be maintained at up to 2 years; however, these data may not be reliable.
- Radiographic data from a single controlled trial for adalimumab in PsA 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 adalimumab. Data from uncontrolled follow-up are inadequate to determine whether any potential delay in disease progression persists at 1–2 years' follow-up.

TABLE 12 Meta-analysis of adalimumab efficacy data: outcomes at 12 weeks

Trial	Outcomes	Adalimumab	Placebo	RR or mean difference (95% CI)
	PsARC			
ADEPT[51,88,92,93,100–104]		94/151 (62%)	42/162 (26%)	2.40 (1.80 to 3.20)
Genovese 2007[83]		26/51 (51%)	14/49 (24%)	1.78 (1.06 to 3.00)
	Pooled RR (95% CI), *p*-value			2.24 (1.74 to 2.88), $p<0.0001$
	I^2			$I^2=0\%$
	ACR 20			
ADEPT[51,88,92,93,100–104]		88/151 (58%)	23/162 (14%)	4.10 (2.75 to 6.14)
Genovese 2007[83]		20/51 (39%)	8/49 (16%)	2.40 (1.17 to 4.94)
	Pooled RR (95% CI), *p*-value			3.65 (2.57,5.17), $p<0.0001$
	I^2			$I^2=38\%$
	ACR 50			
ADEPT[51,88,92,93,100–104]		54/151 (36%)	6/162 (4%)	9.66 (4.28 to 21.79)
Genovese 2007[83]		13/51 (25%)	1/49 (2%)	12.49 (1.70 to 91.90)
	Pooled RR (95% CI), *p*-value			10.08 (4.74 to 21.44), $p<0.0001$
	I^2			$I^2=0\%$
	ACR 70			
ADEPT[51,88,92,93,100–104]		30/151 (20%)	1/162 (1%)	32.19 (4.44 to 233.11)
Genovese 2007[83]		7/51 (14%)	0/49 (0%)	14.42 (0.85 to 5.26)
	Pooled RR (95% CI), *p*-value			26.05 (5.18 to 130.88), $p<0.0001$
	I^2			$I^2=0\%$
	HAQ change from baseline [mean (SD)]			
ADEPT[51,88,92,93,100–104]		–0.4 (0.5)	–0.1 (0.5)	–0.3 (–0.41 to –0.19)
Genovese 2007[83]		–0.3 (0.5)	–0.1 (0.3)	–0.2 (–0.36 to –0.04), $p=0.015$
	Pooled WMD (95% CI), *p*-value			–0.27 (–0.36, –0.18), $p<0.0001$
	I^2			$I^2=0.6\%$

WMD, weighted mean difference.

Efficacy of all three biologics

As described above (see *Data analysis*), the Bayesian indirect comparison enables a comparison to be made across all three biologics despite the lack of head-to-head trial data. The three agents were included in the analysis, with placebo being the common comparator. All of the trials identified in the systematic review were used in the analysis, although not all trials provided data for all of the outcomes analysed. Full details of the methods used are given in *Appendix 5*.

Psoriatic Arthritis Response Criteria response

The results of the evidence synthesis for PsARC response are in the form of probability of response (*Table 14*). The mean probability of a PsARC response was estimated to be 71% for etanercept, 79% for infliximab and 59% for adalimumab, compared with 25% for placebo. While the credible intervals for all three biologics overlap each other, none overlap placebo.

Changes in Health Assessment Questionnaire

The results of the evidence synthesis of HAQ conditional on response are presented as absolute changes in HAQ. These are calculated separately for the patients achieving a PsARC response (*Table 15*) and those who did not achieve a PsARC response (*Table 16*).

TABLE 13 Adalimumab efficacy outcomes: uncontrolled follow-up data

Trial	Type of data	Duration (weeks)	Outcomes	Adalimumab	Adalimumab/placebo
ADEPT[51,88,92,93,100–104]	Uncontrolled	48	ACR 20	–	58.7% (165/281)
			ACR 50	–	42.7% (120/281)
			ACR 70	–	27.8% (78/281)
			HAQ change from baseline: mean (median)	–	(*n*=298) –0.3 (0.5)
			PASI 50	67% (46/69)	61% (42/69)
			PASI 75	58% (40/69)	53% (37/69)
			PASI 90	46% (32/69)	44% (30/69)
			Mean (SD) TSS change from baseline	(*n*=115) 0.1 (1.95)	(*n*=128) 0.8 (4.23)
		104	ACR 20	–	57.3% (161/281)
			ACR 50	–	45.2% (127/281)
			ACR 70	–	29.9% (84/281)
			HAQ change from baseline: mean (median)	–	(*n*=271) –0.3 (0.5)
		144	Mean (SD) TSS change from baseline	(*n*=115) 0.5 (4.20)	(*n*=128) 0.9 (6.36)

TABLE 14 Probability of PsARC response to biologics

		Credible intervals (%)	
Treatment	**Mean**	**2.50**	**97.50**
Placebo	0.249	0.178	0.317
Etanercept	0.713	0.567	0.832
Infliximab	0.795	0.673	0.886
Adalimumab	0.587	0.444	0.713

TABLE 15 Change in HAQ in patients who responded to treatment

		Credible intervals (%)	
Treatment	**Mean**	**2.50**	**97.50**
Placebo	–0.244	–0.337	–0.151
Etanercept	–0.630	–0.805	–0.455
Infliximab	–0.657	–0.793	–0.523
Adalimumab	–0.477	–0.596	–0.351

TABLE 16 Change in HAQ in patients who did not respond to treatment

		Credible intervals (%)	
Treatment	**Mean**	**2.50**	**97.50**
Placebo	0	0	0
Etanercept	–0.190	–0.381	0.000
Infliximab	–0.194	–0.333	–0.057
Adalimumab	–0.130	–0.262	–0.001

Statistically significant reductions in mean HAQ score were achieved with all four treatments compared, i.e. the credible intervals did not include zero. However, patients who responded to placebo achieved an improvement in the HAQ score of –0.244, which is below the minimum clinically significant threshold for PsA of –0.3.[150] Patients who responded to etanercept and infliximab achieved similar mean changes in HAQ (–0.630 and –0.657, respectively), whereas responders to adalimumab achieved a lower mean change in the HAQ score of –0.477, although credible intervals overlap those of the other two treatments.

For all three biologics the changes in HAQ for those patients who did not respond to treatment were below the minimum clinically significant threshold. Placebo non-responders were used as a baseline in the synthesis.

Psoriasis Area and Severity Index

The results of the evidence synthesis for a PASI response are in the form of probability of response (*Table 17*). The mean probability of a PASI 75 response was estimated to be 18% for etanercept, 77% for infliximab and 48% for adalimumab, compared with 4% for placebo. The credible intervals for infliximab and etanercept do not overlap each other and none for the biologics overlap placebo.

American College of Rheumatology model

The results of the evidence synthesis for a ACR response are in the form of probability of response (*Table 18*). The ACR 20 is generally accepted to be the minimal clinically important difference that indicates some response to a particular intervention in terms of arthritis-related symptoms. The mean probability of an ACR 20 response was estimated to be 61% for etanercept, 68% for infliximab and 56% for adalimumab, compared with 14% for placebo. The credible intervals for all three biologics overlap each other, but none overlap those for placebo.

TABLE 17 Probability of PASI response to biologic agents

		Credible intervals (%)	
	Mean	2.50	97.50
PASI 50			
Placebo	0.130	0.092	0.175
Etanercept	0.403	0.236	0.592
Infliximab	0.913	0.823	0.968
Adalimumab	0.738	0.552	0.881
PASI 75			
Placebo	0.044	0.028	0.065
Etanercept	0.177	0.085	0.313
Infliximab	0.769	0.594	0.901
Adalimumab	0.477	0.275	0.693
PASI 90			
Placebo	0.018	0.010	0.026
Etanercept	0.074	0.032	0.145
Infliximab	0.557	0.347	0.767
Adalimumab	0.257	0.120	0.452

TABLE 18 Probability of ACR response to biologics

	Mean	Credible intervals (%)	
		2.50	97.50
ACR 20			
Placebo	0.137	0.108	0.168
Etanercept	0.609	0.459	0.750
Infliximab	0.678	0.533	0.805
Adalimumab	0.560	0.429	0.686
ACR 50			
Placebo	0.053	0.040	0.070
Etanercept	0.362	0.231	0.516
Infliximab	0.433	0.288	0.594
Adalimumab	0.315	0.209	0.438
ACR 70			
Placebo	0.018	0.012	0.025
Etanercept	0.158	0.087	0.260
Infliximab	0.203	0.114	0.326
Adalimumab	0.131	0.077	0.205

Summary of evidence synthesis results

Across all outcomes – PsARC, ACR and PASI – infliximab is associated with the highest probability of response. The response in joint disease (PsARC and ACR) is greater with etanercept than with adalimumab, whereas the response in skin disease (PASI) is greater with adalimumab than with etanercept, although these differences are not statistically significant. In those patients who achieve a PsARC response to treatment the highest mean reductions in HAQ are seen with infliximab and etanercept.

Comparison of evidence synthesis results

Each of the three company submissions combined evidence derived using Bayesian evidence synthesis methods. A brief comparison of these methods and the methods used by the assessment team are presented in *Table 19* and discussed below.

Two of the company submissions – Abbott[151] and Schering-Plough[152] – conducted evidence syntheses to derive estimates that would allow the relative efficacy of the drugs to be compared (*Table 19*). (Since the production of this report, Schering-Plough has merged with Merck.) Wyeth[153] chose not to conduct this synthesis themselves but to use the results of a previously published single technology appraisal (STA) relating to Abbott's adalimumab.[74]

Full details of the evidence synthesis model used by Wyeth[153] were not provided in the Wyeth submission.[153] Further, the methodology of the evidence synthesis from which these results were obtained was not presented in the original report.[151] The synthesis was conducted by Abbott[151] on the request from the Evidence Review Group (ERG) and only the results were presented in the ERG report. For this reason no summary/critique of the methods can be presented. The following section gives a comparative overview of the evidence synthesis results obtained by Schering-Plough,[152] Abbott[151] and by the Assessment Group in this report.

Psoriatic Arthritis Response Criteria response For PsARC response, all of the evidence synthesis models used a fixed-effects meta-analysis to synthesise the evidence. Both the Assessment Group

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TABLE 19 Comparison of industry and Assessment Group evidence syntheses

		Interventions: etanercept, infliximab, adalimumab			
		Abbott[151]	**Schering-Plough**[152]	**Wyeth**[153]	**Assessment team (York)**
Studies used in the analysis		Mease 2000,[78] Antoni 2003,[117] Mease 2004,[52,97,99,105,107,110] Antoni 2005,[82] Kaltwasser 2004,[62] Mease 2005,[51] Mease 2006,[97] Genovese 2007,[83] Kavanaugh 2009,[154] Gottlieb 2009[155]	IMPACT,[79–81,89,96,109,111,113–115,117,118] IMPACT 2,[82,90,91,95,98,106,112,116] Mease 2000,[78] Mease 2004, [52,97,99,105,107,110] ADEPT,[51,88,92,93,100–104] Genovese 2007,[83] York HTA,[73] GO-REVEAL[156]	Mease 2004, [52,97,99,105,107,110] PRESTA,[157] ADEPT,[51,88,92,93,100–104] IMPACT 2,[82,90,91,95,98,106,112,116] STA ADL[74]	IMPACT,[79–81,89,96,109,111,113–115,117,118] IMPACT 2,[82,90,91,95,98,106,112,116] Mease 2000,[78] Mease 2004, [52,97,99,105,107,110] ADEPT,[51,88,92,93,100–104] Genovese 2007[83]
Outcomes of interest	PsARC	12 and 24 weeks (24-week results estimated based on the conditional 12 weeks)	12 or 14 weeks	12 and 24 weeks; derived from STA ADL[74]	12 weeks
	HAQ	12 weeks (dependent on ACR response type via multivariate regression)	Weeks 12 and 24 for adalimumab; week 14 or 16 for infliximab; week 12 for etanercept (conditional on PsARC response)	Derived from Mease 2004; changes in HAQ were predicted via PASI; assumed equal magnitude of change in HAQ for all three biologics	HAQ at 12 weeks conditional on PsARC response at 12 weeks (by biologic)
	PASI 25/50/75	12 and 24 weeks (independently modelled for both 12 and 24 weeks)	Week 24 for adalimumab; week 14 or 16 for infliximab; week 24 for etanercept	PASI 75 only (12 and 24 weeks); derived from STA ADL[74] and Mease 2004	PASI 50/70/90 at 12 weeks (by biologic)
	ACR 20/50/70	12 and 24 weeks (24 week results estimated based on the conditional 12 weeks)	Not estimated	Not estimated	ACR 50/70/90 at 12 weeks (by biologic)
Model		Bivariate probit model; Bayesian fixed-effects meta-analysis of bivariate ordinal data	Two joint meta-analyses: PsARC/HAQ and PASI	Model used not reported; the results were taken from a published evidence synthesis[74]	Fixed-effects meta-analysis (PsARC, HAQ, ordered logit model PASI/ACR)
Results reported		PsARC, ACR and PASI responses at 12 and 24 weeks: estimated means of marginal probabilities. Joint distribution of PsARC and ACR response at 12 weeks. Joint distribution of PASI 75 at 12 and 24 weeks	Incremental HAQ change given PsARC response in treatment; incremental HAQ change given PsARC non-response in treatment; incremental HAQ change given PsARC response in placebo; incremental HAQ change given PsARC non-response in placebo	PsARC (% patients), PASI 75, HAQ change from baseline, change in PASI	Probability of response in terms of PsARC, ACR and PASI; changes in HAQ given PsARC response/non-response to treatment
Comments		Results 'borrow' information from trials of therapies not of interest (golimumab, leflunomide, alefacept and ustekinumab)		It was not possible to fully assess the results of the evidence synthesis performed as no details were provided even in the original publication[159]	

ADL, adalimumab; GO-REVEAL, Golimumab-Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody; PRESTA, Psoriasis Randomized Etanercept STudy in Subjects with Psoriatic Arthritis.

and Schering-Plough[152] identified and included six RCTs in their synthesis. Abbott,[151] with slightly broader inclusion criteria, identified and included 10 RCTs. Abbott[151] included RCTs in which the drug golimumab was administrated to the comparator arm of the RCT and, although no results were presented for this comparator, the other estimates do 'borrow strength' from these data. Although including the same six RCTs, both the Assessment Group and Schering-Plough[152] estimated PsARC response using slightly different data. The Assessment Group used the closest follow-up outcome to 12 weeks, whereas Schering-Plough[152] used the latest available end points (*Table 20*). This meant that, with the exception of the adalimumab data, the data inputs were principally the same. Abbott[151] took a more complex bivariate approach, which enabled them to model the joint distribution of ACR/PsARC response at 12 weeks. Taking a bivariate approach allows the correlation between outcomes, if present, to be accounted for. However, if the correlation is zero then any bivariate joint modelling will arrive at the same estimates as two independent models. Given the lack of transparency of the Abbott[151] evidence synthesis, it was not possible to unpick and decipher the subtleties of their model. The Assessment Group, following clinical advice, have used PsARC at 12 weeks to determine response to treatment. This follows clinical practice.

TABLE 20 Key assumptions in the synthesis models

Abbott[151]	Schering-Plough[152]	Assessment team (York)
1. Estimation for an average patient, the joint probability of an ACR response and a PsARC response at 12 weeks 2. The 24-week results of the PsARC and ACR were estimated based on the conditional 12 weeks' response 3. The PASI response independently modelled for both 12 and 24 weeks	1. The change in HAQ from baseline was modelled conditionally on PsARC response 2. PASI is modelled as an aggregate across patients with or without a PsARC response 3. Uses absolute changes in HAQ and PASI. Where trials only report the relative change in PASI (e. g. average 54% improvement) or 'response criteria', such as PASI 50, PASI 75, etc., the absolute changes have to be inferred 4. PASI is only modelled for the subset of patients with initial BSA $\geq$3% 5. All patients with BSA >3% are assumed to have identical PASI baseline values equal to the mean PASI baseline score reported for this subgroup in the trial 6. If the trial does not report the baseline PASI for a group, it is assumed to be equal to the average score reported in the other trials 7. The PASI change is not correlated with the PASI baseline score 8. The PASI change and HAQ change are not correlated in the BSA >3% group 9. The HAQ change is conditional on PsARC response 10. Where trials do not report the HAQ outcomes separately by PsARC response group, it has been assumed that the HAQ change for the PsARC non-responders is equivalent to the average HAQ change in non-responders seen in other trials, and the HAQ change for the PsARC responders is inferred to match the reported mean HAQ change 11. The HAQ change from baseline to the last RCT controlled data point up to week 24 is the main outcome of interest and is the main determinant of the outcomes of the economic model 12. The HAQ change is not correlated with baseline HAQ score 13. The HAQ change is assumed identical for the subgroups with or without BSA $\geq$3% at baseline	*PsARC response* 1. Common-effects meta-analysis 2. Probability of response to placebo as a common baseline for each treatment effect 3. Common treatment effect by class of treatment 4. Treatment effects on probability of response were additive to the placebo probability of response on the log-odds scale 5. Outcomes at 14 weeks were included in the analysis and assumed equivalent to outcomes at 12 weeks *Changes in HAQ* 1. Random-effects meta-analysis 2. For each of the different trials the true effect may be study specific and vary across studies although remain common across biologics 3. Changes in HAQ given placebo non-responders as common baseline 4. The effects of treatment response and non-response on HAQ change are treatment specific and additive to the placebo probability of non-response on the log-odds scale *PASI and ACR* 1. Ordered multinomial logit model 2. Common effect model was used to estimate baseline 3. Common effects were assumed for each treatment class 4. Thresholds were assumed to be fixed across trials

As can be seen from the results presented for the probability of response to the biologics under appraisal (and placebo) (*Table 21*), all of the mean estimates obtained were very similar, despite the different modelling assumptions and evidence used. There does appear to be some difference in the level of uncertainty, as presented by the confidence/credible intervals, but generally the means were close and the ranking consistent. The Abbott[151] evidence synthesis model was extremely difficult to interpret; however, the analysis enabled the estimation of the joint probability of an ACR response and a PsARC response at 12 weeks. The 24-week results of the PsARC and ACR were then estimated individually, conditional on the 12-week response. Schering-Plough[152] based their evidence synthesis on a previous HTA report,[73] which linked two meta-analyses, one estimating PsARC the other HAQ conditional on PsARC.

Health Assessment Questionnaire conditional on a Psoriatic Arthritis Response Criteria response The economic models developed by both the Schering-Plough[152] and the Assessment Group required an estimate of the expected change in HAQ in the first 3 months for treatment responders and non-responders, as measured by PsARC. HAQ conditional on a PsARC response was modelled by both the Assessment Group and Schering-Plough.[152] The two modelling approaches were based on fixed-effects meta-analysis. The Schering-Plough[152] approach uses two linked meta-analyses, which estimated the probability of response and then the mean reduction in HAQ score conditional on that response. The Assessment Group estimated the probability of PsARC response in one meta-analysis and then used this result to inform a second HAQ model. Both synthesis models used the same clinical trials to inform the HAQ–PsARC estimates. However, Schering-Plough[152] used the latest available end points for HAQ, in contrast with the Assessment Group, who elected to use the 12- to 16-week HAQ data to reflect short-term benefits. Long-term benefits are considered explicitly in the economic model.

The results obtained (*Table 22*) were generally similar, with the drugs maintaining the same ranking. The differences may reflect the slightly differing modelling approaches or the difference in data used. The Assessment Group included only the five trials that reported HAQ outcomes for responders and non-responders. To enable them to include all six trials, Schering-Plough[152] assumed that for the one trial where the data were not stratified by responder/non-responder[78] the HAQ change for the PsARC non-responder was equivalent to the average HAQ change in the non-responders, as seen in other trials, and that the HAQ change for the PsARC responders could be inferred to match the reported mean HAQ change. The Assessment Group opted not to make this assumption, as it was not clear that it was appropriate or that it would have a significant impact on the results obtained. The Assessment Group took the decision to use only data that

TABLE 21 Psoriatic Arthritis Response Criteria model results

	Probability of response							
	Current assessment		Abbott[151]		Schering-Plough[152]		Wyeth[153]	
Treatment	Mean	Credible interval	Mean	Credible interval	Mean	Credible interval	Mean (%)	Credible interval (%)
Placebo	0.249	(0.1779 to 0.3169)	0.258	NR	AiC	AiC	26	(21 to 31)
Etanercept	0.713	(0.5665 to 0.8317)	0.743		AiC	AiC	76	(46 to 96)
Infliximab	0.795	(0.6725 to 0.8855)	0.76		AiC	AiC	75	(45 to 95)
Adalimumab	0.587	(0.4441 to 0.713)	0.591		AiC	AiC	57	(24 to 85)

AiC, academic-in-confidence data removed; NR, not reported.

TABLE 22 Health Assessment Questionnaire conditional on response: different treatment effects (common baseline)

	Current assessment			Schering-Plough[152]		
Treatment	Mean	Credible interval	Abbott[151]	Mean	Credible interval	Wyeth[153]
Changes in HAQ – response						
Etanercept	–0.630	(–0.805 to –0.455)	NC	AiC	AiC	NC
Infliximab	–0.657	(–0.793 to –0.523)	NC	AiC	AiC	NC
Adalimumab	–0.477	(–0.596 to –0.351)	NC	AiC	AiC	NC
Changes in HAQ – no response						
Etanercept	–0.190	(–0.381 to 0.000)	NC	AiC	AiC	NC
Infliximab	–0.194	(–0.333 to –0.057)	NC	AiC	AiC	NC
Adalimumab	–0.130	(–0.1878 to 0.0652)	NC	AiC	AiC	NC
Placebo			NC			NC
Changes in HAQ – response						
All treatments	–0.244	(–0.337 to –0.151)	NC	AiC	AiC	NC

AiC, academic-in-confidence data removed; NC, not conducted.

reported in a manner that facilitated modelling. The Schering-Plough[152] report clearly states that six trials were considered; however, the detailed appendix and model code both appear to consider a seventh trial of the biologic golimumab. Although they state that this was used only to inform relationships between variables, the coding and appendix do not make this clear.

Abbott[151] did not model HAQ conditional on response, although HAQ for the economic modelling section of their report they did state that relationships between ACR response rate and HAQ improvement, and PASI response and PASI improvement were developed in order to obtain estimates of HAQ and PASI improvement for responders and non-responders for each treatment.

This analysis estimated the expected change in HAQ in the first 3 months, conditional on treatment response. PsARC is not a baseline variable and therefore conditioning the analysis on PsARC response may be potentially biased. The analysis assumes there are no confounding factors (unrelated to treatment received) that change during the trial and affect both PsARC response and, independently, the change in HAQ.

Psoriasis Area and Severity Index 50/75/90 response The PASI outcomes were synthesised by Abbott,[151] Schering-Plough[152] and the Assessment Group. Schering-Plough[152] elected to use absolute PASI change as their main outcome, on the basis that this was the most appropriate outcome for the economic modelling. As a result, the estimates obtained are not comparable with the Assessment Group or Abbott[151] results, both of which elected to use probability of achieving each PASI outcome (50/75/90) as their main outcome. This was achieved using two different modelling approaches. The Assessment Group elected to use an ordered multivariate logit model, whereas Abbott[151] chose to use a bivariate probit model. The logit and probit models are similar; both allow the different thresholds of PASI (50/75/90) to be modelled simultaneously, the ordered nature of the data to be maintained and an estimate of patients' percentage reduction in PASI score from baseline to be obtained. The results estimated and presented in *Table 23* are similar. As previously stated, the Abbott model[151] was complex and (as felt by the assessment team) difficult to fully understand. As such it is not clear if data from all 10 included trials were used in the Abbott PASI model.[151] The data inputs for the Assessment Group model are reported in

TABLE 23 Psoriasis Area and Severity Index common effects model

		Probability of response						
		Current assessment		Abbott[151]			Wyeth[153]	
Treatment	Outcome	Mean	Credible interval	Mean	Credible interval	Schering-Plough[152]	Mean (%)	Credible interval
Placebo								
	PASI 50	0.1305	(0.0917 to 0.1747)	0.151	NR	NC	12	(0.03 to 0.25)
	PASI 75	0.0445	(0.0281 to 0.0654)	0.049	NR	NC	4	(0.01 to 0.09)
	PASI 90	0.0167	(0.0098 to 0.0261)	0.009	NR	NC		
Etanercept								
	PASI 50	0.4026	(0.2361 to 0.5916)	0.393	NR	NC	39	(0.03 to 0.81)
	PASI 75	0.1768	(0.085 to 0.313)	0.189	NR	NC	20	(0.01 to 0.59)
	PASI 90	0.0737	(0.0317 to 0.145)	0.057	NR	NC		
Infliximab								
	PASI 50	0.9128	(0.823 to 0.968)	0.915	NR	NC	82	(0.47 to 0.97)
	PASI 75	0.7687	(0.5943 to 0.901)	0.774	NR	NC	64	(0.2 to 0.88)
	PASI 90	0.5571	(0.347 to 0.767)	0.515	NR	NC		
Adalimumab								
	PASI 50	0.7383	(0.5518 to 0.881)	0.732	NR	NC	65	(0.11 to 0.92)
	PASI 75	0.4772	(0.275 to 0.693)	0.500	NR	NC	43	(0.03 to 0.78)
	PASI 90	0.2571	(0.119 to 0.4524)	0.239	NR	NC		

NC, not conducted; NR, not reported.

Appendix 5. Owing to a lack of reporting in some trials, the Assessment Group model included data from five trials, one of which provided data on only two of the outcomes (PASI 50/75).

American College of Rheumatology 20/50/70 response Schering-Plough[152] did not synthesise for this outcome. Both the Assessment Group and Abbott[151] did, but again elected to use two differing modelling approaches, ordered logit and bivariate probit. The comparative results are presented in *Table 24*. The results are again similar, with the ranking of the drugs being maintained.

Abbott's model[151] produced estimates of 24-week ACR response conditional on the 12-weeks ACR response rate. The 12-week response rate was modelled as a joint distribution of 12-week PsARC and ACR response rates. The code and explanation of this modelling was not clear and therefore it was not possible to fully interpret all of the modelling conducted. As the Abbott

TABLE 24 American College of Rheumatology model common effects

		Probability of response					
		Current assessment		Abbott[151]			
Treatment	Outcome	Mean	Credible interval	Mean	Credible interval	Schering-Plough[152]	Wyeth[153]
Placebo							
	PASI 50	0.1369	(0.108 to 0.168)	0.132	NR	NC	NC
	PASI 75	0.05347	(0.04 to 0.07)	0.048	NR	NC	NC
	PASI 90	0.01806	(0.013 to 0.025)	0.012	NR	NC	NC
Etanercept							
	PASI 50	0.6093	(0.459 to 0.75)	0.578	NR	NC	NC
	PASI 75	0.362	(0.231 to 0.516)	0.362	NR	NC	NC
	PASI 90	0.1583	(0.088 to 0.26)	0.174	NR	NC	NC
Infliximab							
	PASI 50	0.6775	(0.533 to 0.81)	0.615	NR	NC	NC
	PASI 75	0.4333	(0.288 to 0.59)	0.398	NR	NC	NC
	PASI 90	0.2028	(0.1138 to 0.326)	0.199	NR	NC	NC
Adalimumab							
	PASI 50	0.5595	(0.429 to 0.686)	0.537	NR	NC	NC
	PASI 75	0.3146	(0.209 to 0.438)	0.323	NR	NC	NC
	PASI 90	0.1313	(0.077 to 0.205)	0.148	NR	NC	NC

NC, not conducted; NR, not reported.

economic model[151] included both PsARC and ACR there was a need for them to estimate the correlation between these two outcomes. The correlation was estimated using the available evidence. However, it was unclear as to the number of trials informing the Abbott ACR synthesis[151] and the correlation estimate. The Assessment Group have presented an ordered logit model, using data from all six trials. The estimates obtained were not used in the Assessment Group economic model, so it was not necessary to make any assumptions on the correlation between PsARC and ACR outcomes.

The annotated WINBUGS code, assumptions and data have been presented for all models used by the Assessment Group. Although it can be difficult to justify some of the differences in modelling assumptions taken by the various groups, the Assessment Group have tried to reflect clinical reality, minimise generalising assumptions and allow the results obtained to reflect the evidence obtained as part of the clinical review.

Review of adverse events

Overview of existing systematic reviews of adverse events

Several existing systematic reviews have investigated the safety of biologic agents. This section provides an overview of those reviews that were sufficiently rigorous to meet the Database

of Abstracts of Reviews of Effects (DARE) inclusion criteria.[75] The searches (see *Appendix 1*) resulted in 16 potentially relevant reviews; 10 were excluded because of a failure to meet the DARE criteria or to report relevant data on adverse events of biologics. Six systematic reviews (*Table 25*) were therefore included in this overview.

All of the six systematic reviews were published between 2006 and 2009. Three reviews[158–160] included patients with RA and three reviews[161–163] included patients with PsA or psoriasis. Almost all reviews evaluated the safety of more than two biologics. The sample size of included reviews varied from 982 to 7931. Almost all systematic reviews included RCTs to assess the safety of biologics, whereas only one review[160] included both RCTs and observational studies. The search strategies were generally adequate to identify both published and unpublished studies, thereby minimising the potential of publication bias.[164,165] However, in the majority of these reviews[158–161,163] it was unclear whether any language restrictions on study inclusion were made, which may have introduced the possibility of language bias.[166]

There were variations in methods of pooling the adverse event data in these reviews. Five reviews[158,159,161–163] used meta-analyses to synthesise the evidence of adverse event data of biologics, whereas one review used a narrative synthesis.[160] For those using meta-analyses, the included studies were combined using either a fixed-effects or random-effects model; one review by Bongartz *et al.*[159] also used the individual patient data (IPD) to pool the results. Where there were no direct head-to-head studies comparing one biologic with another, an indirect comparison was undertaken using placebo as the common comparator in two reviews.[158,162] Statistical heterogeneity[167,168] was adequately assessed in most reviews. In addition, three reviews assessed the adverse events for more than two biologics combined,[158,161,162] whereas the other reviews evaluated them for each biologic respectively.[159,160,163]

A range of adverse events of biologics were evaluated in these reviews. Three reviews[160,162,163] evaluated both common and serious adverse events of biologics, whereas two reviews exclusively focused on serious adverse events such as malignancy.[158,159] Two reviews[161,162] used withdrawal rate due to toxicity/adverse events of biologics as the review outcome.

There were considerable variations in the effect estimations between the reviews. Brimhall *et al.*[163] reported that there were no significant increased incidences of one or more adverse events or serious adverse events for patients receiving etanercept; they also reported that there was no significant increase in the incidence of serious adverse events for patients receiving infliximab compared with those receiving placebo, although patients who received infliximab experienced a significant increased incidence of one or more adverse events. It should be noted that this systematic review was limited to short-term safety data of over 10–30 weeks of the biologic treatment. The review by Gartlehner *et al.*,[160] which principally evaluated the common adverse events of biologics, showed similar results based on the data from 18 experimental and observational studies for patients with RA. This review reported that biologics appeared to have a good tolerability profile; injection site reactions or infusion reactions were the most commonly reported adverse events for biologics of etanercept, infliximab and adalimumab. However, a lack of sound long-term safety data prevented this review from drawing a firm conclusion about the comparative safety between these three biologics for patients with RA.

Both the review by Ravindran *et al.*[161] and the review by Saad *et al.*[162] used the withdrawal rate due to toxicity/adverse events as the outcome measure to assess the safety of biologics. These are two reviews that exclusively include patients with PsA. The review by Ravindran *et al.*[161] reported that biologic treatment for patients with PsA was associated with a non-significant increase of withdrawal rate due to toxicity compared with placebo, when pooling the data from five RCTs of etanercept, infliximab and adalimumab. Similar results were found in the review by Saad *et al.*[162] on the basis of the pooled results of five RCTs (including the same four RCTs as Ravindran

TABLE 25 Published systematic reviews of adverse events of biologics

Study details	Intervention and patients	Searching and included studies	Analyses	Outcomes
Bongartz *et al.* 2006[158]	Infliximab and adalimumab 5014 patients with RA	*Data sources*: MEDLINE, EMBASE and the Cochrane Library were searched from inception to December 2005. The abstract databases of annual scientific meetings of EULAR and the ACR were searched from 1996 to 2005 *Included studies*: Nine RCTs (four RCTs of infliximab; five RCTs of adalimumab)	Studies were combined using a fixed-effects model of Mantel–Haenszel method. Pooled ORs with 95% CIs were calculated, with a continuity correction method for sparse data. The effects for high and low doses of anti-TNFs were estimated separately. The number-needed-to-harm with 95% CI was also calculated. Statistical heterogeneity was assessed using I^2-statistic. Sensitivity analyses were performed with exclusion of trials of moderate or high risk of bias, omission of malignancies diagnosed within the first 6 weeks of a trial, and omission of malignancies that were classified as NMSCs	The pooled OR for malignancy was 3.3 (95% CI 1.2 to 9.1) and for serious infection was 2.0 (95% CI 1.3 to 3.1). Malignancies were significantly more common in patients received higher doses of biologics compared with patients received lower doses of biologics. For patients with biologic treatment in included RCTs, the NNH was 154 (95% CI 91 to 500) for one additional malignancy within a treatment period of 6–12 months. For serious infections, the NNH was 59 (95% CI 39 to 125) within a treatment period of 3–12 months
Bongartz *et al.* 2009[159]	Etanercept 3316 patients with RA	*Data sources*: MEDLINE, EMBASE, the Cochrane Library and the Web of Science were searched from inception to December 2006. Pharmaceutical companies were contacted for unpublished trials *Included studies*: Nine RCTs	Studies were combined using a random-effects model of DerSimonian–Laird model. Pooled HRs with 95% CIs were calculated using IPD. A survival analysis of time-to-first-event using the Cox's proportional hazards model stratified by trial and assuming a fixed treatment effect was conducted. Sensitivity analyses were performed by omitting cancers diagnosed within 6 weeks of trial entry and omitting all NMSCs from case definition. Subgroup analyses were performed for three non-overlapping periods of follow-up time (<6 months, 6–12 months, >24 months). In addition, pooled ORs with 95% CIs were calculated using the Mantel–Haenszel model with a continuity correction method	The pooled HR for malignancies based on IPD data was 1.84 (95% CI 0.79 to 4.28) in patients using etanercept compared with control patients. The random-effects model resulted in a similar estimate of an HR of 1.82 (95% CI 0.78 to 4.22). When using Mantel–Haenszel methods, the pooled OR for malignancies in patients using etanercept compared with patients receiving control treatment was 1.93 (95% CI 0.85 to 4.38). When using a random-effects DerSimonian–Laird model, the pooled HR malignancies in patients receiving etanercept compared with patients receiving control treatment was 1.71 (95% CI 0.73 to 4.01) With the exclusion of four malignancies that were diagnosed during the first 6 weeks after the first treatment dose, the HR for malignancies in patients treated with etanercept compared with the non-etanercept group was 1.87 (95% CI 0.75 to 4.62). With the exclusions of all NMSC from analyses, similar results were found (HR 1.86, 95% CI 0.62 to 5.59). When the data were stratified according to three different time points: 0–6 months; 6–12 months and >12 months, it did not show a particular time period in which the risk of cancer was significantly increased

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Study details	Intervention and patients	Searching and included studies	Analyses	Outcomes
Brimhall *et al.* 2008[163]	Etanercept and infliximab 7931 patients with moderate-to-severe psoriasis	*Data sources*: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov were searched from inception to June 2005, and an updating search was conducted in July 2006 to capture reports from the interim period. Industry sponsors were contacted to additional unpublished data FDA reports were reviewed *Included studies*: 16 RCTs	Studies were combined in meta-analyses using the Mantel–Haenszel method, with a constant continuity correction. The synthesis results from the random-effects models were also reported. Bioequivalent or equivalent FDA-approved doses were pooled for each biologic agent. The safety of biologic agents was assessed by RR of one or more AEs and SAEs for all doses. All dosages were combined for comparison. The NNT and the NNH, with 95% CIs, were calculated. Statistical heterogeneity was measured using Q-statistic	*Etanercept*: The pooled RR of one or more AEs was not significantly increased for patients receiving etanercept (RR 1.05, 95% CI 0.96 to 1.16, $p=0.28$). Similar results were observed for the incidence of SAEs (RR 1.17, 95% CI 0.59 to 2.33, $p=0.66$). The most common reported AEs reported were injection-site reaction, headache and URTI. The most common SAEs were malignancy ($n=10$), serious infection ($n=4$) and worsening psoriasis ($n=3$). Both AEs and SAEs were evaluated cumulatively over 12–24 weeks of the treatment *Infliximab*: The pooled RR for one or more AEs was significantly associated with an increased one or more AEs compared with placebo (RR 1.18, 95% CI 1.07 to 1.29, $p<0.001$), with NNH of 9 (95% CI 5.99 to 19.61). The most common reported AEs were URTI, headache, increased hepatic enzymes and infection. Infliximab was not associated with a significant increase in SAEs (RR 1.26, 95% CI 0.56 to 2.84, $p=0.58$). The most common SAEs reported were malignancy ($n=12$), serious infection ($n=6$), serious infusion reaction ($n=4$) and lupus-like syndrome ($n=4$). Both AEs and SAEs were evaluated across 10–30 weeks of the treatment
Gartlehner *et al.* 2006[160]	Etanercept, infliximab and adalimumab The review included patients with RA who have failed to respond to traditional DMARD therapy. For indirect comparison, the authors pooled data for 2354 patients receiving adalimumab (five studies), for 1151 patients receiving etanercept (five studies) and for 704 patients receiving infliximab (four studies). The total number of patients in the review was not reported	*Data sources*: MEDLINE, EMBASE, The Cochrane Library, and the international pharmaceutical abstracts were searched from 1980 to 2006. Reference lists of relevant publications were searched. The Centre for Drug Evaluation and Research database was searched for unpublished research. Pharmaceutical companies were contacted for unpublished trials *Included studies*: 26 RCTs for efficacy and 18 studies (experimental and observational) for AEs	Studies were combined in meta-analyses using random-effects models. Subgroup analyses were conducted for the population who had remained symptomatic despite the MTX treatment. Subgroup analyses were also performed by only including data to FDA-approved dosage ranges to achieve better equivalency across drugs Statistical heterogeneity was measured using I^2-statistic and metaregression. Publication bias was assessed using funnel plots and Kendall's tests. Where there were no direct head-to-head studies comparing an anti-TNF with another, an indirect comparison was undertaken using placebo as the common comparator. For the AE data, the evidence was summarised qualitatively	*Adalimumab*: When the studies were pooled, adalimumab was associated with weighted mean incidence of diarrhoea (8.16, 95% CI 4.44 to 11.88), headache (18.23, 95%CI 6.51 to 29.95), infection site (18.98, 95% CI 9.21 to 28.76), nausea (8.84, 95% CI 5.55 to 12.13), rhinitis (14.8, 95% CI 7.26 to 22.35) and URTI (17.05, 95% CI 9.5 to 24.59) *Etanercept*: Etanercept was associated with weighted mean incidence of diarrhoea (18.14, 95% CI 3.45 to 32.84), headache (17.54, 95%CI 1.9 to 33.18), infection site (24.67, 95% CI 11.21 to 38.13), nausea (20.86, 95% CI 2.65 to 39.08), rhinitis (18.42, 95% CI 6.97 to 35.71) and URTI (20.89, 95% CI 6.97 to 34.82) *Infliximab*: Infliximab was associated with weighted mean incidence of diarrhoea (9.31, 95% CI 7.94 to 10.68), headache (17.7, 95% CI 3.03 to 33.36), rhinitis (7.77, 95% CI 0 to 18.12) and URTI (24.05, 95% CI 0 to 49.81) In addition, rare but SAEs (e.g. serious infections, lymphoma or neutropenia) were of concern in the included trials but could not be reliably assessed

continued

TABLE 25 Published systematic reviews of adverse events of biologics *(continued)*

Study details	Intervention and patients	Searching and included studies	Analyses	Outcomes
Ravindran *et al.* 2008[161]	Etanercept, infliximab and adalimumab 2039 patients with PsA, in total, receiving the treatment of anti-TNFs, sulfasalazine, gold salts, leflunomide and DMARDs (882 patients with PsA receiving anti-TNFs)	*Data sources*: MEDLINE, EMBASE were searched from 1966 to June 2006. The Cochrane Clinical Trials Register and Cochrane Database for Systematic Reviews were also searched. Reference lists of relevant publications were also searched *Included studies*: 18 RCTs	Studies were combined in meta-analyses using random-effects models. The pooled RRs with 95% CIs for dichotomous outcomes were calculated. The pooled Peto ORs with 95% CIs were calculated for the outcome of overall toxicity, based on withdrawals due to side-effects. Sensitivity analyses were performed. based on agents used and outcome measured. The ratio of NNT to NNH was calculated to assess the benefit vs risk of each treatment	When the studies (two RCTs of etanercept, two RCTs of infliximab and one RCT of adalimumab) were pooled, anti-TNF treatment was associated with a non-significant increase of withdrawal rate due to toxicity compared with placebos (RR 2.2, 95% CI 0.82 to 5.91, $p=0.12$; five RCTs). Anti-TNFs were associated with a high ratio (0.25) of NNT) to NNH
Saad *et al.* 2008[162]	Etanercept, infliximab and adalimumab 982 patients with PsA	*Data sources*: MEDLINE, EMBASE, CINAHL, and the CCTR were searched from inception to May 2007. The US FDA and European Medicines Evaluation Agency websites were searched. Reference lists of relevant publications were also screened *Included studies*: Six RCTs	Studies were combined in meta-analyses using random-effects models. The pooled RRs and RDs for dichotomous outcomes, with 95% CIs, were calculated. The WMDs for continuous outcomes, with 95%CIs were also calculated. Statistical heterogeneity was measured using chi-squared and I^2-statistics. Where there were no direct head-to-head studies comparing an anti-TNF with another, an indirect comparison was undertaken using placebo as the common comparator	There were no significant differences between biologics and placebos in the proportion of patients experiencing withdrawals for any reason (RR 0.48, 95% CI 0.20 to 1.18), withdrawal due to AEs (RR 2.14, 95% CI 0.73 to 6.27), SAEs (RR 0.98, 95% CI 0.55 to 1.77), and URTIs (RR 0.91, 95% CI 0.65 to 1.28). The pooled rate for injection site reactions were significantly higher for adalimumab and etanercept compared with placebos (RR 2.48, 95% CI 1.16 to 5.29). There was no significant difference in the proportion of patients experiencing infusion reactions with infliximab compared with placebos (RR 1.03, 95% CI 0.48 to 2.20) Significant heterogeneity was only observed in the outcome of withdrawal for any reason ($I^2=53.1\%$, $p=0.07$). Indirect analyses did not show any significant differences between these biologics in the proportion of patients experiencing SAEs. Five RCTs ($n=922$) monitored the incidence of malignancies during treatment; only one patient in the placebo group developed a basal cell carcinoma of the skin

AE, adverse event; CCTR, Cochrane Controlled Trials Register; EULAR, European League Against Rheumatism; NMSC, non-melanoma skin cancer; NNH, number-needed-to harm; NNT, number-needed-to treat; RD, risk difference; SAE, serious adverse events; US FDA, US Food and Drug Administration; URTI, upper respiratory tract infection; WMD, weighted mean difference.

et al.[161]), which also reported a non-significant difference between biologics and placebo in the proportion of patients with PsA experiencing withdrawals due to adverse events or serious adverse events. It should be noted that this outcome measure is associated with a methodological limitation: it is difficult to discern withdrawals due to adverse events from those due to poor efficacy, and those that result from a combination of both. In addition, the lack of long-term adverse event data in these two reviews makes it difficult to assess rare but potentially serious adverse events (e.g. malignancy or serious TB infection) of biologics for patients with PsA.

Two reviews assessed the serious adverse events of malignancy and/or serious infections due to use of biologics for patients with RA.[158,159] Bongartz *et al.*[158] reported that malignancies were significantly more common in patients treated with biologics compared with placebo: the pooled odds ratio (OR) for malignancy in patients receiving infliximab and adalimumab compared with placebo was 3.3 (95% CI 1.2 to 9.1) and for serious infection was 2.0 (95% CI 1.3 to 3.1). Malignancies were also significantly more common in patients receiving higher doses of biologics than in patients receiving lower doses of biologics. However, some inconsistent findings were reported in the review by Bongartz *et al.*,[159] which exclusively assessed the serious adverse event of malignancy for etanercept. This review reported that the pooled increased hazard ratio (HR) for malignancies based on IPD was not statistically significant (HR 1.84, 95% CI 0.79 to 4.28) in patients using etanercept compared with placebo or mixed control patients being treated with one DMARD. Similar non-significant results were also generated from the random-effects models. It is noteworthy that the pooled estimate of malignancy due to use of biologics in both of the reviews was limited to short-term follow-up; there is a necessity to evaluate the risk of malignancy of biologics on long-term follow-up durations.

Based on these reviews of adverse events of biologics, in general there is a concern that biologics may be associated with an increased risk of infection and malignancy. Due to some inconsistencies in the results and variations in methods of synthesising the data, no firm conclusions could be drawn from these reviews about the evidence of adverse events of biologics, especially for these serious adverse events. The lack of long-term adverse event data in the majority of reviews could compromise any comparative safety estimation between biologics. Furthermore, a probable exacerbation of latent TB is also considered to be potentially associated with use of biologics.[146,169–171] However, no reviews have addressed this outcome. In particular, adalimumab is a new drug for which there is only limited experience on long-term monitoring; further investigation on its safety is warranted.

In light of the outstanding uncertainties around the findings of previous reviews of biologic safety, our systematic review (see the following section) specifically focused on the serious potential adverse events of these biologics: malignancies, severe infections (i.e. those that require i.v. antibiotic therapy and/or hospitalisation or cause death) and reactivation of latent TB. Apart from RCTs, our systematic review also included observational studies in order to evaluate the long-term adverse events of biologics.

Review of primary studies

Two main sources of information on adverse events were incorporated into the review: RCTs evaluating etanercept, infliximab and adalimumab in PsA, and controlled and uncontrolled studies or registry data in which at least 500 patients with any indication received one or other of these agents.

As the identified non-randomised studies were highly heterogeneous, and because some studies using the same registry at different time points (thereby being likely to contain an overlap in patient data), the range of rates have summarised in a narrative synthesis, and no attempt has been made to pool values across studies. Reported percentage rates of adverse events are

presented for randomised trials and single-arm studies. For non-randomised controlled studies in which the length of follow-up differed between groups, results are presented as the number of events per 100 patient-years where reported.

Etanercept

Randomised controlled trials in psoriatic arthritis Two placebo-controlled RCTs evaluated etanercept in patients with PsA. The first, which followed 60 patients for 12 weeks, reported more infections in the etanercept group than the placebo group for respiratory tract infection (27% vs 13%, respectively), pharyngitis (17% vs 10%), rhinitis (17% vs 13%) and sinusitis (10% vs 7%). Influenza was more commonly reported in the placebo group (0% vs 20%).[78] However, given the small numbers of patients in each group, these differences could be attributable to the play of chance. No deaths or withdrawals due to adverse events were reported for either group. Data on cancer and TB were not clearly reported.

A second, larger placebo-controlled RCT by the same authors, followed 205 patients over 24 weeks.[52,97,99,105,107,110] One patient in the placebo group died following surgical complications, and one patient from each group withdrew from the study. There were no reported cancers. Similar rates were observed between the etanercept and placebo groups for upper respiratory tract infection (URTI) (21% vs 23%), sinusitis (6% vs 8%) and urinary tract infection (6% vs 6%), although again, this efficacy study was not powered to detect a difference between groups in terms of adverse events. TB was not reported.

Non-randomised studies/large randomised controlled trials in other conditions Thirteen non-randomised studies, in which more than 500 patients received biologic agents, reported adverse event data for etanercept. The majority of treated patients had RA, although outcomes for PsA, juvenile idiopathic arthritis, ankylosing spondylitis and patients with other chronic inflammatory conditions were also reported (*Table 26*). Average length of follow-up ranged from 48 weeks to 7 years.

The total reported rate of infections ranged from 9.6% to 54.4% (reported by five studies), with serious infections (requiring hospitalisation) ranging from 2.6% to 16.2% (nine studies). Only

TABLE 26 Adverse events reported for etanercept

Study	Total infections	Serious infections (%)	Cancers	TB (%)	Mortality	Withdrawals to AE
Brassard 2006[135]	–	–	–	1.40	–	–
Carmona 2005[141]	–	–	–	0.00	–	–
Dixon 2006[136]	–	5.80	–	0.06	–	–
Dixon 2007[147]	–	11.20	–	–	–	–
Favalli 2009[129]	–	4.50	–	0.40	–	–
Feltelius 2005[142]	11	2.60	1	–	0.30	5.50
Fleischmann 2006[99]	54.40	4.90	–	0	0.90	6.50
Gomez-Reino 2003[146]	–	–	–	0	–	–
Gomez-Reino 2007[132]	–	–	–	0	–	–
Horneff 2009[125]	9.60	4.30	–	–	0	–
Klareskog 2006[120]	26.50	16.20	1.30	0	1.80	4.60
Listing 2005[122]	21.30	6.10	–	0	–	–
Mease 2006[97]	1.80	0.60	–	–	0	0
Moreland 2006[121]	–	13.20	5.70	0	3.10	13.60

AE, adverse event.

three studies clearly reported cancer, with rates ranging from 1% to 5.7%. Seven out of eleven studies reporting rates of TB in patients receiving etanercept found no cases. The remaining four studies reported rates ranging from 0.03% to 1.4%. Four studies reported rates of withdrawal due to adverse events, ranging from 4.6% to 13.6%. Where reported, mortality ranged from 0% to 3.1% (five studies).

Two of these studies compared adverse event rates in patients receiving etanercept against control.[99,122] One cohort study[122] reported significantly more infections in patients with RA receiving etanercept than control patients (22.6 vs 6.8 infections per 100 patient-years, $p < 0.01$; 6.4 vs 2.3 serious infections per 100 patient-years, $p < 0.01$). However, a second study, an analysis of collated trial data on the use of etanercept reported no significant difference in overall infection rates between etanercept and control (placebo or MTX) across a range of conditions (54.4% vs 41.4%, $p > 0.05$).[99]

Infliximab

Randomised controlled trials in psoriatic arthritis Two placebo-controlled RCTs evaluated infliximab in patients with PsA.[79–82,89–91,95,96,98,106,109,111–118] One RCT followed 104 patients over 16 weeks, reporting more respiratory tract infections in placebo-treated patients than in infliximab-treated patients (9.8% vs 1.9% respectively), though reported rates of bronchitis (7.8% vs 5.8%) and rhinitis (3.9% vs 5.7%) were similar between groups.[79–81,89,96,109,111,113–115,117,118] However, the very small numbers of events reported preclude any meaningful interpretation of these differences. No deaths or withdrawals were reported for either group.

The second RCT followed 200 patients over 24 weeks and reported similar rates between infliximab and placebo groups for URTI (10% vs 14%), pharyngitis (5% vs 4%) and sinusitis (5% vs 4%), although as with other RCTs, the study was not powered to detect differences in adverse events.[82,90,91,95,98,106,112,116] One patient in the placebo group developed basal cell carcinoma of the skin, although no deaths or withdrawals due to adverse events were reported.

Non-randomised studies/large randomised controlled trials in other conditions Eighteen non-randomised studies and two RCTs in indications other than PsA reported adverse event data for infliximab. Outcomes were reported for patients with PsA, juvenile idiopathic arthritis and ankylosing spondylitis, although the vast majority of patients had RA (*Table 27*). Average length of follow-up ranged from 22 weeks to 6 years.

The total reported rate of infections ranged from 8.7% to 26.6% (reported by four studies). Where detailed separately, the most common infections were URTIs, ranging from 10.8% to 38.5% (three studies). Serious infections (requiring hospitalisation) ranged from 0.8% to 13.8% (12 studies). Eight studies reported total cancers, with rates ranging from 0.16% to 5.1%. Sixteen studies reported rates of TB in patients receiving infliximab, 11 of which reported rates less than 0.5%, with the overall range being 0% to 4.6%. Where reported, mortality ranged from 0.06% to 2% (seven studies). Four studies reported rates of withdrawal due to adverse events, ranging from 5.3% to 12.8%.

Four of the studies compared adverse event rates for patients receiving infliximab against some form of control group.[119,122,139,143] Two of these were RCTs of infliximab versus placebo plus MTX in RA,[139,143] of which one found no difference in serious infections between groups at 22 weeks (3.3% vs 1.7%, $p > 0.05$),[139] and one reported significantly more serious infections associated with infliximab at around 54 weeks (5.3% vs 2.1%, $p < 0.05$).[143] Two cohort studies compared adverse event rates between infliximab and control patients: one reported significantly higher rates of overall infections (28.3 per 100 patient-years vs 6.8 per 100 patient-years, $p < 0.01$) and serious infections (6.2 per 100 patient-years vs 2.3 per 100 patient-years) among patients with RA

TABLE 27 Adverse events reported for infliximab

Study		Total infections (%)	Serious infections	Cancer (%)	TB (%)	Mortality	Withdrawals to AE (%)
Antoni 2008[89]		URTI 38.5 Diarrhoea 9.0 Pharyngitis 9.0 Sinusitis 5.1 UTI 5.1	2.6	5.1	0	–	6.4
Brassard 2006[135]		–	–	–	1.8	–	–
Caspersen 2008[128]		–	10.1	0.6	0.3	2.0	–
Carmona 2005[141]		–	–	–	4.6	–	–
Colombel 2004[124]		9.6	3.0	1.8	–	2.0	–
Dixon 2006[136]		–	8.9	–	0.2	–	–
Dixon 2007[147]		–	13.8	–	–	–	–
Favalli 2009[129]		–	8.1	–	0.6	–	–
Fidder 2009[119]		–	6.5	2.9	0.1	1.6	–
Gomez-Reino 2003[146]		–	–	–	1.1	–	–
Gomez-Reino 2007[132]		–	–	–	0.4	–	–
Listing 2005[122]		26.6	5.8		0.3		
Oka 2006[137]		–	3.1	–	0.3	0.06	–
Schnitzler 2009[127]		–	0.8	0.16	–	1.6	12.8
St. Clair 2004[143]		URTI 26.7 Sinusitis 9.7 Pharyngitis 13.8	5.3	0.5	0.5	0.27	9.6
Takeuchi 2008[130]		8.7	Bacterial pneumonia 2.2 Interstitial pneumonitis 0.5	0.16	0.3	–	–
Westhovens 2006[139]	0–22 weeks	URTI 10.8 Pharyngitis 4.7 Sinusitis 4.2 Pneumonia 0.8 TB 0.4 Cellulitis 0.3 UTI 0.3	Pneumonia 0.8 TB 0.4 Cellulitis 0.3 UTI 0.3	2.6	0.4	–	5.3
	22–54 weeks	35.4	3.1	2.6	0.4	0.4	8.0
Wolfe 2004[144]		–	–	–	0.06	–	–

UTI, urinary tract infection.

receiving infliximab,[122] the second reported no significant differences in serious infections (1.6 per 100 patient-years vs 1.1 per 100 patient-years) or cancer (0.4 per 100 patient-years vs 0.5 per 100 patient-years) or mortality (0.3 per 100 patient-years vs 0.2 per 100 patient-years).[119]

Adalimumab

Randomised controlled trials in psoriatic arthritis The smaller of the two RCTs evaluating adalimumab (102 patients over 12 weeks) reported more overall infections in placebo-treated than adalimumab-treated patients (32.7% vs 17.6%, respectively), with the infection classified as 'serious' for a single patient in each group. Reported rates of URTI were 8.2% and 13.7%, respectively.[83] As with other RCTs, small numbers of events reported limit meaningful interpretation of these differences. No deaths were reported for either group, and the small proportions of withdrawals were comparable.

The larger trial, which randomised 315 patients over 24 weeks, reported similar rates between adalimumab and placebo groups for URTI (12.6% vs 14.8%, respectively) and nasopharyngitis (9.9% vs 9.4%).[51,88,92,93,100–104] Serious infections were reported in three patients; two receiving adalimumab and one receiving placebo. No deaths were reported.

Non-randomised studies/large randomised controlled trials in other conditions Eight non-randomised studies and two RCTs in indications other than PsA reported adverse event data for adalimumab. Outcomes were reported for patients with PsA, juvenile idiopathic arthritis and ankylosing spondylitis, although, as for the other agents, most patients had RA (*Table 28*). Average length of study follow-up ranged from 12 weeks to 5 years.

The total reported rate of infections ranged from 9.1% to 45.3% (three studies), with serious infections ranging from 0.4% to 7.3% (nine studies). Four studies reported total cancer, with rates ranging from 0.1% to 1.1%. Eight studies reported rates of TB in patients receiving infliximab, ranging from 0% to 0.4%. Four studies reported rates of withdrawal due to adverse events, ranging from 5.8% to 10.7%. Where reported, mortality ranged from 0.2% to 0.9% (three studies).

Two of these studies were RCTs of adalimumab in conditions other than PsA.[133,140] One RCT of adalimumab alone or in combination with MTX against MTX alone in patients with RA, reported no difference between adalimumab monotherapy and MTX monotherapy in terms of overall infections (110 per 100 patient-years vs 119 per 100 patient-years), serious infections (0.7 per 100 patient-years vs 1.6 per 100 patient-years), or cancer (0.9 per 100 patient-years in each group). However, significantly more serious infections were observed for combined adalimumab/MTX therapy than for adalimumab monotherapy (2.9 per 100 patient-years vs 0.7 per 100 patient-years, $p < 0.05$).[140] The second RCT reported that, after 56 weeks of treatment in patients with Crohn's disease, no significant differences were found between adalimumab and placebo in terms of overall (45.3% vs 36.8%) or serious infection rates (2.7% vs 3.4%).[133]

Studies reporting more than one agent

No RCTs exist that provide a head-to-head comparison between any of the three agents of interest, and substantial clinical heterogeneity precludes any meaningful comparison of rates between the different uncontrolled studies summarised above. However, limited information on the relative rates of certain adverse events between agents was reported by 10 of these uncontrolled studies (*Table 29*).

TABLE 28 Adverse events reported for adalimumab

Study		Total infections (%)	Serious infections (%)	Cancers (%)	TB (%)	Mortality	Withdrawals to AE (%)
Breedveld 2006[140]		9.12	2.20	1.10	0.18	0.90	10.70
Burmester 2007[131]		–	3.10	0.70	0.30	0.50	10.30
Carmona 2005[141]		–	–	–	0	–	–
Dixon 2006[136]		–	5.10	–	0.08	–	–
Dixon 2007[147]		–	7.30	–	–	–	–
Colombel 2007[133]	0–4 weeks	15.20	1.20			0.20	6.30
	4–56 weeks	45.30	2.70	0.20	0.40		5.80
Favalli 2009[129]		–	6.60	–	0.30	–	–
Gomez–Reino 2007[132]		–	–	–	0.20	–	–
Rudwaleit 2009[126]		–	0.40	–	–	–	–
Schiff 2006[138]		–	6.30	0.10	0.30	–	–

TABLE 29 Studies reporting adverse events for more than one biologic agent

Study	Total infections	Serious infections (%)	Cancers	TB (%)	Mortality (%)	Withdrawals to AE
Brassard 2006[135]	–	–	–	Etanercept 1.4 Infliximab 1.8	–	–
Carmona 2005[141]	–	–	–	Infliximab 4.6 Etanercept 0 Adalimumab 0	–	–
Curtis 2007[134]	–	2.70	–	–	–	–
Dixon 2006[136]	–	Etanercept 5.8 Infliximab 8.9 Adalimumab 5.1	–	Etanercept 0.06 Infliximab 0.2 Adalimumab 0.08	–	–
Dixon 2007[147]	–	Etanercept 11.2 Infliximab 13.8 Adalimumab 7.3	–	–	–	–
Dreyer 2009[148]	–	–	0.76	–	–	–
Favalli 2009[129]	–	Etanercept 4.5 Infliximab 8.1 Adalimumab 6.6	–	Etanercept 0.4 Infliximab 0.6 Adalimumab 0.3	0.40	–
Gomez-Reino 2003[146]	7.60	0.65	–	Etanercept 0 (0) Infliximab 17 (1.1)	0.10	–
Gomez–Reino 2007[132]	–	–	–	Etanercept 2 (0.1) Infliximab 5 (0.4) Adalimumab 1 (0.2)	–	–
Listing 2005[122]	Etanercept 21.3 Infliximab 26.6	Etanercept 6.1 Infliximab 5.8	–	Etanercept 0 (0) Infliximab 1 (0.3)	0.50	–

Patients with RA predominated and the average length of study follow-up (where reported) ranged from 1 to 5 years. One prospective cohort study reported a total rate of infections of 21.3% (6.1% serious) and 26.6% (5.8% serious) for etanercept and infliximab, respectively.[122] Three more studies reported rates of serious infections for all three agents: etanercept (5.8%, 11.2%, 4.5%), infliximab (8.9%, 13.8%, 8.1%) and adalimumab (5.1%, 7.3%, 6.6%).[129,136,147]

Rates of TB were reported in seven studies of patients receiving etanercept (0%–1.4%) and infliximab (0%–4.6%), four of which also included patients receiving adalimumab (0%–0.3%).

One large prospective cohort study of reported that 0.76% of patients treated with biologic agents developed cancer during follow-up.[148] None of the studies provided adequate data on rates of withdrawal, and no studies provided separate mortality data for each agent.

Summary of serious adverse events across all three agents

Table 30 summarises the rates of serous adverse events, where reported, among the included non-randomised studies and large RCTs. This indicates that the rates of serious adverse events cover a broadly similar range across the three different biologic agents. However, it should be noted that all of these estimates are derived from a highly heterogeneous group of studies in terms of participants (e.g. inflammatory condition, disease severity), study design (e.g. length of follow-up) and treatment regimens (e.g. dose and frequency). Consequently, reliable estimates of the relative rate of serious adverse events for each drug cannot be made.

TABLE 30 Range of serious adverse event and withdrawal rates across non-randomised studies/large RCTs

Drug	Serious infections (%)	Cancer (%)	TB (%)	Mortality (%)	Withdrawals due to AE (%)
Etanercept	0.6–13.2	1–5.7	0–1.4	0–3.1	0–13.6
Infliximab	0.8–13.8	0.16–5.1	0.06–4.6	0.06–2.0	6.4–12.8
Adalimumab	0.4–5.1	0.1–1.1	0–0.4	0.5–0.9	5.8–10.7

Withdrawal rates due to adverse events were typically < 10% for all drugs, with the highest reported single estimate being 13.8% for one etanercept study. This would suggest that the majority of patients can tolerate biologic treatment in the medium term, although again these estimates are derived from a highly heterogeneous group of studies, therefore poorer tolerability in specific patient groups cannot be ruled out.

Discussion of clinical evaluation

Efficacy

Study design and quality

All six included studies were randomised, double-blind controlled trials. Based on the quality assessment using the pre-specified criteria, all the included trials were rated as 'good' quality. Concealment allocation and blinding were adequate in almost all included trials. All of the trials appeared to deal with withdrawals appropriately by using intention-to-treat (ITT) analyses. The completeness of follow-up was fairly good in all trials, with losses to follow-up of < 20%, thereby minimising attrition bias.[172] All the trials reported the use of a power calculation to determine the sample size. Five of them had an open-label extension after the randomisation period. However, it should be noted that the maximum randomised follow-up period across these trials was only 24 weeks.

Though there were some differences relating to patients' characteristics at baseline across the trials, participants were generally similar in terms of disease activity and severity, and were likely to represent a population with moderate to severe PsA requiring further treatment. This was reflected by the lack of evidence for statistical heterogeneity in most efficacy analyses in this review. However, although the majority of patients in the trials had previously received at least one DMARD, no trial specified the failure to respond to at least two DMARDs (patients whom the current BSR guidelines consider eligible for biologic treatment) as a recruitment criterion. Therefore, trial participants were not precisely representative of patients receiving these agents in practice, and were likely to have had less severe disease, having often received biologic therapy after failing a single DMARD.

There were inconsistencies in the choice of primary outcome between included studies. Most studies used the ACR 20 as the primary outcome measure, while one trial used the PsARC as the primary outcome. However, it should be noted that ACR 20 is not frequently used in routine clinical practice to measure response to a biologic treatment.

Outcomes relating to joint disease

There were limited efficacy data from RCTs for the three biological agents. For each agent, there were two RCTs with around 200 or fewer patients receiving active treatment. However, all six trials were of good quality and provided clear indication of a response to treatment at 12–16 weeks, with continued efficacy at 24 weeks for each biologic agent.

Point estimates of effect sizes were generally moderate to large, implying that these treatment effects could be clinically significant. Moreover, although a very small number of studies were

pooled for each estimate, the CIs indicate reasonable precision of these estimates. However, pooling the long-term efficacy data from trials was impossible due to lack of data.

In general, there was no significant heterogeneity in the treatment effect for almost all of the efficacy outcomes, with the PsARC in infliximab being the only exception. The radiographic data from RCTs of etanercept and adalimumab in PsA demonstrated a beneficial effect on joint disease progression at 24 weeks. Follow-up this early is often considered insufficient to detect radiological changes, although if the 24-week effect is reliable it would indicate a rapid onset of action in terms of joint disease for these agents. The open-label extensions of these RCTs also provided data on radiographic assessment at long-term follow-up, indicating that the effect on joint disease progression may persist over time. However, the reliability of these longer-term data was compromised by the lack of a control group.

Functional status (Health Assessment Questionnaire)

All three agents appeared to have beneficial effects on functional status as measured by HAQ. The estimates with relatively high precision indicated that all of the biologic therapies significantly improved the functional status of patients with PsA at around 3 months' follow-up. The clinical significance of these effects was not entirely clear, for example, adalimumab was associated with a significant absolute mean reduction of HAQ score from baseline of –0.27 (95% CI –0.36 to –0.18). However, only changes > –0.3 have been considered as clinically meaningful improvement in PsA.[150]

In this systematic review, the benefit of the biologic treatment compared with placebo on joint disease outcomes was consistent with the previous systematic review, which investigated the efficacy of etanercept and infliximab in the treatment of PsA.[73] In general, both of the systematic reviews used the same rigorous methodology and revealed similar magnitudes of the treatment effect of etanercept and infliximab. The current review also assessed effects of the recently licensed biologic agent 'adalimumab' and demonstrated its beneficial treatment effects compared with placebo.

Outcomes relating to skin disease (psoriasis component)

Skin outcomes (i.e. PASI response) were less commonly reported than joint response measures. Where reported, these results were generally statistically significant, although CIs were wide – possibly due to the small sample size of patients evaluable for psoriasis in the trials. Overall, biologic treatment appears to have a broadly beneficial effect on skin disease in patients with PsA. Evidence of response from trials in patients with psoriasis lay outside the scope of this evaluation.[173,174]

Relative efficacy of the biologics

As data for the direct head-to-head comparison between these biologic agents were not available from trials, the relative efficacy of these biologic agents in the treatment of PsA was evaluated using Bayesian indirect comparison methodology.

The results of this evidence synthesis highlighted the superior efficacy of biologics over placebo across the outcomes evaluated. Infliximab appears to be the most effective among the three biologics. Patients treated with infliximab had a higher probability of responding to treatment regarding both the skin and arthritis aspects of disease. Additionally, we have estimated that infliximab allows improvements in the functional and psychological impact of the disease, measured by HAQ. However, patients who responded to etanercept achieved similar mean changes in HAQ (–0.6275 for infliximab and –0.6235 for etanercept) with placebo non-responders being used as a baseline in the synthesis. For all three biologics the changes in HAQ for those patients who did not respond to treatment were below the suggested minimum

clinically significant threshold,[150] and only those for infliximab achieved statistical significance. A comparison of the indirect comparison undertaken by the Assessment Group with those of the manufacturers shows similar mean estimates of treatment effect despite the rather different methods used.

Safety

Study design and quality

For the evaluation of adverse events of these biological agents, this review included a range of study types including RCTs, trial open-label extensions and observational studies. The quality of studies therefore varied across these different study designs; in particular, observational studies were subject to confounding, thereby threatening the internal validity of their findings. In addition, the definition of serious adverse events was also unclear in most studies.

Outcomes relating to serious adverse events

Previous systematic reviews have focused on short-term follow-up and reported conflicting findings on the risk of serious infections and cancer associated with biologic treatment. Our current systematic review contributes an evaluation of potential serious adverse events of biologic treatment in the longer term, incorporating the risk of activation of latent TB. Although the estimates of the rates of these adverse events varied widely, the findings from our review did raise a concern that treatment with etanercept, infliximab and adalimumab might be associated with an increased risk of serious infection, malignancy and activation of latent TB. The adverse event analyses demonstrated that etanercept, infliximab and adalimumab were associated with a broadly similar range of incidences of these events. However, there was considerable uncertainty around these estimates, in part due to the high degree methodological and clinical diversity between the included studies. In addition, the adverse event data were derived primarily from patients with RA or other indications, so the generalisability of these findings to patients with PsA remains unclear. Overall, the limited evidence prevents firm conclusions about the comparative safety of the three biologic agents being drawn from our systematic review.

Chapter 4

Assessment of cost-effectiveness evidence

Systematic review of existing cost-effectiveness evidence

The purpose of this section of the report is to review existing evidence on the cost-effectiveness of biologic therapy in PsA. It includes submissions made to NICE by the manufacturers of the three biologic agents included in this assessment.

Methods

A broad range of studies was considered for inclusion in the assessment of cost-effectiveness, including economic evaluations conducted alongside trials and modelling studies. Only full economic evaluations that compared two or more options, and considered both costs and consequences, were included.

The following databases were searched for relevant published literature: Cochrane Controlled Trials Register (CCTR), EMBASE, HEED, MEDLINE, National Research Register (NRR), NHS EED, PsycINFO and SCI. Full details of the main search strategy for this review are presented in *Appendix 1*.

Two reviewers assessed all obtained titles and abstracts for inclusion, with any discrepancies resolved by discussion. In addition, the industry submissions to NICE were included in the review.

The studies have been summarised within the text of the report. A summary of effectiveness, costs and cost-effectiveness is presented along with a critique of the studies. The quality of the cost-effectiveness studies was also assessed according to a checklist updated from that developed by Drummond *et al.*[175]

Results

Identified studies

The systematic literature of published literature identified three studies,[176–178] which met the inclusion criteria for the cost-effectiveness review (one of which is the journal publication of the previous York Assessment Report model for NICE on etanercept and infliximab[73]). In addition there were three industry submissions to NICE from Abbott,[151] Schering-Plough[152] and Wyeth.[153]

Of the six cost-effectiveness studies available, described above, five of these are decision-analytic models, incorporating evidence from a variety of sources, and one is a cost-effectiveness study, using evidence from a single trial.

Available data

Table 31 summarises the data available from each of the six cost-effectiveness studies.[151–153,176–178] The studies by Olivieri *et al.*[178] and Bansback *et al.*[176] are only available as journal articles. The study by Bravo Vergel *et al.*[177] is available as a journal article, but also as a full assessment report with an accompanying electronic model.[73] The three industry submissions included full reports

TABLE 31 Summary of information sources available for the cost-effectiveness studies

	Journal article	Full report	Electronic model	Additional utility regression	Clarifications
Olivieri 2008[178]					
Bansback 2006[176]	✓				
Bravo Vergel 2007[177]	✓	✓	✓		
Abbott submission 2009[151]		✓	✓	✓	✓
Schering-Plough submission 2009[152]		✓	✓	✓	
Wyeth submission 2009[153]		✓	✓	✓	✓

and electronic models. Where an electronic model has been made available it has been possible to provide some validation of the model by ensuring that the base-case results provided by the manufacturer in its report can be replicated. It was also possible to check parameter estimates presented in the reports against those used in the relevant models.

Due to differences in the regression methods used to generate utility estimates in the industry submissions, the Assessment Group requested that each manufacturer provide new utility estimates using a common methodology (see *Appendix 17*) and report the results of this regression, as coefficients, a variance–covariance matrix, the number of observations, the number of clusters (if appropriate) and indicating the source of data. This information was provided by manufacturers for all three of the submissions.

In addition, a number of further clarifications on data sources and methodology were sought from the three manufacturers on data sources and methodology (full details in *Appendix 6*). Wyeth[153] clarified that 12- and 24-week response rates were modelled independently, provided an estimation of HAQ without PASI as a predictor, and clarified how withdrawal rates were calculated (see *Critique of manufacturers' submissions and justification for current York modelling approach*). Abbott[151] clarified how many DMARDs were sequenced in the model, how withdrawal rates were calculated (see *Chapter 4*, *Critique*) and clarified the degree of correlation between arthritis and skin outcomes. No further clarifications were sought from Schering-Plough[152] other than the additional utility regressions.

Summaries of cost-effectiveness studies

A full description of each of the six cost-effectiveness studies, along with a quality assessment checklist, is presented in *Appendix 7*. *Table 32* summarises the key features and data sources for each of the studies.

As shown in *Table 32*, the six cost-effectiveness studies produce different costs and quality-adjusted life-years (QALYs), resulting in different incremental cost-effectiveness ratios (ICERs) for the various options being compared. The study by Olivieri *et al.*[178] is difficult to compare with the others, as all biologics were considered as a group compared with DMARDs. This produced an ICER of around €40,000 for biologics. Bansback *et al.*[176] produced an ICER of around £38,000 for etanercept compared with the next best strategy – leflunomide. Bravo Vergel *et al.*[177] produced a much lower ICER for etanercept, of between £26,361 and £30,628, depending on the rebound scenario used. The studies including all three biologics in this assessment – adalimumab, etanercept and infliximab – also show large differences in results. Abbott[151] generates an ICER for adalimumab of £29,827, with etanercept dominated by adalimumab and infliximab, with

TABLE 32 Summary of cost-effectiveness evidence identified in the review

	Olivieri[178]	Bansback[176]	Bravo Vergel[177]	Abbott[151]	Schering-Plough[152]	Wyeth[153]
Comparators	Biologics (as a group) compared with non biologics	Etanercept, ciclosporin and leflunomide	Etanercept, infliximab and palliative care	Etanercept, infliximab, adalimumab and DMARDs (which includes different combinations of DMARDs)	Etanercept, infliximab, adalimumab and palliative care	Etanercept, infliximab, adalimumab and DMARDs
Model structure	No model Economic evaluation alongside a before/after study	Response according to PsARC determined and associated HAQ score. Changes in HAQ and further withdrawals are modelled over 10-year time horizon	Response according to PsARC determined and associated HAQ score. Changes in HAQ and further withdrawals are modelled over 40- and 10-year time horizons	Response according to the joint distribution of PsARC and ACR response rates. Associated HAQ and PASI changes by type of response. Changes in HAQ and further withdrawals are modelled over a lifetime time horizon	Response according to PsARC determined and associated HAQ score. Changes in HAQ and further withdrawals are modelled over a lifetime time horizon	Response according to PsARC determined and associated changes in HAQ and PASI. Initial change in HAQ is a function of PASI and PsARC. Longer-term changes in HAQ were modelled using observed changes in PASI score, PASI 75 response and PsARC response. Changes in HAQ and further withdrawals are modelled over a 50-year time horizon
Patient inputs	Single trial of 107 patients from nine tertiary referral centres in Italy	Individual sampling model using patient-level data from Mease *et al.*[52]	Baseline HAQ is assumed to be average from the three trials (Mease *et al.*[52,78] and Antoni *et al.*[81])	Individual sampling model using baseline patient characteristics from the ADEPT trial[88] used to determine the distribution of patients characteristics in the model	Baseline HAQ of 1.1 is assumed. Baseline PASI of 11 is assumed. The sources of these are not presented. For patients with no clinically significant psoriasis component to their disease only the change in HAQ is modelled	Individual sampling model using baseline characteristics of patients were taken from the Mease *et al.*[52] Subgroups were: mild, moderate and severe HAQ, and mild, severe and very severe PASI

continued

an ICER over £199,000. Schering-Plough[152] report results for all patients, psoriatic patients and non-psoriatic patients. For all patients, etanercept is the most cost-effective strategy, assuming a patient weight of 70 or 80 kg (ICER of £12,606 compared with adalimumab). For a 60-kg patient etanercept is the most cost-effective strategy for patients without psoriasis (ICER of £12,432 compared with adalimumab) and infliximab is the most cost-effective for psoriatic patients and all patients, dominating etanercept. Wyeth[153] produces a base-case ICER for etanercept of £12,480 compared with DMARDs. All other biologics are dominated or extendedly dominated.

TABLE 32 Summary of cost-effectiveness evidence identified in the review *(continued)*

	Olivieri[178]	Bansback[176]	Bravo Vergel[177]	Abbott[151]	Schering-Plough[152]	Wyeth[153]
Sources of effectiveness evidence	Effectiveness from a single trial	Mease *et al.*[52] used to determine response rates and HAQ	Short-term trial data (Mease *et al.*[52,78] and IMPACT[81]) were used to model the PsARC response of patients	Data from 10 different sources to determine short-term efficacy	In many cases results from the York model were used as priors in the Bayesian evidence synthesis. Data from the previous York model[177] along with IMPACT,[81] IMPACT 2,[82] Mease *et al.*[52,78] GO-REVEAL,[156] Genovese *et al.*[83] and ADEPT[51] were used in the evidence synthesis model	Data from the published MTC for adalimumab[179] and the Mease *et al.* trial[52] comparing etanercept with placebo were used to estimate effects
Synthesis of effectiveness evidence	Effectiveness from a single trial	Effectiveness from a single trial	A Bayesian evidence synthesis was used to generate estimates of PsARC and mean improvements in HAQ score conditional on response using the three trials via indirect comparisons methods	A Bayesian evidence synthesis was used to determine: (1) joint distribution of 12-week PsARC and ACR response rates; (2) 24-week PsARC response conditional on the 12-week PsARC response; and (3) 24-week ACR response conditional on the 12-week ACR response Patient-level data from ADEPT[88] used to estimate HAQ and PASI changes	A Bayesian evidence synthesis was used to generate estimates of PsARC and mean improvements in HAQ and PASI score conditional on response	A published MTC for adalimumab[179] and the Mease *et al.* trial[52] was used to estimate PsARC response and improvements in HAQ and PASI

It is difficult to disentangle exactly why, in some cases, the six studies produce markedly different results. However, there are a number of key differences between the modelling approaches and the data sources used in the six cost-effectiveness studies that may provide some explanation.

1. *Choice of comparator* All biologics were grouped together in the Olivieri *et al.* study,[178] although the majority of patients were taking etanercept. It is, therefore, not possible to estimate any differences in the cost-effectiveness between the biological agents. Bansback *et al.*[176] compare only etanercept with DMARDs, omitting all other biologics, whereas Bravo Vergel *et al.*[177] compare only infliximab and etanercept with palliative care. The models from Abbott,[151] Schering-Plough[152] and Wyeth[153] all include the three biologics etanercept, infliximab and adalimumab. However, Abbott[151] and Wyeth[153] compare these with DMARDs, whereas Schering-Plough[152] use palliative care as the comparator. The patient group specified by the decision problem (see *Executive summary*, *Objectives*) are those who have previously

TABLE 32 Summary of cost-effectiveness evidence identified in the review *(continued)*

	Olivieri[178]	Bansback[176]	Bravo Vergel[177]	Abbott[151]	Schering-Plough[152]	Wyeth[153]
Sources of cost data	Resource use collected retrospectively from patients Diagnosis-related group costs were used to cost hospitalisations. Little detail on other medical costs. Transportation costs from patients' reports. Carers' costs and days lost from work were costed using the human capital approach	Drug costs were taken from MIMS and administration and monitoring costs generated using resource use recommended in the BSR guidelines The cost offsets of improving disability were also estimated using a study of patients with RA	Drug costs were taken from the *BNF*. Administration and monitoring costs were estimated using industry assumptions regarding resources use and published unit costs The costs associated with PsA were estimated as a function of HAQ score using a published study in RA	The cost of drugs was estimated using MIMS. Resource use associated with monitoring and administering drugs was estimated according to BSR guidelines The relationship between HAQ score and disease-related hospital costs was estimated using the NOAR database. A physician survey was conducted to assess the ongoing costs of psoriasis	Resource use associated with treatment, administration and monitoring was taken from the previous York model. Health-care costs as a function of HAQ were derived from the Kobelt *et al.* study[41] (CiC information has been removed)	The costs of medication were taken from the *BNF*.[65] A Administration and monitoring was costed as recommended in the BSR guidelines. Health-care costs associated with PsA were taken from an evaluation by HODaR, using data from BSRBR and THIN (reference not given). PASI are not included, as PASI is assumed to be a predictor of HAQ
Utilities	EQ-5D utility scores were used in the cost-effectiveness analysis. These were collected directly from patients at 6 months preceding biologics treatment, baseline, 6 months and 12 months	Leeds cohort study used to estimate utilities. The relationship between health utilities and HAQ was examined using linear regression models	Leeds cohort study used to estimate utilities. The relationship between health utilities and HAQ was examined using linear regression models	In the base-case data from the ADEPT trial[88] of adalimumab was used. SF-36 was converted to EQ-5D	Two alternative methods to generate utilities were explored: the Gray *et al.* algorithm[180] (selected as the base case) and the Brazier algorithm[181]	The relationship between HAQ and EQ-5D observed in the PRESTA data set[157] was used in the base case to generate utilities. The relationship between PASI and EQ-5D was not included

continued

failed two DMARDs. Therefore, these patients may be unlikely to be considered for further DMARD treatment, which suggests that they would instead receive palliative care.

2. *Sources and synthesis of effectiveness data* Olivieri *et al.*[178] use a relatively small sample of patients recruited from a single site. The analysis has a limited length of follow-up (12 months) and, as PsA is a chronic disease, it is unlikely that all differences in costs and outcomes between comparators can be captured in this short time frame. This is also a before/after study, so there may be a problem of selection bias. Bansback *et al.*[176] similarly use data from a single phase II trial to determine effectiveness. Other relevant randomised trials are now available, and this evidence should be appropriately synthesised to inform cost-effectiveness. The models by Bravo Vergel *et al.*,[177] Abbott,[151] Schering-Plough[152] and Wyeth[153] all use multiple sources to determine the short-term effectiveness of treatments, all of these synthesising data using a Bayesian methods in WINBUGS. However, in the Abbott[151] and Schering-Plough[152] models, some of these data sources relate to treatments not included as comparators in the model, such as golimumab (see *Chapter 3, Results of review of clinical*

TABLE 32 Summary of cost-effectiveness evidence identified in the review *(continued)*

	Olivieri[178]	Bansback[176]	Bravo Vergel[177]	Abbott[151]	Schering-Plough[152]	Wyeth[153]
Base-case results	At 12 months there was a gain of 0.25 in utility for biologics, equating to a 0.12 gain in QALYs. Direct costs increased by €5052. This produces an ICER of €40,876 for the NHS and an ICER of €37,591 for society	QALYs were 4.49 for etanercept, 3.67 for ciclosporin and 3.84 for leflunomide Total costs of etanercept over 10 years is estimated as £51,122, ciclosporin was £28,010 and leflunomide £26,822 This gives an ICER for etanercept of £28,000 compared with ciclosporin and £38,000 compared with leflunomide	Infliximab is the most effective strategy in both scenarios (4.636 and 4.455 QALYs). Total mean costs were highest for infliximab in both rebound scenarios (£64,274 and £64,418, respectively) The ICERs for infliximab are unlikely to be considered reasonable. The ICER for etanercept for rebound equal to gain is £26,361 and for rebound equal to natural history is £30,628	Infliximab was associated with the highest QALYs (8.49) at a cost of £104,772 The ICER for infliximab is unlikely to be considered acceptable. Adalimumab has an ICER of £29,827 compared with a DMARD	Infliximab is the most effective strategy, for all patients as a group and psoriasis patients (8.65 QALYs for all patients and 8.40 QALYs for patients with psoriasis), but is also associated with the highest cost (between £107,954 and £123,475) Infliximab is the most cost-effective strategy for a 60-kg patient, for all patients, and for psoriatic patients. For a 70-kg patient etanercept is the most cost-effective strategy for all patients and for psoriatic patients. For an 80-kg patient etanercept is the most cost-effective strategy for all patients and for psoriatic patients, with ICERs of £12,696 and £12,606 compared with adalimumab. For all patient weights, etanercept is the most cost-effective with an ICER of £12,432 compared with adalimumab for non-psoriatic patients	Etanercept was associated with the highest gain in QALYs (6.90). Infliximab had the highest total costs (£66,867). The base-case results show that infliximab is dominated by adalimumab and adalimumab extendedly dominated by etanercept. Comparing etanercept with ciclosporin results in an ICER of £12,480

effectiveness). The implications of using this wider selection of treatments in the evidence synthesis are uncertain.

3. *Effect of treatment on skin component of disease* Although PsA is associated with psoriasis as well as an inflammation of the joints, Bansback *et al.*[176] and Bravo Vergel *et al.*[177] do not include the effect of treatments on the skin component of PsA, whereas the models by Abbott,[151] Wyeth[153] and Schering-Plough[152] all include the effect of both conditions. In the Wyeth model,[153] however, the initial change and longer-term changes in HAQ were determined, including PASI as an explanatory variable. Although PASI and HAQ are used to measure the severity of the two components of PsA, psoriasis and arthritis, there are only

TABLE 32 Summary of cost-effectiveness evidence identified in the review *(continued)*

	Olivieri[178]	Bansback[176]	Bravo Vergel[177]	Abbott[151]	Schering-Plough[152]	Wyeth[153]
Key sensitivity analysis	–	Sensitivity analysis showed that the ICER was sensitive to the baseline HAQ and annual HAQ progression	Results were sensitive to many of the changes in parameters, in particular not using a specific stopping rule for biologic therapy and instead using no response test and withdrawal rates from BSRBR and the rebound assumption	Results were sensitive to the stopping rule for BSRBR withdrawal rates and the rebound assumption	Biologics appear to be robust to the sensitivity analysis compared with palliative care, apart from changing the algorithm for estimating QoL	Results are sensitive to the rebound effect, the utility function used and annual progression on standard care

BSRBR, British Society for Rheumatology Biologics Register; DRG, diagnosis-related group; EQ-5D, European Quality of Life-5 Dimensions; GO-REVEAL, Golimumab-Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody; HODaR, Health Outcomes Data Repository; ICER, incremental cost-effectiveness ratio; MIMS, online and print prescribing database for health professionals; NH, natural history; NOAR; Norfolk Arthritis Register; SF-36, Short Form questionnaire-36 items; QALY, quality-adjusted life-year; THIN, The Health Improvement Network.

limited circumstances in which a patient's psoriasis should affect their degree of functional disability or joint disease, as measured by HAQ.

4. *Model structure* Olivieri *et al.*[178] does not use a model to generate estimates of costs and QALYs and instead uses the results of an economic evaluation conducted alongside a single trial. The models by Bansback *et al.*,[176] Bravo Vergel *et al.*[177] and Schering-Plough[152] all determine response according to PsARC and then model the associated HAQ score. Schering-Plough[152] includes PASI change from baseline to 12 weeks, but estimates this for weeks for PsARC responders/non-responders. Wyeth[153] similarly determines response according to PsARC and calculates the associated change in HAQ and PASI. However, initial change in HAQ is modelled using changes in PASI and PsARC, and longer-term changes in HAQ were modelled using observed changes in PASI score, PASI 75 response and PsARC response. Abbott[151] use ACR response rates in addition to PsARC to determine the joint distribution of response, and then associated HAQ and PASI changes by type of response. Schering-Plough[152] assumes that changes in HAQ in the first 3 months are a function of PsARC response and the biologic used, whereas Abbott[151] and Wyeth[153] assume that changes in HAQ are independent of the biologic used after conditioning on other predictive clinical and demographic variables (such as ACR and age).
5. *Patient characteristics* Of the five model-based studies, three of these use an individual sampling approach, with baseline characteristics taken from IPD from trials.[151,153,176] Bravo Vergel *et al.*[177] and Schering-Plough[152] both use cohort models, with common baseline HAQ/PASI scores, which are then varied in a sensitivity analysis. The individual sampling models are complex and time intensive in order to run probabilistic sensitivity analysis. They are also difficult to audit and there may be differences in methodology used in these models that the Assessment Group were not able to fully explain in the constrained timescale.
6. *Sources of cost data* In their trial-based evaluation, Olivieri *et al.*[178] collected resource use data retrospectively from patients and valued these using appropriate unit costs. The model-based studies all include the same set of costs: drug acquisition, drug administration and monitoring, and costs of disability and psoriasis (where PASI was included in the model). However, the cost estimates generated differ quite significantly between models (see *Critique of manufacturers' submissions and justification for current York modelling approach*), reflecting different methodology and sources of data.

7. *Sources of utility data* Olivieri *et al.*[178] collected utilities directly from patients who were enrolled in the trial, using the European Quality of Life-5 Dimensions (EQ-5D questionnaire). These were collected for the 6 months preceding biologic treatment, baseline, and 6 months and 12 months after starting treatment. The other studies use different external data sets to generate utilities and used regression analysis to link the utility data to clinical parameters. Each of the studies assumed that utility was independent of the biologic treatment used, after conditioning on HAQ and PASI. However, each used a different function to relate utility to HAQ and PASI, and it is possible that different utility regressions result in differences in the relative impact of HAQ/PASI on utility between treatments. Bansback *et al.*[176] and Bravo Vergel *et al.*[177] both use the Leeds cohort study as a source of utility estimates. Abbott[151] use the ADEPT trial[88] of adalimumab, which reports Short Form questionnaire-36 items (SF-36 data), which are then converted to EQ-5D to generate utilities. Schering-Plough[152] use the same approach, but use the GO-REVEAL (Golimumab-Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody)[156] trial data set. Wyeth[153] use the relationship between HAQ and EQ-5D observed in the Psoriasis Randomized Etanercept STudy in Subjects with Psoriatic Arthritis (PRESTA) data set in the base case to generate utilities, and the relationship between PASI and EQ-5D was indirectly included only through the effect of PASI on HAQ.

Relevance of cost-effectiveness evidence for NICE decision-making

The evidence provided from the cost-effectiveness study conducted alongside a single trial[178] is not considered relevant for UK decision-making because of its lack of a concurrent control group, narrow use of evidence (a single trial) and limited length of follow-up (12 months). The five modelling studies are, however, potentially relevant for UK decision-making. The current appraisal has recognised the need to assess the effect of biologics on both the arthritis and the psoriasis component of the disease. Only the three industry models include the psoriasis aspect of PsA, and therefore only these models are relevant to address the decision problem as specified by the NICE scope.

There are a number of issues with the three industry models that require further consideration. These are discussed in further detail in the section *Critique of manufacturers' submissions and justification for current York modelling approach,* later in this chapter, but can be summarised as:

- The use of DMARDs as a comparator to biologics used in the Wyeth[153] and Abbott[151] models. This approach can be criticised if it is considered unrealistic for patients who have previously failed two or more DMARDs, as defined in the BSR guidelines[149] to receive a third DMARD.
- In estimating the treatment effect, the Abbott[151] and Schering-Plough[152] models use data sources relating to comparators not included in the model, such as golimumab, and the implications of this are not clear. It is uncertain whether the relative treatment effects can be transferred from one biologic to another.
- Also for the Wyeth submission[153] data from an existing synthesis for adalimumab[179] and the Mease *et al.* trial[52] were used to estimate effects. Although data were included from a number of trials in the adalimumab MTC, new trial evidence may be available and efforts should be made to identify any new relevant data.
- In estimating the treatment effect, it is also important to consider what treatment effect is likely to be observed in general practice. RCTs might overestimate the *absolute* response rates in both placebo and treatment groups. Schering-Plough[152] assume that this is the case and adjust the expected effectiveness of biologics, whereas the Wyeth[153] and Abbott[151] models do not make any such adjustment. The models do not use sensitivity analysis to assess how much difference this adjustment makes to the results.

- Withdrawals after 3 months due to adverse events and lack of efficacy were estimated from a single data set (BSR register) in all of the industry models. There are other potential biologic registry data sets available, which could have been synthesised.
- The prediction of initial change in HAQ and longer-term changes in HAQ using PASI as an explanatory variable in the Wyeth model[153] is questionable. There is no evidence to suggest that one component of the disease is a good predictor of the other, although there may be a correlation between joint and skin response, which has not been explored in any detail by the industry models.
- There are some considerable differences in the sources of costs and the costing methodology used in each of the three industry models (see *Critique of manufacturers' submissions and justification for current York modelling approach*). It is therefore important to understand what these differences are and to generate appropriate costs for the model.
- The results from each of the industry models are also markedly different. There is therefore a need to develop a de novo model that considers and addresses each of these limitations. This model is presented below.

York Economic Assessment

Methods of York Economic Assessment

Introduction

The review of models detailed in published literature (including the earlier one by the York Assessment Group) and those in the company submissions to this appraisal (see *Systematic review of existing cost-effectiveness evidence*) indicates that a wide range of assumptions and evidence was used in model development. None of the models reviewed can be considered unequivocally superior to the others. In this section we further develop the earlier York Assessment Group model, reflecting more recent evidence about PsA and the use of biologics in its treatment. This model also provides a framework within which to compare the assumptions and evidence used in the different models and to assess their implications for the cost-effectiveness results.

Previous guidance has been issued by NICE on the use of biologics in PsA.[182,183] The main limitation of the economic assessments informing this earlier guidance was that they did not take account of the effect of the drugs on psoriasis. Therefore, a key objective of the updated York model is to assess the cost-effectiveness of etanercept, infliximab and adalimumab for PsA, taking account of the cost and health impact of the patient's psoriasis and joint disease, and the impact of therapy.

Methods

Overview

A probabilistic decision-analytic model was developed to estimate the costs and QALYs of the three biologics over a lifetime (40 years) compared with palliative care only. The model has similarities with the earlier York Assessment Group model, but a number of changes have been implemented, necessitating a full description of the model here. The model aims to be consistent with licensed indications and current BSR[149] and BAD[173] guidelines for the use of biologics in PsA (*Box 1*).

The parameters of the model were obtained from published literature, manufacturers' parameter estimates, the results of the evidence synthesis in *Chapter 3*, *Efficacy of all three biologics* and a structured elicitation of expert opinion. The model adopts the perspective of the UK NHS and Personal Social Services. The price year is 2008–9 and the annual discount rate is 3.5%.[184] The population is assumed to be 47 years old, with at least 7 years since diagnosis of PsA, based on the average characteristics of participants in the RCTs (see *Table 1*). The body weight is assumed to

BOX 1 Licensed indications and guidelines for commencing biologics in PsA

Licensed indications for use of biologics in PsA

Etanercept, infliximab and adalimumab are licensed for the treatment of active and progressive PsA in adults when the response of previous DMARD therapy has been inadequate. Infliximab should be administered in combination with MTX or alone in patients who show intolerance to MTX or for whom MTX is contraindicated

BSR guidelines for commencing biologics in PsA

Biologic therapy, within its licensed indications, is recommended for the treatment of adults with active PsA only when the following criteria are met:

- The person has peripheral arthritis with three or more tender joints and three or more swollen joints on two separate occasions, at least 1 month apart, based on a 78-tender and 76-swollen-joint count
- The PsA has not responded to adequate trials of at least two standard DMARDs, administered either individually or in combination

BAD guidelines for commencing biologics in psoriasis and PsA

To be considered eligible for treatment with biologic therapy, patients must have:

- severe disease, defined as a PASI score of 10 or more and a DLQI > 10

and

- contraindications to (have developed, or are at risk of developing) clinically important drug-related toxicity, where phototherapy and alternative standard therapy cannot be used, or are intolerant or unresponsive to standard systemic therapy, have significant, coexistent, unrelated comorbidity that precludes use of systemic agents, such as ciclosporin or MTX, or have severe, unstable, life-threatening disease

Eligibility criteria for patients with SKIN and JOINT disease

- Patients who have active PsA or skin disease that fulfils defined BSR or BAD guideline criteria, respectively
- Patients with severe skin psoriasis and PsA who have failed, or cannot use, MTX may need to be considered for biologic treatment, given the potential benefit of such treatment on both components of psoriatic disease

be between 60 and 80 kg, based on the mean adult weight in the UK general population (women 69.7 kg, men 83.5 kg[185]). Patients are assumed to have failed at least two DMARDs. In the base case, patients are assumed to fulfil BSR criteria (see *Box 1*). In the base case the HAQ at the start of the model is 1.05, based on the average in the RCTs (see *Table 1*). Although the mean HAQ when patients start biologics in the BSR register was 1.8,[186] clinical opinion suggests that, in current practice, clinicians are more likely to offer biologics early in the course of the disease.

Clinical opinion suggests that about 50% of patients starting biologics have mild or minimal psoriasis (< 3% BSA or a PASI score of < 2.5), 25% have mild-to-moderate psoriasis (a baseline PASI score of between 2.5 and 10), and 25% have moderate-to-severe psoriasis (a PASI score > 10) (Ian Bruce, Arc Epidemiology Unit, University of Manchester, UK, 20 November 2009, personal communication). Approximately 50% of patients in the RCTs had < 3% BSA psoriasis or a baseline PASI < 2.5 (see *Table 1*), indicating the trials are broadly representative of skin involvement in general practice. We assume patients in the base case have mild-to-moderate psoriasis with a PASI score of 7.5. The effect of biologic treatments in other patient subgroups is explored in scenario analyses.

Model structure

The model is a cohort model, assuming a homogeneous baseline population. The model has a Markov structure (see *Figure 2*). Patients enter the model either (i) when commencing therapy with etanercept, infliximab or adalimumab or (ii) with no therapy (assumed to be palliative care only).

Initial response at 3 months

Table 33 shows the parameters used in the base-case model. Initial response of the drug is defined in the model as PsARC for joints and PASI 75 for psoriasis, based on the BSR[149] and the BAD guidelines[173] (*Box 2*). These parameters were estimated by the evidence synthesis (see *Chapter 3*, *Efficacy of all three biologics*).

TABLE 33 Model parameters and assumptions used in the base case of the York Assessment Group model

Description	Variable name	Mean	SE	Source/appendix
Gender male = 1, female = 0	Male	1		
PsA minimum duration (years)	PsA.dur	3		
Concomitant MTX in all strategies: yes = 1, no = 0	MTX	1		
Baseline HAQ	HAQ0	1.05		Mean of RCTs (*Table 1*)
Baseline PASI	PASI0	7.5		Clinical opinion
Baseline age	Age	47		Mean of RCTs (*Table 1*)
Model time horizon (years)	Years	40		Clinical opinion
Discount rate (per year)	r	0.035		NICE[184]
Utility function intercept	h0	0.897	0.006	*Appendix 17*
Change in utility for 1 unit change in HAQ	h1	–0.298	0.006	*Appendix 17*
Change in utility for 1 unit change in PASI	h2	–0.004	0.0003	*Appendix 17*
Interaction term HAQ PASI	h3	0	10 x E-5	*Appendix 17*
Cost function intercept (per 3-month period)	c0	233		*Appendix 15*
Change in cost for 1 unit change in HAQ	c1	103	67	Kobelt *et al.*,[41] *Appendix 15*
Three-month cost for mild-to-moderate psoriasis if uncontrolled by biologics	c2.1	198	9	DoH *Reference Costs 2007–08*,[187] *Appendix 16*
Three-month cost for psoriasis in remission	c2.2	16	1	Hartman *et al.*,[188] *Appendix 16*
Change in HAQ while on treatment per 3-month period	HAQ1.d	0	0.02	Experts, *Appendix 11*
Change in HAQ while not on treatment per 3-month period	HAQ1.w	0.018	0.007	NOAR, *Appendix 14*
Rebound in HAQ in 3 months after withdrawal (compared to HAQ at baseline) (zero means 'rebound equal to initial gain')	loss.w	0	0.3	Experts, *Appendix 11*
Intercept of regression of log-mortality vs age in men	ln.R.g.m	–10.25	0.046	England and Wales life table, *Appendix 19*
Intercept of regression of log-mortality vs age in women	ln.R.g.f	–11.10	0.046	
Change in log-mortality with additional year of age in men over 40 years	a.g.m	0.094	0.0006	
Change in log-mortality with additional year of age in women over 40 years	a.g.f	0.101	0.0006	
Log withdrawal rate from biologics per year	ln.long.yr	–1.823	0.2044	Registers, *Appendix 12*
Probability of PsARC response on placebo	p.psarc.plac	0.249	0.0384	*Results of review of clinical effectiveness*
Change in HAQ given a PsARC response on placebo	HAQ.resp.plac	–0.2436	0.04746	
Probability of PASI 50 response on placebo	p.pasi.50.plac	0.130	0.021	*Results of review of clinical effectiveness*
Probability of PASI 75 response on placebo	p.pasi.75.plac	0.044	0.009	
Probability of PASI 90 response on placebo	p.pasi.90.plac	0.016	0.004	

continued

TABLE 33 Model parameters and assumptions used in the base case of the York Assessment Group model *(continued)*

Description	Variable name	Mean	SE		Source/appendix
Standardised mortality ratio for PsA vs general population	SMRmen	1.65			Wong *et al.*,[29] *Appendix 19*
	SMRwomen	1.59			
Generalisability of trial (1 = no, 2 = yes)	plac.effect	1			*Appendix 9*
Rules on continuation (1–5)	continue	1			BSR and BAD
		Etan (mean)	**Inflix (mean)**	**Adal (mean)**	
Cost of drugs (first 3 months)	c.drug1	£2495	£5523	£2495	BSR, *Appendix 13*
Cost of drugs for months 4–6	c.drug2	£2443	£2965	£2443	
Cost of drugs, subsequent 3 months	c.drug3	£2385	£2965	£2385	
Probability of PsARC response on biologic	p.psarc	0.713	0.795	0.587	*Results of review of clinical effectiveness*
	p.psarc_SE	0.071	0.058	0.072	
Change in HAQ in first 3 months given no PsARC response of biologic	HAQ.no.resp	–0.190	–0.194	–0.130	*Results of review of clinical effectiveness*
	HAQ.no.resp_SE	0.10	0.070	0.066	
Change in HAQ in first 3 months given PsARC response of biologic	HAQ.resp	–0.630	–0.657	–0.477	*Results of review of clinical effectiveness*
	HAQ.resp_SE	0.090	0.069	0.062	
Probability of PASI 50 response on biologic	p.pasi.50	0.4026	0.9128	0.7383	*Results of review of clinical effectiveness*
Probability of PASI 75 response on biologic	p.pasi.75	0.1768	0.7687	0.4772	
Probability of PASI 90 response on biologic	p.pasi.90	0.0737	0.5571	0.2571	
	p.pasi.50_SE	0.0916	0.0374	0.0853	
	p.pasi.75_SE	0.0586	0.0795	0.1085	
	p.pasi.90_SE	0.0292	0.1088	0.0863	
Correlation between PASI 75 and PsARC	Rho	0.435	0.435	0.435	ADEPT,[51] *Appendix 10*
	rho_SE	0.112	0.112	0.112	

Adal, adalimumab; Etan, etanercept; Inflix, infliximab; NOAR, Norfolk Arthritis Register; SE, standard error.

The BAD guidelines highlight that the recommended time points for assessing the initial response vary between drugs and between guideline-making bodies. The licences for psoriasis recommend an assessment at 14 weeks for infliximab, at 12 weeks for etanercept and at 16 weeks for adalimumab. Current NICE guidelines for psoriasis recommend an assessment at 10 weeks for infliximab. In the current appraisal we do not make these distinctions and assume that an assessment is made for all drugs at 'around 3 months' or between 12 and 16 weeks. The assessment of effectiveness in *Chapter 3* (see *Assessment of effectiveness*) did not find any appreciable differences in the biologics' response rates for joint disease or psoriasis between approximately 12 weeks and 24 weeks.

In the decision model, the change in HAQ compared with baseline is conditional on whether a PsARC response was achieved. These parameters were estimated by the evidence synthesis in *Chapter 3*, *Efficacy of all three biologics*. It is uncertain whether the change in HAQ is the same for all PsARC treatment responders, or depends on the particular biologic treatment followed. In the opinion of our clinical advisor, either scenario could be plausible (Ian Bruce, personal communication). In the base-case model, we allow the change in HAQ for treatment responders

BOX 2 British Society for Rheumatology and BAD guidelines for treatment response in patients with PsA and/or psoriasis

BSR guidelines for treatment response

Primary joint response: PsARC at 12 weeks/3 months

Primary skin response: PASI 75

Treatment will be withdrawn in the event of adverse events or inefficacy, defined as patients who fail to achieve the PsARC response within 3 months of treatment

BAD guidelines for treatment response

An adequate response to treatment is defined as either (1) a 50% or greater reduction in baseline PASI (or % BSA where the PASI is not applicable) and a ≥5-point improvement in DLQI or (2) a 75% reduction in PASI score compared with baseline. Initial response to therapy should be assessed at time points appropriate for the drug in question.

For patients on TNF antagonist treatment with psoriasis and PsA, treatment may be continued if there has been a sufficient response in at least one of these components (see BSR guidelines for definition of disease response in PsA).

to depend on PsARC response and the biologic treatment, and consider the alternative scenario as a sensitivity analysis. According to the evidence synthesis in *Appendix 5*, the mean change in HAQ in the first 3 months for PsARC responders, across all biologic drugs, is –0.5688 [standard error (SE) 0.0315] and the mean change in HAQ for PsARC non-responders, across all biologic drugs, is –0.1697 (SE 0.0338).

During the initial 3-month trial period the model assumes that patients on biologics have some improvement in HAQ even if they do not reach the PsARC threshold. These parameters were estimated by the evidence synthesis in *Chapter 3*, *Efficacy of all three biologics*. Patients who do not achieve the required level of response during the first 3 months and are withdrawn from therapy are assumed to return to the same HAQ score after withdrawal as patients who had palliative care only.

The model assumes that patients who achieve a PASI 75 response will gain at least a 75% improvement in psoriasis compared with baseline PASI. The calculation of the expected improvement in PASI for PASI 75 responders is described in *Appendix 18*. Patients who do not achieve a PASI 75 response will also have some proportionate gain in PASI while they continue taking a biologic, although this will be less than a 75% improvement (see *Appendix 18*).

A proportion of patients in the placebo arms of the RCTs achieved a PsARC response and an improvement in HAQ. Part of the response in both the placebo and treatment arms of RCTs may be due to non-pharmacological aspects of medical care that would be common to both arms (sometimes called a 'placebo' or 'expectancy' effect). It is uncertain whether this effect would be reproducible in general practice.[189] In the base case we assume that part of the predicted response for treatment observed in the trial is attributable to the controlled trial setting and would not be reproducible in general practice. The change in HAQ in patients using biologics is reduced by the mean change in HAQ across the placebo arms of the RCTs. A similar adjustment is made for the expected change in PASI in patients using biologic therapy. *Appendix 9* gives further details of the conceptual framework and adjustments made for the possible placebo/expectancy effects. An alternative scenario assumes that the response rate to treatment in the RCTs is fully generalisable to general practice and no adjustment for placebo/expectancy effects is made.

Because there are two response variables (PsARC and PASI), there are four possible outcomes at 3 months: skin response only, joints response only, response of both and response of neither (*Figure 2*). The base-case model assumes that the responses to psoriasis and arthritis might be correlated. *Appendix 10* reviews the evidence on the correlation between these responses and how the decision model calculates the probabilities of each of the four outcomes at 3 months. An alternative scenario assumes that the responses to psoriasis and arthritis are independent.

The BSR guidelines recommend that biologics are withdrawn if a PsARC response is not achieved at 3 months. This rule is used in the base-case analysis of the model. However, in patients who have significant skin and joint disease, some patients may achieve PsARC but not PASI 75, or achieve PASI 75 but not PsARC. In these cases, one could specify that patients should continue biologic therapy irrespective of the psoriasis response (BSR guideline), or those that respond to either can continue (BAD guidelines) or (in principle at least) only those that achieve both should continue. These alternative continuation rules are explored in sensitivity analyses.

The model assumes that no patients withdraw due to adverse events in the first 3 months. This is because the RCTs estimate responses on an ITT basis, whereby withdrawals for any reason are considered treatment failures and counted as non-response. Including withdrawals during the first 3 months in the model would, therefore, be double-counting.

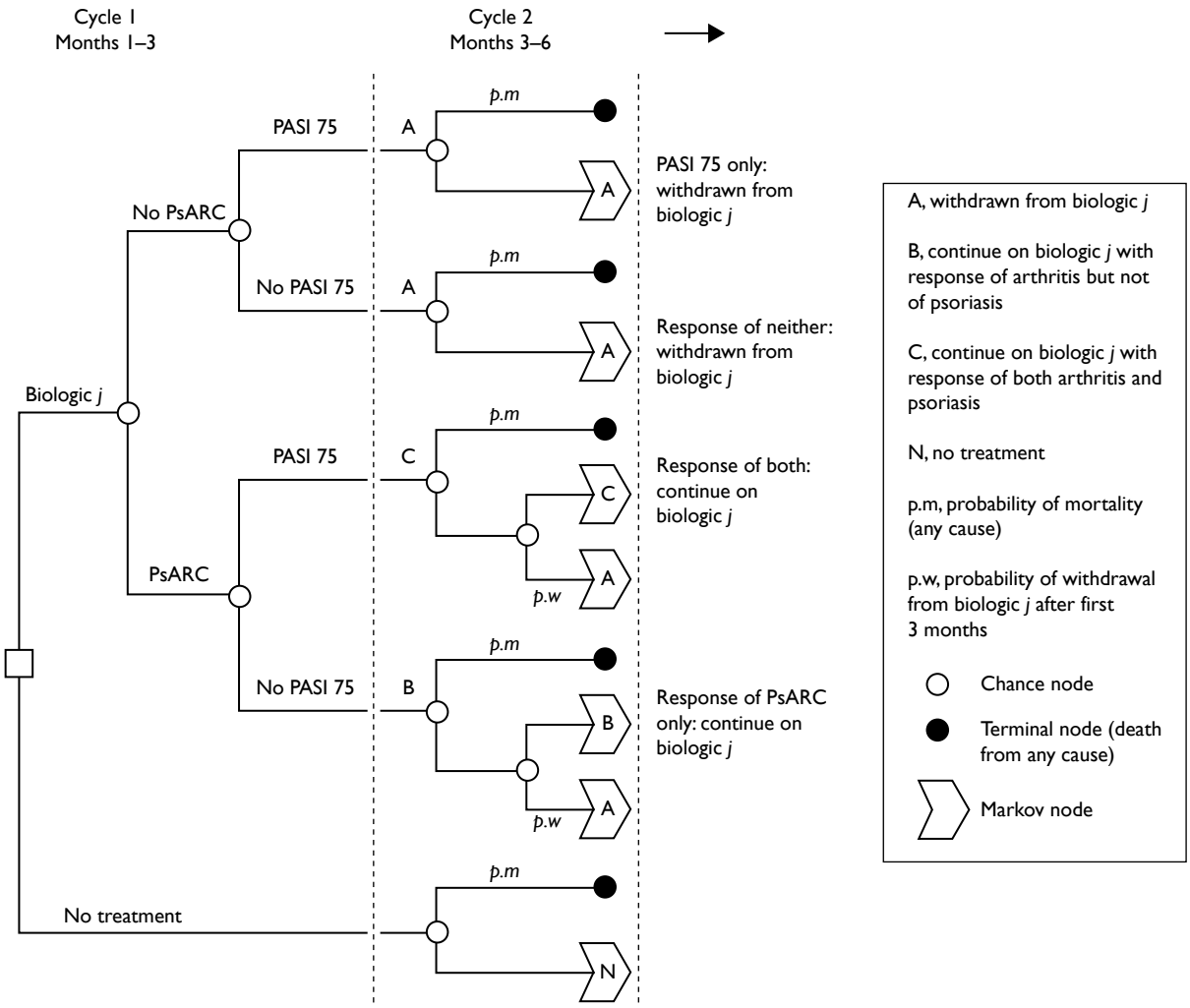

FIGURE 2 Structure of the decision model, assuming patients continue beyond 3 months if they achieve a PsARC response.

Long-term outcomes and withdrawal from biologic therapy

If the decision is made to continue with the biologic therapy beyond 3 months, it is assumed that patients maintain their initial improvement in HAQ while on that therapy. This is based on evidence from an opinion elicitation exercise from clinical experts, and supported by data on HAQ and HRQoL from biologics registers.[186,190] *Appendix 11* describes the opinion elicitation methods and results used to inform the model. It is assumed that patients maintain the improvement in PASI while on biologic therapy. This assumption has been made in other decision models (see *Systematic review of existing cost-effectiveness evidence*).

There is an ongoing risk of withdrawal from biologic therapy. Withdrawal might occur for lack of continuing efficacy ('secondary non-response'), adverse events or other reasons. The rate of withdrawal after 3 months is assumed to be independent of the HAQ and PASI score in the model, to be independent of whether the initial response was for both psoriasis and arthritis or just arthritis, and to be constant over time. The rate is estimated from a meta-analysis of registry data from several countries to be –1.823 (SE 0.2044) on the log scale, or $\exp(-1.823 + 0.5 \times 0.2044^2) = 0.165$ per year (see *Appendix 12*). Although the registries present withdrawal rates by drug, these data are not randomised and patient cohorts starting on different biologic therapies are unlikely to be similar.[191] Therefore, the decision model assumes the same withdrawal rates for all biologics. *Appendix 12* gives further details. As the withdrawal rate is constant over time after the first 3 months, patients who achieve an initial PsARC response will on average remain on biologic drugs for just over 6 years in the model ($1/0.165 = 6.06$ years).

Patients withdraw from biologic to palliative care only. On withdrawal, it is assumed that mean PASI returns to its initial score at baseline (rebound equal to initial gain). There is considerable uncertainty about change in HAQ associated with withdrawal (rebound). Previous modelling work assumed rebound of HAQ follows either of two alternative scenarios, with no data to inform which scenario is the more likely: rebound equal to initial gain, and rebound equal to natural history (NH).[177] These scenarios are explained in more detail in *Appendix 11*. The current model is informed by the expert opinion elicitation exercise conducted with five experts, described in *Appendix 11*. All experts suggested that not all the initial gain in HAQ is lost following late withdrawal of patients who initially responded to biologic therapy at 3 months. This scenario, that the HAQ rebound might be *less* than initial gain, has not been considered in any of the previous models of PsA, nor, to our knowledge, in any model of RA. Given the difficulty and limitations of eliciting expert opinion and the novelty of these findings, the current model assumes that rebound is *equal* to initial gain in the base case, and explores other scenarios (rebound *less* than initial gain and rebound equal to NH) in sensitivity analyses.

Outcomes for patients on palliative care

The PASI is assumed not to change on average compared with baseline for patients undergoing palliative care. HAQ is assumed to progressively worsen in such patients at a constant rate, estimated by an analysis requested from Deborah Symmons and colleagues at Manchester University for this appraisal using data from the Norfolk Arthritis Register (NOAR) (see details in *Appendix 14*).

Illustration of progression of HAQ in the model

Figure 3 illustrates the progression of HAQ over time for three different patient histories in the model. For a patient whose arthritis is controlled by biologic therapy, HAQ score is initially reduced (improves) and then maintained over time. For a patient who does not start biologic therapy, HAQ increases (deteriorates) over time to a maximum score of 3. For a patient who withdraws at 5 years, HAQ 'rebounds' (quickly increases) to the baseline level after withdrawal and then increases at the same rate as those who never started biologic therapy. However, in

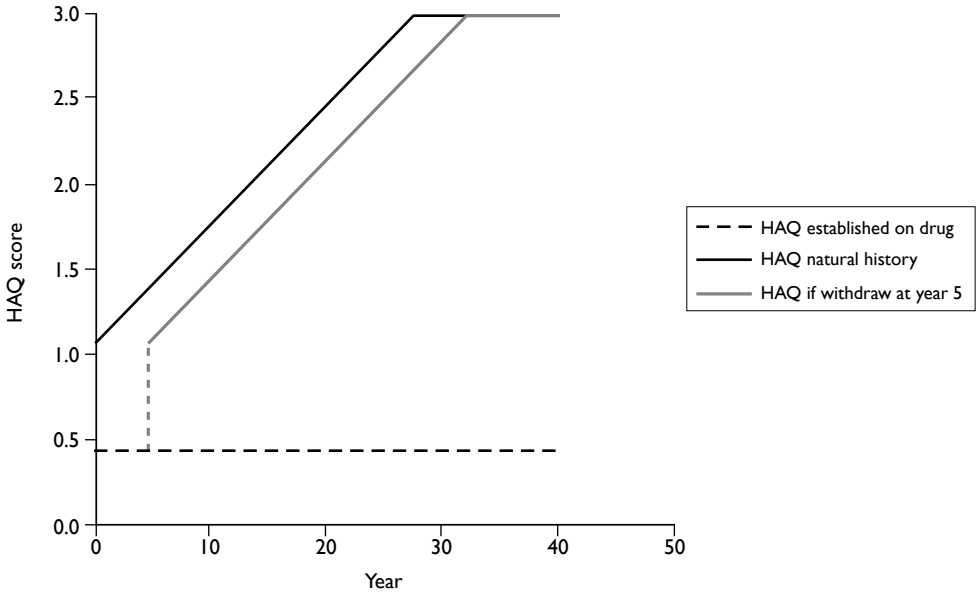

FIGURE 3 Illustration of the progression of arthritis for a patient successfully maintained on biologic, a patient without biologic and a patient who withdraws at 5 years. Note: a greater HAQ score indicates worse disability.

this scenario ('rebound equal to initial gain') the 5-year delay in progression obtained while on biologic drugs is permanently maintained after withdrawal.

Utility

Health utility is measured as a function of HAQ and PASI. This relationship was estimated from analyses provided by the manufacturers, who carried out linear regressions of EQ-5D utility versus HAQ and PASI in participants in key RCTs (see *Appendix 17*). The base-case utility function is:

$$\text{Expected utility} = 0.897 - 0.298 \times \text{HAQ} - 0.004 \times \text{PASI}$$

$$\text{(Standard error)}\ (0.006)\ (0.006)\qquad (0.0003)$$

Other utility functions, supplied by the manufacturers, were used as sensitivity analyses.

Figure 4 illustrates the change in utility over time for different patients in the model. For a patient who is maintained on biologic therapy, utility is initially improved as a consequence of the reduction in HAQ and PASI, the latter depending on the proportion of patients who respond to psoriasis, given a response of arthritis (see *Figure 2* and *Appendix 10*). This utility gain is assumed to be maintained over time. For a patient who did not start biologic therapy, utility deteriorates over time to a minimum value that is < 0, indicating that the general population would consider HRQoL with the severest arthritis symptoms and uncontrolled psoriasis to be worse than death. For a patient who withdraws at 5 years, utility 'rebounds' to the baseline level after withdrawal and then deteriorates at the same rate as those on NH. The area between these curves (area 'A + C' in *Figure 4*) represents the difference in lifetime QALYs between a patient who withdraws at 5 years and a patient who never uses biologic therapy.

Time horizon for maintaining treatment effects

It is uncertain whether the effectiveness of biologic therapy is maintained in the very long term. Previous models considered a scenario where it is assumed that all patients withdraw from

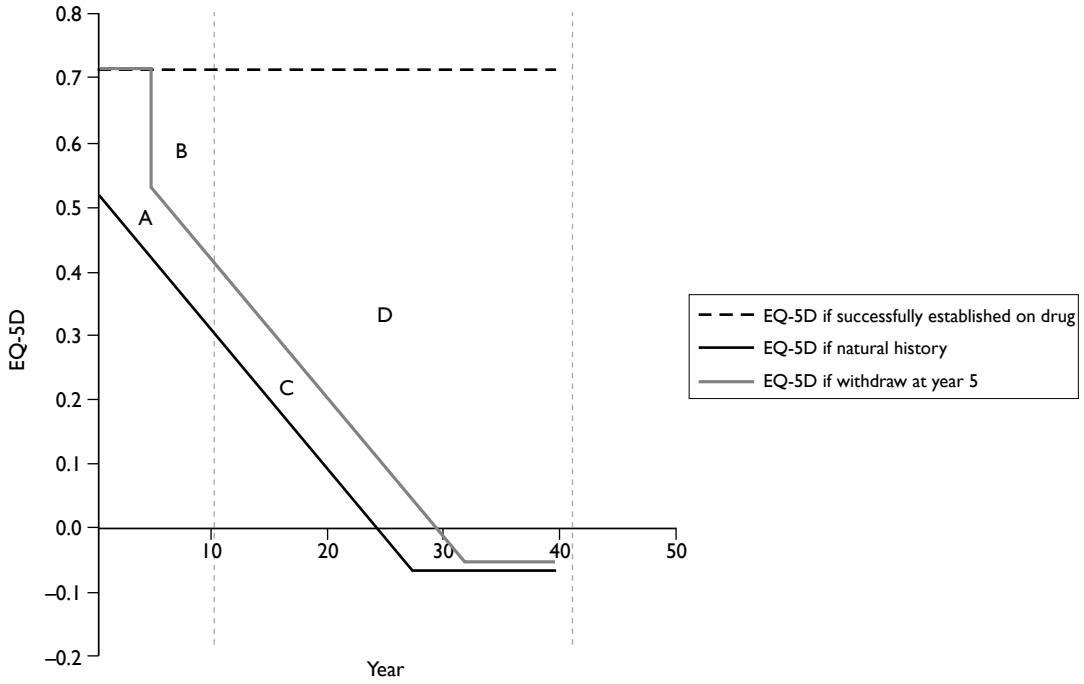

FIGURE 4 Illustration of utility (HRQoL) of a patient successfully maintained on biologic, a patient without biologic and a patient who withdraws at 5 years. Note: EQ-5D utility takes a maximum value of 1, indicating full health; values of < 0 correspond to health states that are considered worse than death by the general population.

biologic therapy at 10 years, and all gains in HAQ with respect to NH are lost at this point.[177] *Figure 4* illustrates the effect on utility of this '10-year time horizon for treatment effects' scenario compared with the base case that assumes that treatment effects are maintained over the lifetime.

The difference in lifetime QALYs for a patient who is maintained successfully on a biologic, compared with NH, is area A + B + C + D. However, if is assumed that treatment effects last for only 10 years, the difference in QALYs over 10 years between being on a biologic and NH is only area A + B. For a patient who withdraws from a biologic at 5 years, the difference in lifetime QALYs compared with NH is area A + C. The difference in QALYs between assuming a 10-year time horizon and assuming a 40-year time horizon for a patient who withdraws from therapy at 5 years is area 'C'. Biologic therapy appears much more effective if it is assumed that treatment effects in those who withdraw and those who do not withdraw are maintained over the long term. The base-case model assumes that the benefits of biologic therapy are maintained for a lifetime. Time horizons for treatment remaining effective for up to 10 years and up to 20 years are considered in sensitivity analyses.

Health service costs

The acquisition costs of the drugs and of their administration and monitoring were obtained from BSR recommendations and pharmaceutical list prices[65] (see *Appendix 13*). The base case assumes that four vials of infliximab are administered and that vial sharing is not permitted.

Health-care costs increase with severity of both arthritis[36] and psoriasis.[37] The health service costs of treating arthritis were measured from a UK-based study that estimated the effect of HAQ on costs in patients with RA[41,59] (see *Appendix 15*). The NHS costs used for treating mild-to-moderate psoriasis in patients who do not use biologics or who do not respond to biologics were obtained from NHS unit costs of phototherapy[187] and a UK RCT.[192] No UK studies based on prospective IPD were identified to estimate the health service costs of treating moderate or severe

psoriasis in patients who do not use biologics or who do not respond to biologics. In the model these costs were obtained from a Dutch RCT and adjusted to UK price levels[188] (see *Appendix 16*).

All-cause mortality

All-cause mortality was estimated from UK life tables. A Gompertz function was fitted to these data (see *Appendix 19*). The base case uses a published estimate of the additional mortality risk in PsA.[29] The effect of biologics on mortality in PsA is uncertain. The US VA study of MTX in psoriasis and patients with RA found that MTX was associated with significantly reduced incidence of vascular disease.[193] Long-term control of chronic inflammation may reduce mortality. However, long-term use of biologics might increase other mortality risks. The decision model assumes that there is no difference in mortality rates between treatments, or between biologic treatments and no treatment.

Subgroup analyses

The base-case model assumes a cohort of patients with PsA with baseline HAQ of 1.05, the mean of HAQ across the RCTs (see *Table 1*), and mild-to-moderate psoriasis (baseline PASI of 7.5). The model considered other cohorts in subgroup analyses:

- A more severe baseline HAQ of 1.8, which is the mean HAQ of patients entering the British Society for British Society for Rheumatology Biologics Register (BSRBR).[186]
- No skin involvement, with PASI of 0. Clinical opinion suggests 50% of patients with PsA starting biologics in clinical practice would have mild or no skin involvement (Ian Bruce, personal communication).
- A baseline PASI of 12.5, corresponding to moderate-to-severe psoriasis.[194,195] Clinical opinion suggests that 25% of patients with PsA starting biologics in clinical practice would have a baseline PASI > 10 (Ian Bruce, personal communication).

The review described in *Chapter 3* did not find any evidence with which to assess whether treatment effects might differ by baseline severity, and, consequently, these analyses assume no change in relative treatment effects and focus just on variation between subgroups in baseline severity.

The base-case model assumes patients have failed at least two DMARDs, but are naive to biologics at baseline. The model was also used to estimate the cost-effectiveness of biologics used as a second course of therapy, if the first biologic is withdrawn. For example, if etanercept has been tried and failed, then the next alternative in sequence is adalimumab, infliximab or no biologic therapy. The reason why the patient failed the first course of therapy is potentially important information in deciding on the second course. Therefore, we consider two subgroups: one who failed the first biologic because of adverse events, and another who failed because of lack of efficacy. No RCTs have evaluated outcomes in these subgroups, and we estimate treatment response and withdrawal rates for these subgroups from observational data from the BSR register, which showed that if a patient failed first-line therapy for lack of efficacy, then the risk of failing the second-line therapy for lack of efficacy increased by 2.7 (95% CI 2.1 to 3.4). If a patient failed first-line therapy because of an adverse event then the risk of failing the second-line therapy for adverse events increased by 2.3 (95% CI 1.9 to 2.9).[196] *Appendix 20* describes how these data were used to estimate the probability of initial response and later withdrawal for biologic therapies used as second line.

Analytic methods

The uncertainty in each parameter was represented using a probability distribution. The probabilities in *Table 33* were assigned beta distributions. If $p \sim Beta(\alpha,\beta)$ then $\alpha = E(p) \times E(p) \times (1 - E(p))/Var(p)$ and $\beta = E(p) \times (1 - E(p)) \times (1 - E(p))/Var(p)$. The rate of change of HAQ while not on treatment was assigned a gamma distribution to ensure that values are strictly

positive. If $x \sim Gamma(a,s)$ then $a = E(x) \times E(x)/Var(x)$ and $s = Var(x)/E(x)$. All other uncertain parameters were assigned normal distributions with the mean and SE shown in *Table 33*. Probabilistic sensitivity analysis was carried out using Monte Carlo simulation.

The results of the model are presented in two ways. First, mean lifetime costs and QALYs for the three strategies are reported and their cost-effectiveness compared, estimating ICERs using standard decision rules.[197] Briefly, the alternative strategies are ranked by mean cost. Strategies that are more costly than another, but offer no greater expected benefit are known as 'dominated', and excluded. Strategies that are dominated by a linear combination of other strategies are considered subject to 'extended domination' and are also excluded. ICERs are then calculated for each of the remaining strategies, compared with the next best alternative. Although NICE does not specify a particular cost-effectiveness threshold, a strategy is more likely to be considered cost-effective if the ICER were < £20,000 per QALY, and less likely to be considered cost-effective if the ICER were > £30,000 per QALY.[184] Second, the decision uncertainty is shown as the probability that each intervention is the most cost-effective for a given cost-effectiveness threshold.

A series of alternative scenarios is also presented to explore the effect of changing one or more parameters/assumptions in the model.

Results of York Economic Assessment

Estimated probabilities of response at 3 months in the base case

Based on the results of the evidence synthesis in *Chapter 3* (see *Results of review of clinical effectiveness*), and an estimate of the correlation between PsARC and PASI 75 outcomes in biologic therapy from an RCT,[51] the model estimated the probability that a patient would respond for psoriasis only, joints only, both outcomes or neither outcome with each biologic therapy. These outcomes are shown under two assumptions: positive correlation (base case) and independence (*Table 34*).

Results of the base-case cost-effectiveness analysis

The results of the base-case cost-effectiveness analysis are shown in *Table 35*, and univariate sensitivity analyses in *Table 36*. The base-case analysis suggests that infliximab is the most effective treatment (in terms of expected QALYs), followed by etanercept then adalimumab. Infliximab is also the most costly treatment, followed by etanercept then adalimumab. The

TABLE 34 The mean probabilities of PsARC and PASI 75 responses at 3 months

Response	Etanercept	Infliximab	Adalimumab
Positive correlation ρ = 0.435			
Skin only	0.000	0.083	0.090
Joints only	0.536	0.110	0.200
Both	0.177	0.685	0.387
Neither	0.287	0.122	0.323
No correlation (independence)			
Skin only	0.051	0.157	0.197
Joints only	0.587	0.184	0.307
Both	0.126	0.611	0.280
Neither	0.236	0.047	0.216

TABLE 35 Results of the base-case analysis

Strategy	QALY	Cost (£)	Incremental QALY	Incremental cost (£)	ICER	PCE	
						20K	30K
N	5.171	42,168			NA	0.472	0.309
A	6.580	68,638	1.409	26,470	Ex dom	0.046	0.032
E	7.001	74,841	0.422	6203	17853	0.436	0.475
I	7.308	88,442	0.307	13,601	44326	0.046	0.184

A, adalimumab; E, etanercept; Ex dom, extended dominated; I, infliximab; N, palliative care; NA, not available; PCE 20K/30K – probability that the treatment is cost-effective at a threshold of £20,000/30,000 per QALY.

ICER of etanercept compared with palliative care is about £18,000, and the ICER of infliximab compared with etanercept is about £44,000 per QALY. Of the three biologic therapies, etanercept has the highest probability of being cost-effective at a threshold of between £20,000 and £30,000 per QALY. Etanercept is the most cost-effective strategy in 44% of simulations of the base-case model, at a threshold ICER of £20,000 and in 48% of simulations at a threshold of £30,000 per QALY.

Adalimumab is extendedly dominated by palliative care and etanercept. This means that if NICE were considering adalimumab, the ICER relative to palliative care would be £26,470/1.409 = £18,786. However, the expected QALY per patient achieved with etanercept is greater than for adalimumab (7.00 vs 6.58), while the ICER of etanercept versus palliative care is £17,853. Therefore, it would not, on average, be cost-effective to recommend adalimumab because a greater QALY gain can be achieved from etanercept within the threshold of £20,000 per QALY.

Expected QALYs are low in this model. The total lifetime discounted health associated with palliative care is about 5.17 QALYs. This is because the base-case scenario assumes that utility declines fairly rapidly in patients with uncontrolled arthritis, and may be < 0 in later years (see *Figure 4*). For comparison, if HAQ and PASI could be reduced to 0 for the complete time horizon of the model (40 years), the model predicts that this cohort would expect 15 QALYs, given the rate of mortality, the intercept of the utility function and the discount rate. *Figure 5* partitions the lifetime discounted QALYs gained by biologic therapies into those associated with improving arthritis and those associated with improving psoriasis, relative to palliative care. In the base case, utility gains as a result of improvement in arthritis are predicted to be much greater than utility gains as a result of improvement in the psoriasis component of PsA.

The expected lifetime (40-year) discounted costs without biologics (palliative care only) are about £42,000 in the base case for a patient with PsA and mild-to-moderate psoriasis. This can be partitioned into £29,000 for the treatment of arthritis and £13,000 for the treatment of psoriasis. *Figure 6* partitions the total lifetime discounted health-care costs of the strategies into costs associated with the acquisition, monitoring and administration cost of the biologic drugs, the cost savings associated with treating arthritis (i.e. the reduction in HAQ score) and the cost savings associated with treating psoriasis (i.e. the reduction in PASI score). All costs are shown relative to the costs of palliative care.

The lifetime discounted acquisition, administration and monitoring cost of infliximab is about £52,000; etanercept is about £33,000 and adalimumab is about £27,000. These prescribing costs are much greater than any offset health-care cost savings elsewhere. Infliximab is associated with

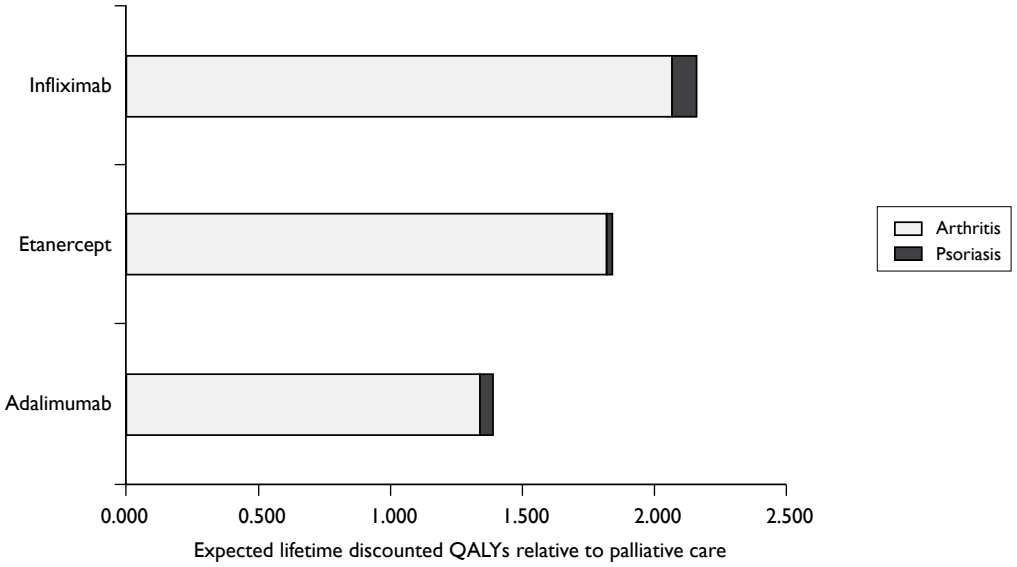

FIGURE 5 Gains in lifetime discounted QALYs associated with treating arthritis and psoriasis in PsA with biologic therapies relative to palliative care.

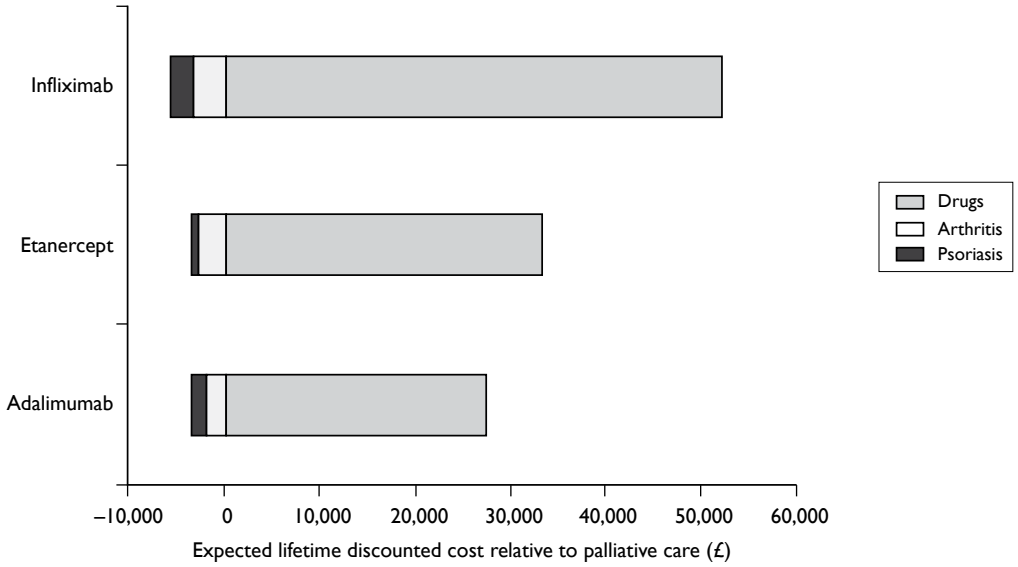

FIGURE 6 Lifetime discounted costs of biologic drugs, and cost savings for arthritis and psoriasis relative to non-biologic treatments for PsA.

the greatest gains in PASI and HAQ, and the greatest cost savings. Adalimumab has the second greatest gains in PASI and associated cost savings, and etanercept has the second greatest gains in HAQ and associated cost savings.

Results of sensitivity analyses

Table 36 shows the results of the univariate sensitivity analyses. *Table 37* shows the cost-effectiveness of the alternatives in each of the scenarios, assuming that an ICER of £20,000 or less is likely to be cost-effective and a strategy with an ICER of ≥ £30,000 is unlikely to be accepted.

TABLE 36 Univariate sensitivity analyses

Scenario	Description	Trt	QALY	Cost (£)	ICER	PCE 20K	PCE 30K
1	Base case	N	5.171	42,168	NA	0.472	0.309
		A	6.580	68,638	Ex dom	0.046	0.032
		E	7.001	74,841	17,853	0.436	0.475
		I	7.308	88,442	44,326	0.046	0.184
2	Rebound in HAQ is small after withdrawal (base case = initial gain)	N	5.171	42,168	NA	0.214	0.114
		A	7.225	67,710	Ex dom	0.051	0.029
		E	7.792	73,706	12,035	0.609	0.521
		I	8.188	87,174	34,006	0.126	0.336
3	Rapid worsening in HAQ with no treatment (upper 95% of CI)	N	3.309	44,434	NA	0.358	0.187
		A	4.967	70,829	Ex dom	0.047	0.029
		E	5.447	76,985	15,221	0.528	0.544
		I	5.786	90,609	40,248	0.067	0.240
4	Log-PASI utility function (Abbott[151]) (base case linear)	N	4.558	42,168	NA	0.459	0.308
		A	6.001	68,638	Ex dom	0.069	0.040
		E	6.390	74,841	17,835	0.400	0.390
		I	6.769	88,442	35,898	0.072	0.262
5	No correlation between PASI 75 and PsARC (base case = 0.4)	N	5.171	42,168	NA	0.479	0.311
		A	6.571	68,968	Ex dom	0.040	0.032
		E	6.997	74,990	17,979	0.434	0.476
		I	7.303	88,641	44,558	0.047	0.181
6	RCT results fully generalisable to clinical practice (no adjustment for placebo effect)	N	5.171	42,168	NA	0.451	0.282
		A	6.637	68,561	Ex dom	0.053	0.037
		E	7.068	74,752	17,178	0.446	0.482
		I	7.381	88,344	43,371	0.050	0.199
9	Exponential HAQ-cost function (Abbott[151]) (base case linear)	N	5.171	63,052	NA	0.375	0.266
		A	6.580	82,129	Ex dom	0.048	0.032
		E	7.001	86,502	12,813	0.477	0.457
		I	7.308	99,045	40,878	0.100	0.245
12	Inpatient treatment for uncontrolled psoriasis	N	5.171	151,496	NA	0.255	0.151
		A	6.580	165,282	9787	0.114	0.055
		I	7.308	175,157	13,557	0.621	0.769
		E	7.001	178,530	Dom	0.010	0.025
13	Cost per 3 months per 1-unit change in HAQ is £183 (US data)[42] (base case £103)	N	5.171	52,548	NA	0.444	0.303
		A	6.580	77,518	Ex dom	0.047	0.032
		E	7.001	83,224	16,761	0.453	0.467
		I	7.308	96,562	43,468	0.056	0.198
14	Change in utility per 1-unit change in HAQ is –0.45 (Wyeth[153]) (base case = 0.29)	N	0.846	42,168	NA	0.312	0.203
		A	2.905	68,638	Ex dom	0.024	0.011
		E	3.589	74,841	11,913	0.522	0.474
		I	3.954	88,442	37,280	0.142	0.312

TABLE 36 Univariate sensitivity analyses *(continued)*

Scenario	Description	Trt	QALY	Cost (£)	ICER	PCE 20K	PCE 30K
15	HAQ improves while on drug (lower 95% of CI) (base case no change)	N	5.171	42,168	NA	0.029	0.007
		A	7.845	66,823	Ex dom	0.075	0.023
		E	8.492	72,704	9194	0.712	0.516
		I	8.959	86,065	28,635	0.184	0.454
16	High rate of withdrawal (upper 95% of CI)	N	5.171	42,168	NA	0.464	0.316
		A	6.302	62,085	Ex dom	0.041	0.029
		E	6.635	66,604	16,690	0.436	0.460
		I	6.876	77,323	44,451	0.059	0.195
17	Low rate of withdrawal (lower 95% of CI)	N	5.171	42,168	NA	0.485	0.322
		A	6.891	76,566	Ex dom	0.060	0.035
		E	7.411	84,811	19,038	0.427	0.462
		I	7.793	101,890	44,731	0.028	0.181
18	All treatments have the same probability of PsARC response at 3 months	N	5.197	41,416	NA	0.472	0.312
		A	7.104	77,174	Ex dom	0.176	0.193
		E	7.236	78,115	17,999	0.351	0.467
		I	7.316	87,889	122,073	0.001	0.028
19	All treatments have the same probability of psoriasis responses (PASI 50/75/90) at 3 months	N	5.273	41,746	NA	0.418	0.275
		A	6.722	67,892	Ex dom	0.016	0.016
		E	7.186	72,834	16,254	0.554	0.602
		I	7.414	87,951	66,219	0.012	0.107
20	Cost of drugs as in Wyeth submission[153]	N	5.171	42,168	NA	0.425	0.273
		A	6.580	65,847	Ex dom	0.067	0.057
		E	7.001	71,478	16,015	0.505	0.614
		I	7.308	92,632	68,944	0.003	0.056
22	All biologics have the same change in HAQ at 3 months for a PsARC responder	N	5.171	42,168	NA	0.470	0.314
		A	6.659	68,526	17,717	0.165	0.174
		E	6.949	74,920	22,056	0.341	0.395
		I	7.217	88,573	50,806	0.024	0.117
23	Three vials of infliximab (base case: four vials)	N	5.171	42,168	NA	0.423	0.259
		A	6.580	68,638	Ex dom	0.000	0.000
		E	7.001	74,841	Ex dom	0.034	0.061
		I	7.308	76,550	16,809	0.543	0.680
26	Rebound to NH after withdrawal (base case: rebound to initial gain)	N	5.171	42,168	NA	0.983	0.687
		A	5.846	69,701	Ex dom	0.004	0.038
		E	6.104	76,145	36,408	0.013	0.273
		I	6.307	89,900	67,759	0.000	0.002
31	No costs of psoriasis (base case: UK data[187,192])	N	5.171	28,908	NA	0.485	0.317
		A	6.580	56,792	Ex dom	0.037	0.022
		E	7.001	62,209	18,196	0.459	0.513
		I	7.308	77,704	50,499	0.019	0.148

continued

TABLE 36 Univariate sensitivity analyses *(continued)*

Scenario	Description	Trt	QALY	Cost (£)	ICER	PCE 20K	PCE 30K
32	Schering-Plough estimates[152] of cost per PASI point excluding phototherapy[152]	N	5.171	55,479	NA	0.456	0.298
		A	6.580	80,496	Ex dom	0.065	0.042
		E	7.001	87,252	17,361	0.414	0.423
		I	7.308	99,438	39,715	0.065	0.237
33	Schering-Plough estimates[152] of cost per PASI point including phototherapy[152]	N	5.171	112,633	NA	0.370	0.237
		A	6.580	131,482	13,381	0.146	0.057
		E	7.001	141,118	Ex dom	0.145	0.161
		I	7.308	146,187	20,188	0.339	0.545
99	The effectiveness of biologic therapy lasts no longer than 10 years compared with palliative care	N	5.171	42,168	NA	0.861	0.534
		A	5.875	66,044	Ex dom	0.017	0.038
		E	6.130	71,556	30,645	0.122	0.408
		I	6.325	83,779	62,746	0.000	0.020
35	Continue on biologic after 3 months if respond to *either* PsARC *or* PASI 75 (base case: PsARC only)	N	5.171	42,168	NA	0.475	0.312
		A	6.763	72,421	Ex dom	0.078	0.040
		E	7.006	74,934	17,859	0.376	0.382
		I	7.476	92,890	38,194	0.071	0.266
38	Assume that adalimumab and etanercept are equally effective for PsARC response, HAQ change and PASI response	N	5.231	41,524	NA	0.509	0.335
		E or A	7.033	74,489	18,296	0.441	0.611
		I	7.338	88,405	45,557	0.050	0.054

A, adalimumab; E, etanercept; I, infliximab; Dom, dominated; Ex dom, extended dominated; N, palliative care; NA, not available; PCE 20/30K, probability that the treatment is cost-effective at a threshold of £20,000/30,000 per QALY; Trt, treatment.

The ICER of adalimumab falls below £20,000 per QALY and is no longer dominated by other strategies in any of the following univariate sensitivity analyses, assuming all other variables take mean values as in the base case:

- All responders to PsARC have the same change in HAQ at 3 months, regardless of biologic therapy used.
- If etanercept and adalimumab are considered equally effective for PsARC response, HAQ change and PASI response.
- A patient who does not respond for psoriasis, or does not use biologic therapy, undergoes annual inpatient psoriasis treatment rather than annual ultraviolet light, type B (UVB), treatment.

The higher cost per PASI point (including phototherapy) from the Schering-Plough model[152] are used.

The ICER of etanercept increases above £20,000 per QALY or is dominated by other strategies in any of the following univariate sensitivity analyses, assuming that all other variables take mean values, as in the base case:

TABLE 37 Cost-effectiveness of the strategies under different scenarios

Scenario	Description	Adalimumab	Etanercept	Infliximab
1	Base case	Ex dom	<20K	>30K
2	Rebound in HAQ is small after withdrawal (base case = initial gain)	Ex dom	<20K	>30K
3	Rapid worsening in HAQ with no treatment (upper 95% of CI)	Ex dom	<20K	>30K
4	Log-PASI utility function (Abbott[151]) (base case linear)	Ex dom	<20K	>30K
5	No correlation between PASI 75 and PsARC (base case = 0.4)	Ex dom	<20K	>30K
6	RCT results fully generalisable to clinical practice (no adjustment for placebo effect)	Ex dom	<20K	>30K
9	Exponential HAQ-cost function (Abbott[151]) (base case linear)	Ex dom	<20K	>30K
12	Inpatient treatment for uncontrolled psoriasis	<20K	Dom	<20K
13	Cost per 3 month per 1 unit change in HAQ is £183 (US data)[42] (base case £103)	Ex dom	<20K	>30K
14	Change in utility per 1 unit change in HAQ is –0.45 (Wyeth[153]) (base case –0.29)	Ex dom	<20K	>30K
15	HAQ improves while on drug (lower 95% of CI) (base case no change)	Ex dom	<20K	20–30K
16	High rate of withdrawal (upper 95% of CI)	Ex dom	<20K	>30K
17	Low rate of withdrawal (lower 95% of CI)	Ex dom	<20K	>30K
18	All treatments have the same probability of PsARC response at 3 months	Ex dom	<20K	>30K
19	All treatments have the same probability of psoriasis responses (PASI 50, 75 and 90) at 3 months	Ex dom	<20K	>30K
20	Cost of drugs as in Wyeth submission[153]	Ex dom	<20K	>30K
22	All biologics have the same change in HAQ at 3 months for a PsARC responder	<20K	<20K	>30K
23	Three vials of infliximab (base case: four vials)	Ex dom	Ex dom	<20K
26	Rebound to NH after withdrawal (base case: rebound to initial gain)	Ex dom	>30K	>30K
31	No costs of psoriasis (base case: UK data)	Ex dom	<20K	>30K
32	Schering-Plough estimates[152] of cost per PASI point without phototherapy[152]	Ex dom	<20K	>30K
33	Schering-Plough estimates[152] of cost per PASI point with phototherapy[152]	<20K	Ex dom	<20K
99	The effectiveness of biologic therapy lasts no longer than 10 years, compared with palliative care	Ex dom	20–30K	>30K
35	Continue on biologic after 3 months if respond to either PsARC or PASI 75 (base case: PsARC only)	Ex dom	20–30K	>30K
38	Assume that adalimumab and etanercept are equally effective for PsARC response, HAQ change and PASI response	<20K	<20K	>30K

<20K, mean ICER is <£20,000 per QALY; 20–30K, mean ICER is between £20,000 and £30,000 per QALY; >30K, , mean ICER is >£30,000 per QALY; Dom, dominated; Ex dom, extended dominated.

- A patient who does not achieve a PASI 75 response is offered one course of therapy as a hospital inpatient per year to treat psoriasis. The base case assumed that these patients are offered UV therapy.
- HAQ rebounds after withdrawal from biologic to NH rather than to initial gain.
- Biologic treatment becomes ineffective (relative to no treatment) after 10 years.
- If the Schering-Plough[152] estimates of the cost of treating psoriasis with phototherapy are used in the York Assessment Group model.

The ICER of infliximab falls below £30,000 per QALY in any of the following univariate sensitivity analyses, assuming that all other variables take mean values as in the base case:

- A patient who does not respond for psoriasis, or does not use biologic therapy, undergoes annual inpatient psoriasis treatment rather than annual UVB treatment.
- Infliximab requires three vials rather than four vials per administration.
- The higher cost per PASI point (including phototherapy) from the Schering-Plough[152] model are used.
- HAQ improves while on a biologic drug.

No biologic appears cost-effective at a threshold of £30,000 per QALY if rebound of HAQ is to NH, rather than initial gain. In the scenario where treatment remains effective for only up to 10 years, the ICER for etanercept versus palliative care is £31,000 per QALY and is therefore is likely to be on the boundary of what would be considered cost-effective. If treatment remains effective for up to 20 years then the ICER of etanercept versus palliative care is £19,000 per QALY and the ICER for infliximab versus etanercept is £60,000 per QALY.

It should be noted that these are univariate analyses, where one variable in the base case is changed, holding others constant. Changes in combinations of variables might generate different results.

TABLE 38 Subgroup analyses

						PCE	
Scenario	Description	Trt	QALY	Cost (£)	ICER	20K	30K
10	Baseline HAQ 1.8 (BSRBR[186]) (base case 1.05)	N	2.090	46,594	NA	0.528	0.350
10		A	3.397	73,207	Ex dom	0.044	0.029
10		E	3.804	79,431	19,156	0.389	0.447
10		I	4.101	93,046	45,898	0.039	0.174
11	Baseline PASI 12.5 (base case 7.5)	N	4.810	66,811	NA	0.431	0.274
11		A	6.257	90,422	16,310	0.115	0.057
11		E	6.661	98,214	19,319	0.294	0.269
11		I	7.012	107,988	27,778	0.160	0.400
7	Baseline PASI 12.5, and continue after 3 months only if respond to *both* PsARC *and* PASI 75 (base-case PsARC only)	N	4.810	66,811	NA	0.399	0.246
7		E	5.315	74,865	Ex dom	0.030	0.039
7		A	5.790	81,637	15,125	0.174	0.073
7		I	6.717	101,796	21,739	0.397	0.642
8	Baseline PASI 12.5, and continue after 3 months if respond to *either* PsARC *or* PASI 75	N	4.810	66,811	NA	0.435	0.278
8		A	6.448	93,601	16,349	0.170	0.076
8		E	6.665	98,293	21,609	0.208	0.177
8		I	7.187	111,940	26,177	0.187	0.469
21	Baseline PASI 12.5, and annual inpatient treatment for uncontrolled psoriasis (base-case UVB)	N	4.810	171,746	NA	0.185	0.079
21		A	6.257	183,184	7,901	0.101	0.053
21		I	7.012	191,216	10,636	0.710	0.855
21		E	6.661	197,741	Dom	0.004	0.013
30	Baseline PASI zero (base case 7.5)	N	5.713	28,908	NA	0.498	0.330
30		A	7.064	56,792	Ex dom	0.018	0.019
30		E	7.512	62,209	18,512	0.471	0.549
30		I	7.752	77,704	64,744	0.013	0.102

A, adalimumab; E, etanercept; I, infliximab; Dom, dominated; Ex dom, extended dominated; N, palliative care; NA, not available; Trt, treatment.

Results of subgroup analyses

Table 38 shows the results of the subgroup analyses.

Biologics are slightly less cost-effective if the baseline HAQ is 1.8; however, etanercept still has an ICER below £20,000 per QALY. In this model, the size of the absolute gain in HAQ for responders is assumed to be independent of baseline HAQ, although there is a ceiling effect as the maximum HAQ score is 3. There is less scope for biologics to alter the course of the disease if they are started when patients already have a high degree of disability.

Etanercept is the most cost-effective strategy in patients with negligible baseline psoriasis. The ICER of infliximab versus etanercept increases to £65,000 per QALY. If baseline PASI were moderate-to-severe (12.5 instead of 7.5) the ICER of adalimumab versus palliative care would be < £16,000 per QALY, the ICER of etanercept versus adalimumab would be around £19,000 per QALY and the ICER of infliximab versus etanercept would be about £28,000 per QALY. If patients with uncontrolled moderate-to-severe psoriasis receive annual inpatient treatment instead of annual UVB the ICER for infliximab is below £20,000 per QALY and it is likely to be the most cost-effective strategy.

If the patient is indicated for biologics because of both severe skin disease and severe joint disease, we can consider alternative rules for continuing therapy. The base case follows the BSR guidelines, i.e. treatment is withdrawn from patients who fail to achieve the PsARC response within 3 months of treatment. Alternative decision rules (see *Box 2*) can change the conclusions. If patients with PsA and moderate-to-severe psoriasis are allowed to continue beyond 3 months if they respond to either PsARC or PASI 75 then all biologics have a similar probability of being cost-effective at a threshold of £20,000 per QALY, and infliximab has the highest probability of being cost-effective at a threshold of £30,000 per QALY. If patients with PsA and moderate-to-severe psoriasis are allowed to continue beyond 3 months only if they respond to both PsARC and PASI 75 then infliximab has the highest probability of being cost-effective at thresholds of £20,000 and £30,000 per QALY.

Table 39 shows the outcomes for each strategy if the biologic drugs are used as a second course of therapy after a first biologic has failed for patients with PsA with mild-to-moderate skin disease. The ICERs depend on which drug was used as first-line therapy, and which is therefore ineligible for use as second-line.

TABLE 39 Costs and QALYs of biologics used as second-line therapy for patients with mild-to-moderate skin disease if first biologic fails

					ICER assuming:		
Scenario	Description	Trt	QALY	Cost (£)	I was used first line	E was used first line	A was used first line
24	Second-line biologic if first failed for inefficacy	N	5.171	42,168			
24		A	5.827	54,394		18,652	
24		E	6.142	58,783	17,114		17,114
24		I	6.410	68,630		24,406	36,746
25	Second-line biologic if first failed for AEs	N	5.171	42,168			
25		A	6.273	61,430		17,486	
25		E	6.597	65,780	16,554		16,554
25		I	6.831	76,205		26,445	44,569

A, adalimumab; E, etanercept; I, infliximab; N, palliative care; NA, therapy is not available for second-line use as failed in first-line; Trt, treatment.

- For patients who failed adalimumab as first line for inefficacy, etanercept has an ICER of < £20,000, and the ICER for infliximab is above £40,000 per QALY.
- For patients who failed etanercept as first line for inefficacy, adalimumab has an ICER of < £20,000 and infliximab is around £25,000 per QALY.
- For patients who failed infliximab as first line for inefficacy, etanercept has an ICER of < £20,000 per QALY and adalimumab is extendedly dominated compared with palliative care and etanercept.
- The ICERs are broadly similar for patients who failed first-line therapy for adverse effects compared with results for those who failed first-line therapy for inefficacy.

Comparison of the York Economic Assessment with the manufacturers' models

The following sections compare the assumptions and data sources used in each of the industry models with the current York model (see *York Economic Assessment*). A full description of the three industry models is provided in *Appendix 7* and a critique is detailed in *Appendix 8*.

Summary of the models' results

The three industry models, along with the current York model, are all potentially relevant to address the decision problem as specified by the NICE scope. However, each generates a different set of results. Abbott's base case[151] is for a 40-year time horizon, baseline HAQ = 1.3, baseline PASI = 6.9, proportion with psoriasis = 40%, and rebound of HAQ after withdrawal from biologic therapy equal to initial gain. Only results averaged across all patients are presented in the base case. The results show that infliximab was associated with the highest QALYs (8.49), followed by etanercept and adalimumab (both 8.33) and then DMARDs (7.47). Infliximab is the most costly strategy (£104,772). The ICER for adalimumab compared with DMARDs is £29,827. Etanercept is dominated by adalimumab and infliximab has an ICER of £199,596 compared with adalimumab.

Schering-Plough's base case[152] is for a 40-year time horizon, baseline HAQ = 1.14, baseline PASI = 11, proportion with psoriasis = 66% and rebound equal to gain. Results are reported for all patients, psoriatic patients and non-psoriatic patients. The results show that palliative care is the strategy associated with the lowest QALYs in all base-case scenarios (5.79–6.68, depending on the group of patients). Infliximab is the most effective strategy for all patients with PsA and those with a psoriasis component (8.65 QALYs for all patients and 8.40 QALYs for patients with psoriasis). For patients without psoriasis, etanercept is the most effective (9.14 QALYs). For all patients the model estimates a total cost of £64,704 for palliative care, £99,278 for adalimumab, £108,481 for etanercept and between £107,954 and £123,475 for infliximab, depending on the weight of patients. Similar estimates were generated for minimal psoriasis and psoriasis patients separately. Therefore, for all patients, etanercept has an ICER of £12,606 (compared with adalimumab) assuming a patient weight of 70 or 80 kg. For a 60-kg patient etanercept has an ICER of £12,432, compared with adalimumab, for patients without psoriasis. Infliximab dominates etanercept for psoriatic patients and all patients.

Wyeth's base case[153] is for a 40-year time horizon, baseline HAQ = 0.69, baseline PASI = 3.39, proportion with psoriasis = 62.4% and rebound equal to gain. Only results for all patients are presented in the base case. The results show that etanercept was associated with the highest gain in QALYs (6.90) followed by adalimumab (6.54), infliximab (6.39) and then ciclosporin (5.96). Ciclosporin was associated with the lowest cost (£53,860). Infliximab had the highest total costs (£66,867). Etanercept is the most cost-effective strategy with an ICER of £12,480.

The base-case analysis in the York model assumes a lifetime time (40-year) horizon for costs and QALYs a baseline HAQ = 1.05, baseline PASI = 7.5, rebound equal to gain and incorporates the correlation between PsARC and PASI 75 outcomes. The results for the base case for patients with PsA and mild-to-moderate psoriasis show that infliximab is the most effective treatment followed by etanercept then adalimumab. Infliximab is also the most costly treatment, followed by etanercept then adalimumab. The ICER of etanercept compared with palliative care is £18,000. Adalimumab is extendedly dominated. The ICER for infliximab compared with etanercept is £44,000 per QALY. Results are also presented for other baseline subgroups: HAQ = 1.8, PASI = 0 and PASI = 12.5.

Critique of manufacturers' submissions and justification for current York modelling approach

There are large differences in the results generated by each of the four models. In order to determine which model provides the most appropriate estimates of the cost-effectiveness of biologics for the treatment of PsA, the key features of the models are compared and contrasted in more detail in the sections below. Justification for the approach taken in the current York model is also presented. A full critique of the industry models is also presented in *Appendix 8*. *Table 40* shows the key features of each of the models. A full description of the three industry models is provided in *Appendix 7*.

Choice of comparator

The choice of comparator is crucial in determining the relative cost-effectiveness of biologics. In comparing biologics to DMARDs while using the effectiveness estimates of placebo from randomised trials (i.e. assume DMARD cost and placebo effectiveness), Wyeth[153] and Abbott[151] may artificially inflate the cost-effectiveness of biologics, as DMARDs are liable to be more effective than palliative care in practice. It is also unlikely that patients who have failed two previous DMARDs would be considered for further DMARD treatment, and such patients are likely to receive palliative care (as assumed in the York and Schering-Plough[152] models).

Heterogeneity

Although patients included in the model will be similar in terms of their exposure to DMARDs and the fact that they will be biologic naive, they may be a heterogeneous group in many other respects. The Abbott[151] and Wyeth[153] models use an individual sampling approach, where observed heterogeneity in the group of patients is modelled by sampling over a set of patient characteristics, taken from Mease *et al.*[200] This approach effectively averages over the heterogeneity between patients. In contrast, the Schering-Plough[152] and current York models use a cohort approach which assumes a homogeneous group of patients. To account for any heterogeneity in a cohort model, the models can be ran separately for each homogeneous group to generate estimates of cost-effectiveness, conditional on each set of observed characteristics. In principle, separate NICE decisions can then made for each group of patients. This difference in how heterogeneity is reflected in the different models may partly explain the variation in their results.

Baseline characteristics differ quite markedly between models. In the Wyeth model[153] the baseline HAQ and PASI are both low, at 0.69 and 3.39, respectively. These are higher in the Abbott[151] model at 1.3 for HAQ and 6.9 for PASI. In the Schering-Plough[152] model baseline HAQ is about the average for the RCTs at 1.14; however, a baseline PASI score of 11 suggests that patients have relatively severe psoriasis. The Schering-Plough[152] model also includes the highest proportion of patients with psoriasis at 66%; however, these are run as a separate subgroup to those without any significant psoriasis rather than as a model input. The current York model also distinguishes between those with little or no psoriasis (PASI scores < 5) and moderate or severe psoriasis (PASI scores > 5) with 7.5 as the base case. Baseline HAQ in the York model is 1.05, based on

TABLE 40 Comparison of the key features of each of the models

	Wyeth[153]	Schering-Plough[152]	Abbott[151]	Current York model
Comparators	Ciclosporin (a DMARD)	Palliative care	Unspecified DMARD	Palliative care
Model structure	Initial response determined. HAQ and PASI tracked over time, accounting for withdrawals	Initial response determined. HAQ and PASI tracked over time, accounting for withdrawals	Initial response determined. HAQ and PASI tracked over time, accounting for withdrawals	Initial response determined. HAQ and PASI tracked over time, accounting for withdrawals
Patient characteristics	Heterogeneous cohort (first-order simulation)	Homogeneous cohort	Heterogeneous cohort (first-order simulation)	Homogeneous cohort
	Baseline HAQ = 0.69	Baseline HAQ = 1.14	Baseline HAQ = 1.3	Baseline HAQ = 1.05
	Baseline PASI = 3.39	Baseline PASI = 11	Baseline PASI = 6.9	Baseline PASI = 7.5
	Proportion with psoriasis = 60.4%	Proportion with psoriasis = 66%	Proportion with psoriasis = 40%	
Adjustment for placebo effect	No adjustment. Assumes comparator group represents effect of ciclosporin	Average HAQ gain in placebo arm is subtracted from HAQ gain in responders and non-responders on treatment	No adjustment. Assumes comparator group represents effect of DMARD	Average HAQ gain in placebo arm is subtracted from HAQ gain in responders and non-responders on treatment in the base case
Sequencing after failure of first drug	Patients withdraw from biologic drug to no treatment	Patients withdraw from biologic drug to no treatment	Sequence of unspecified DMARDs. There is a 24% reduction in response (i.e. increased probability of withdrawal) for each successive treatment in sequence compared with the previous	Patients withdraw from biologic drug to no treatment
Outcomes of evidence synthesis	PsARC and PASI 75 at 12 and 24 weeks (from previous adalimumab MTC) Regression to predict 4 week PsARC from 12-week PsARC	PsARC at 12 weeks: In subgroup with > 3% body skin area: PASI change from baseline at 12 weeks, by PsARC response/no response HAQ change from baseline at 12 weeks by PsARC response/ no response and treatment drug (CiC information has been removed)	Four regressions specified: 1. Joint distribution of PsARC and ACR response (< 20, ACR 20–50, etc.) at 12 weeks. 2. PsARC at 24 weeks conditional on PsARC at 12 weeks 3. ACR response at 24 weeks conditional on ACR response at 12 weeks 4. Joint distribution of PASI 75 at 12 and 24 weeks	PsARC at 12 weeks: HAQ by PsARC response/no response and specific biologic treatment PASI 50/75/90 at 12 weeks
Decision to withdraw depending on initial response(s)	Withdrawal will be made if patient is a PsARC non-responder at either 12 weeks or 24 weeks	Withdrawal will be made if patient is a PsARC non-responder at 12 weeks	Withdrawal will be made if patient is a PsARC non-responder at 12 weeks	Base case: withdrawal will be made if patient is a PsARC non-responder at 12 weeks Model considers other stopping decisions, e.g. PsARC or PASI responder
Initial change in HAQ for responders and non responders	HAQ at 4, 12 and 24 weeks predicted from PASI, PsARC, any biologic and baseline HAQ. HAQ does not differ by biologic drug after conditioning on other predictive variables	HAQ by PsARC response and treatment from evidence synthesis. HAQ differs by the biologic used, after conditioning on PsARC For responders: maintain HAQ gain for 24 weeks from week 0 to 24 For non-responders (on biologics): maintain HAQ from week 0 to 12	HAQ at 12 and 24 weeks predicted from ACR response (20, 50, etc.), baseline HAQ, age, gender, baseline PsA duration, whether on MTX and whether on any biologic (from ADEPT[51,88,92,93,100–104] data). HAQ does not differ by biologic drug after conditioning on the other predictive variables	HAQ by PsARC response and treatment from evidence synthesis HAQ differs by the biologic used, after conditioning on PsARC

TABLE 40 Comparison of the key features of each of the models *(continued)*

	Wyeth[153]	Schering-Plough[152]	Abbott[151]	Current York model
HAQ progression while on biologic and responder	0	Assumes a HAQ improvement for first year while on biologics, then 0	Worsening by 0.0005 per year (Bath data set)	0
HAQ progression when on DMARD	0.028 per year (Sokoll)	Not applicable	0.024 per year (Leeds)	Not applicable
HAQ progression while on therapy and ACR < 20	Not applicable	Not applicable	0.066 per year (Leeds)	Not applicable
HAQ progression while not on therapy	0.069 per year (Leeds)	0.071 per year (Leeds)	0.066 per year (Leeds)	0.072 per year (NOAR)
Initial change in psoriasis on biologic	Initial improvement in PASI (weeks 4, 12 and 24) was estimated using multivariate regression models	PASI change from baseline to 12 weeks for PsARC Responder/non-responder from evidence synthesis	PASI at 12 and 24 weeks predicted from baseline PASI, age, gender, baseline PsA duration, MTX, whether PASI 50/75/90 response	Predicted from baseline PASI and proportion who are PASI 50/75/90 response
Correlation between PASI and PsARC responses	Assumes PASI is a predictor of HAQ	Predicts PASI by PsARC response, generating a different PASI change for PsARC responders and non responders The change in PASI is dependent on the biologic used, after conditioning on PsARC	Assumed independent	Correlation of PsARC and PASI 75 estimated from 'ADEPT' trial to estimate the joint pdf
Psoriasis progression on biologic	0	0	0	0
Psoriasis progression not on biologic	0	0	0	0
HAQ rebound when stopping therapy	To initial gain OR to NH	To initial gain OR to NH	To initial gain	To initial gain and using elicited values in sensitivity analysis
Psoriasis rebound when stopping therapy	To initial gain	To initial gain	To initial gain	To initial gain
Withdrawal rate: biologics	Different withdrawal rates for each biologic (Saad *et al.*[191]). Weibull estimated using data from three time points	11% per year (Geborek *et al.*[198]) per year	Average withdrawal rate across all biologics (Saad *et al.* [191]). Weibull estimated using data from three time points	Average withdrawal rate across all biologics (meta-analysis of observational studies). 16% per year
Withdrawal rate- DMARD	0.34 per year	Not applicable	Weibull distribution used. Unclear how this was specified as only one data point reported (Malesci *et al.*[199])	Not applicable
Utility (HRQoL)	Predicted from HAQ, age and gender (PRESTA)	Predicted from HAQ and PASI, HAQ-squared and PASI-squared, using regression, (no interaction term) (GO-REVEAL data)	Predicted from HAQ and PASI (no interaction term) (ADEPT)	Wyeth:[153] additional utility regression as the base case and other functions as sensitivity analyses

continued

TABLE 40 Comparison of the key features of each of the models *(continued)*

	Wyeth[153]	Schering-Plough[152]	Abbott[151]	Current York model
Mortality	Same rate for all treatments and no treatment (Wong *et al.*[29])	Same rate for all treatments and no treatment (Wong *et al.*[29])	Same rate for all treatments and no treatment (Wong *et al.*[29])	Same rate for all treatments and no treatment (Wong *et al.*[29])
Costs of treatments	Assumes no wastage of Infliximab	Results shown assuming three vials of infliximab (60 kg), three and a half vials (and four vials (80 kg)	Assumes no wastage of Infliximab (four vials, 80-kg weight)	Assumes no vial sharing (four vials, 70–80 kg weight) in base case. Three vials for a 60-kg patients considered in sensitivity analysis
Costs of start-up, administration and monitoring	BSR recommendations	From York model	BSR recommendations	BSR recommendations validated by clinical opinion
Cost depending on HAQ	THIN data set. HAQ was not recorded in this data, and was predicted based on relationship between HAQ, age, number of prior DMARDs in BSR data set	RA data set (Kobelt *et al.*[59])	NOAR	RA data set (Kobelt *et al.*[59]) in base case
Cost of psoriasis	Not included (other than through HAQ which is in part predicted by PASI)	Physician survey	Physician survey	For mild-moderate psoriasis: Poyner *et al.*[192]
Patient subgroups	Mild, moderate, severe HAQ and mild, moderate/severe and very severe PASI	With psoriasis Without psoriasis	Varying severity of HAQ and PASI at baseline	Varying severity of HAQ and PASI at baseline

pdf, probability density function; PRESTA, Psoriasis Randomized Etanercept STudy in Subjects with Psoriatic Arthritis; THIN, The Health Improvement Network.

the average observed in the RCTs (see *Table 1*). The current York model also run a series of scenarios to vary base-case HAQ and PASI scores (see *Tables 36* and *38*). For patients with a high baseline PASI (12.5) adalimumab is no longer extendedly dominated (ICER is £16,000 compared with palliative care). The ICER for etanercept is similar to the base case at £19,000 compared to adalimumab and the ICER for infliximab falls to £28,000 compared to etanercept. These changes in ICERs are because of the differences in PASI response rates between the drugs. For more severe psoriasis (high baseline PASI), treatments with a better effect on PASI will be more cost-effective. For patients without any significant psoriasis aspect to their disease, the ICER for etanercept increases slightly to £19,000 compared with palliative care. For patients with a higher baseline HAQ (1.8) the ICER for etanercept also increases to £19,000 compared with palliative care.

Model structure

The basic structure in each of the four models is similar. Each determines initial response to treatment and then tracks HAQ and PASI scores over a lifetime, taking account of any withdrawals from treatment.

Measurement of initial response for joints

All models use PsARC to measure the initial response for joints. All models used a Bayesian evidence synthesis to estimate PsARC. However, the results differ, partly because different RCTs are included in the analyses (see *Table 19*). Schering-Plough[152] and the York model predict that infliximab is the most effective drug for PsARC response, then etanercept, then adalimumab. Wyeth[153] predict etanercept is the most effective, then infliximab, then adalimumab (see *Table 21*). Using a bivariate meta-analysis to inform the economic model, Abbott[151] predicts that infliximab is most effective for PsARC and ACR responses, then adalimumab, then etanercept.

These differences have a substantial effect on the results of the economic analysis. The sensitivity analysis shown in *Table 36* shows that by assuming that all treatments have the same probability of psoriasis responses (PASI 50/75/90) at 3 months, the ICER for etanercept falls to £16,000, adalimumab remains extendedly dominated and the ICER for infliximab increases to over £66,000. This is because infliximab had a much higher probability of skin response in the base case. Applying the same PsARC response at 3 months to all treatments also has a minimal effect on the ICERs of adalimumab and etanercept, but increases the ICER for infliximab compared with etanercept to over £100,000. This is because infliximab was associated with a much higher PsARC response in the base case (see *Table 34*).

Continuation on biologic treatment after initial assessment

All of the industry models assume that patients are withdrawn from treatment if they are PsARC non-responders at 12 weeks (and 24 weeks for Wyeth[153]), irrespective of PASI response. The current York model also uses this assumption in the base case, but additionally explores alternative scenarios for discontinuation for patients who are indicated for both moderate-to-severe psoriasis and arthritis. The BAD guidelines recommend that patients continue if they achieve PsARC or PASI 75, although this continuation rule does not change the conclusions for patients with PsA and mild-to-moderate psoriasis.

Correlation between skin and join response

If patients have both joints and skin involvement at baseline then in determining the initial response to treatment it is important to incorporate any correlation between the joint and skin responses, measured by PsARC and PASI respectively. The current York model incorporates the correlation between PsARC and PASI 75 using data from the ADEPT trial[88] and the results of the evidence synthesis in *Chapter 3* (see *Results of review of clinical effectiveness*) to estimate the probability of a response to both psoriasis and joints, the probability of a response to neither, and the probability of a response to one but not the other. The industry models, in contrast, do not afford this issue as much attention. Abbott[151] assumes that PsARC and PASI responses are independent (see *Appendix 7* for further detail). The Schering-Plough model[152] predicts PASI by PsARC response, thus generating a different PASI change for PsARC responders and non-responders by drug. This implicitly incorporates a correlation between PsARC and PASI responses, but is difficult to vary in sensitivity analysis. The Wyeth model[153] assumes PASI is a linear predictor of HAQ (see *Appendix 7* for further detail). This is a strong assumption that is difficult to vary in sensitivity analysis, and Wyeth[153] did not support this by a clinical justification. The York model also considers a scenario where there is no correlation between PASI 75 and PsARC (see *Table 36*). The impact on the ICER for etanercept is minimal, however, with the ICER for etanercept increasing to £16,106.

Effect on joints and skin for responders and non-responders

The models differ in the variables used to predict the change in HAQ for responders. Wyeth[153] estimate HAQ from PsARC response and PASI. Abbott[151] estimate HAQ from ACR response (assumed correlated with PsARC) and other clinical and demographic variables. Abbott[151] assumes the ACR response varies by biologic drug, after conditioning on PsARC. Schering-Plough[152] and the York model estimate HAQ from PsARC response, and assume that HAQ varies by biologic received, after conditioning on PsARC response.

Given the initial response (or lack of response) to treatment, all models then determine an associated HAQ and PASI score. The current York model uses the same approach as Schering-Plough,[152] and predicts HAQ by PsARC response and treatment, and this is estimated by the evidence synthesis model. Abbott[151] predicts HAQ from the ACR response as an explanatory variable, and other clinical and demographic explanatory variables. The same HAQ gain is assumed for all treatments, after conditioning on ACR. Despite this, the Abbott model[151] allows

a different HAQ gain for PsARC responders for each treatment. This is because ACR response is assumed to differ by biologic drug, and ACR was correlated with PsARC in the Abbott[151] evidence synthesis (see *Table 19*). Although this seems an attractive method of predicting changes in HAQ, it was decided not to use this approach in the York model as the Abbott[151] evidence synthesis was very complex. Furthermore, it is not clear what data used in the Abbott[151] evidence synthesis inform their economic model. In the clinical section of the Abbott report,[151] Table 2.7.2.2 shows the marginal probabilities of PsARC and ACR responses were estimated to be higher for etanercept than adalimumab (these results are reproduced in Tables 5.21 and 5.24 of the York Assessment Group report and are similar to those of the York Assessment Group). However, Table 3.4.3.1.1 of the economic section of the Abbott report[151] shows the contingent or joint probabilities of ACR and PsARC, and appears to contradict the results of their clinical section; in this table, adalimumab is shown as more effective for PsARC and ACR response than etanercept. It appears that the Abbott meta-analysis[151] that informed their economic section made use of different data to the clinical section, including data from biologics that are not relevant to this appraisal.

Wyeth[153] estimates the initial change in HAQ, including changes in PASI in the regression. The same HAQ gain is used for all treatments. The use of the skin component of PsA to predict the arthritis component of the disease is considered of doubtful clinical validity. There is no evidence to suggest that one component of the disease is a good predicator of the other: patients can have differing degrees of both components and those with severe arthritis will not necessary have severe psoriasis and vice versa.

The fact that two of the models use treatment specific HAQ gains (Schering-Plough[152] and York) and two use the same HAQ gain for all treatments may explain some of the variability in results. The results of a sensitivity analysis on the York model (see *Table 36*) show that by assuming all biologics have the same change in HAQ at 3 months for a PsARC responder, the results differ quite significantly from those in the base case. Adalimumab is no longer extendedly dominated and the ICER for etanercept increases to £22,000 compared with adalimumab. This is because in the base case etanercept was associated with a much higher HAQ gain for a PsARC responder (–0.63) than adalimumab (–0.48).

To determine the initial change in PASI, the current York model and the Abbott[151] model predict the initial 12-week (and 24-week for Abbott[151]) change in PASI, using baseline PASI and the proportion of patients who are PASI 50/75/90 responders, thereby using all information on PASI response. Wyeth[153] uses only PASI-75 to generate the initial improvement in PASI, thereby ignoring all of the other PASI information. Schering-Plough[152] also estimates PASI change (not specifying which proportion) in the initial period, but do this for PsARC responders/non-responders in their evidence synthesis model. It is not clear why PASI change was estimated for PsARC responders and non-responders and not for PASI responders. Determining the initial differences in PASI response between treatments is likely to be a key driver of the cost-effectiveness results. All of the evidence syntheses predicted that infliximab is most effective for psoriasis response, then adalimumab, then etanercept (see *Table 23*). However, Wyeth[153] predicted that infliximab was less effective in absolute terms than the York and Abbott[151] models. The sensitivity analysis shown in *Table 36* shows that by assuming that all treatments have the same probability of psoriasis responses (PASI 50/75/90) at 3 months, etanercept appears more cost-effective and the other biologic drugs less cost-effective than the base case.

Placebo effects

In determining this initial impact of treatment, it is important to account for any overestimate of the *absolute* response rates in both placebo and treatment groups in RCTs, compared with what

would be expected in routine practice. This is termed the placebo adjustment. However, the York sensitivity analysis found that this adjustment had a minor effect on results.

Health Assessment Questionnaire progression when not on a biologic

For those patients who do not respond to treatment, or who are assigned palliative care, HAQ and PASI progression must be tracked over the model. To determine HAQ progression off treatment, all of the industry models use data from the Leeds cohort study[201] data. As detailed in *Appendix 14*, however, the Leeds data set does have some limitations. The current York model therefore uses data from patients enrolled in the NOAR (see *Appendix 14*) data set to estimate HAQ change in patients who have uncontrolled PsA. The 3-month progression rates are similar to those generated using the Leeds data (0.018 in NOAR compared with 0.016 in Leeds data set) and is unlikely to lead to major differences in the results.

Withdrawal from biologics

For those patients who do initially respond to biologic treatment, each of the models considers the possibility that they may withdraw from treatment beyond the initial period due to either loss of efficacy or adverse events. Each of the industry models makes use of a single data set to estimate withdrawals. Schering-Plough[152] uses the same rates as used in the previous York model (0.11 per year from Geborek *et al.*[198]). Wyeth[153] and Abbott[151] use evidence from a recent paper by Saad *et al.*,[191] which used data from the BSRBR registry to estimate parameters of a Weibull distribution to quantify the rate of withdrawal over time. All models assumed that withdrawal rates did not vary by treatment. However, the sensitivity analysis reported in *Table 36* shows that there is very little impact of changes withdrawal rates within the current York model.

Sequential biologic therapies

Once patients withdraw from biologic treatment they are assumed to move to either palliative care or DMARDs. None of the four models consider the use of sequential biologics in the base-case scenario. The sequential use of biologics is common in clinical practice; however, a lack of data on the effectiveness of biologics beyond first line use limits the scope to consider such an analysis. The current York model conducts an exploratory sensitivity analysis on the issue of sequencing biologics (see *Appendix 20*), utilising available registry data on response rates for subsequent lines of biologics.

Utility and cost estimates

The utilities and costs assigned to treatments are of paramount importance in determining the cost-effectiveness of the included treatments. It is, therefore, important to note that each of the models uses different methodology and data sources to link HAQ and PASI to utilities and to determine the associated costs of treatments. In generating utilities each of the industry models uses both different data sources and different models to predict utilities from HAQ and PASI. To disentangle these two effects the current York model explores various scenarios using regression results provided on request from each of the manufacturers (see *Appendix 17*), which are estimated using a common methodology. In addition, the York model explores the use of alternative assumptions regarding the calculation of utilities in sensitivity analysis (see *Table 36*). Only the scenario where a higher estimate of the effect of a unit change in HAQ on utility is taken from the Wyeth[153] submission (–0.45) has a discernible impact on the results. Etanercept is more cost-effective (ICER is £12,000 compared with palliative care) and the ICER for infliximab falls to £37,000.

Resource use assumed in establishing drug, administration and monitoring costs differs between the industry models. In particular, there were varying assumptions regarding the number of doses given for each of the drugs (see *Appendix 8*) and the number of laboratory tests required for monitoring patients. The costs attached to hospital visits also differed between models. In

the Abbott model,[151] it was not possible to validate the resource use and costs used, and the total costs given in the report could not be replicated in terms of the resource use items and unit costs presented. That is, using the resource use multiplied by the respective unit costs gave different total costs to those presented in the model report. These also differed from those used in the model.

The current York model therefore sought to generate costs for each of the treatments using resource use specified by the BSR guidelines and validated by clinical collaborators (see *Appendix 13*). These differences in costing methodology produce quite different estimates of total costs. For example, in the initial 3-month period the cost of infliximab in the base-case analysis is £5459 in the Abbott model,[151] £4386, in the Schering-Plough model,[152] £6286 in the Wyeth model[153] and £5522 in the current York model. The sensitivity analysis in *Table 36* shows the impact of varying drug costs in the current York model. Using the costs presented in the Wyeth submission[153] in the York model (which are higher for infliximab (see *Appendix 8*) but lower for adalimumab and etanercept than the York estimates, increases the cost-effectiveness of etanercept and increases the ICER for infliximab (£69,000). Reducing the number of vials used for each infliximab infusion from four to three greatly increases the cost-effectiveness of infliximab and reduces the relative cost-effectiveness of the other biologics.

In addition to the costs of drugs, administration and monitoring each of the models considers the ongoing health-service costs of PsA as a function of a patient's HAQ score. Abbott[151] and Schering-Plough[152] also include health-service costs according to PASI scores. The costs associated with PASI score, in particular differ quite markedly (see *Appendix 8*). Abbott[151] and Schering-Plough[152] rely on surveys of clinicians' opinions, based on vignettes of 'typical cases' to estimate the costs associated with treating psoriasis. The York model estimates the costs of treating mild-to-moderate psoriasis that is uncontrolled by biologic drugs from a UK RCT and the costs of treating moderate-to-severe psoriasis that is uncontrolled by biologic drugs from a Dutch RCT. The sensitivity analysis in *Table 36* shows the impact of varying ongoing costs of PsA as a function of a patient's HAQ and PASI score in the current York model. Using the exponential HAQ cost function from the Abbott model[151] reduces the ICER for etanercept to £13,000. Adding in a high inpatient cost of uncontrolled psoriasis had a much more dramatic impact on model results: etanercept is dominated by infliximab, which is itself associated with an ICER of £13,000 compared with adalimumab. This reflects the beneficial effect of infliximab in terms of reducing PASI score compared with other biologics. Infliximab is associated with an ICER likely to be below the threshold when the cost estimates per PASI point (including phototherapy) from Schering-Plough[152] are used. In this situation the ICER for infliximab is £20,000. Other sensitivity analysis on costs dependent on HAQ and PASI had little impact on the model results.

Summary

The key differences between the three industry models and the current York model have been discussed. This has highlighted a number of potentially important limitations with the three industry models, in particular: the choice of comparator, averaging across patient heterogeneity; failure to consider alternative correlations between response types; how initial PsARC response is determined; how the change in HAQ is determined; no consideration of alternative decision rules about continuing beyond the initial 3-month period; generating withdrawals rates from a single observational study; the costs of drugs; drug administration and monitoring; and the health-care costs associated with treating arthritis and psoriasis if these are uncontrolled by biologics.

Discussion of York Economic Assessment

The economic model has evaluated the cost-effectiveness of three alternative biologic therapies and palliative care only. Under base-case assumptions, for patients with PsA and mild-to-moderate skin disease, the ICER of etanercept versus palliative care is about £18,000 per QALY and the ICER of infliximab versus etanercept is about £44,000 per QALY. Adalimumab is extendedly dominated. On average, given the base-case assumptions in the York model, etanercept would be considered the most cost-effective strategy if the threshold for cost-effectiveness were £20,000 per QALY or £30,000 per QALY. The probability etanercept is the most cost-effective treatment is 0.44 at a threshold of £20,000 per QALY and 0.48 at a threshold of £30,000 per QALY. The expected lifetime prescription costs of biologic therapies is considerably greater than the offset cost savings elsewhere in the NHS.

These results are sensitive to several of the scenarios tested in univariate sensitivity analyses:

- All biologics appear less cost-effective if they are assumed to remain effective for a maximum of 10 years rather than 40 years, or if HAQ rebounds to NH after withdrawal.
- Results are sensitive to assumptions about the prescription cost. If three vials of infliximab are required rather than four, infliximab is much more cost-effective and the other biologics are not cost-effective.
- Results are sensitive to assumptions about the cost of treating patients who do not achieve a response to biologics for the psoriasis component of PsA. If these costs are high, etanercept appears less cost-effective as it is considerably less effective in treating psoriasis than the other biologics.
- Results are sensitive to assumptions about the progression of HAQ on and off treatment. If the prognosis for patients without biologics is worse than the base case, or HAQ improves while on biologic drugs, all biologics appear more cost-effective.
- Results are sensitive to assumptions about whether clinical effectiveness differs between the therapies.

Cost-effectiveness also varies between different subgroups of patients:

- For patients with PsA and moderate-to-severe skin disease, and who continue with biologic therapy if they achieve a response for either psoriasis or joint disease, the ICER of adalimumab versus palliative care is about £16,000 per QALY, the ICER of etanercept versus adalimumab is about £21,000 per QALY and the ICER for infliximab versus etanercept is about £26,000 per QALY.
- For patients with PsA and negligible skin involvement, the ICER of etanercept versus palliative care is about £19,000 per QALY, and the ICER of infliximab versus etanercept is about £65,000 per QALY. Adalimumab is extendedly dominated in this group.
- For patients who have failed adalimumab or infliximab as first-line therapy for either adverse events or inefficacy, etanercept is cost-effective at a threshold of £20,000 per QALY. For patients who have failed etanercept as first-line therapy for either adverse events or inefficacy, adalimumab is cost-effective at a threshold of £20,000 per QALY, though infliximab is more likely to be cost-effective if the threshold is £30,000 per QALY.

These are univariate sensitivity and subgroup analyses. Multivariate sensitivity analyses may lead to different conclusions.

The decision model and data sources have several limitations and uncertainties. BAD guidelines recommend that both PASI and DLQI are used to measure the psoriasis component of PsA.

Few RCTs measured DLQI and so this criterion could not be used in the decision model. PASI may be less well correlated with HRQoL than DLQI.[194] The decision model assumes that mean changes in HAQ are a function of PsARC response and the biologic therapy used. This approach has been used in other decision models of PsA (see *Systematic review of existing cost-effectiveness evidence*).[152, 177] Changes in HAQ may be more accurately predicted by other clinical and demographic variables, such as ACR and age. The Abbott model[151] estimated a joint distribution of ACR and PsARC, and predicted HAQ from ACR responses. Although this is an attractive method, we considered the evidence synthesis required to undertake this modelling to be very complex and appeared to use data relating to biologics that are not currently licensed for PsA (see *Systematic review of existing cost-effectiveness evidence*).

There is some debate about whether the RCTs have recruited similar cohorts of patients and the effect on the results. Our review of the trial patients' characteristics (see *Table 1*) indicated that the trials were similar enough to conduct a meta-analysis, and any resultant treatment differences were included in the model. However, other experts suggest that biologic therapies are very similar in their effectiveness and suggest that the RCTs show superior effects for infliximab only because these trials recruited a greater proportion of patients with polyarticular disease who may have better response rates than other types of PsA (Phillip Halliwell, London, UK, 16 February 2010, evidence to NICE committee).

The base-case model assumes that patients who fail therapy will be placed on palliative care. In practice many patients are tried with a second or third biologic. The use of biologics as the second line in a sequence is explored in a secondary, subgroup analysis. This analysis relies on non-randomised comparisons and therefore should be considered with caution.

Some of the patients included in RCTs did not use at least two DMARDs before trialling a biologic, as recommended by the BSR. In contrast, data on the NH of PsA without biologic therapy are from an observational study of rheumatoid factor-negative inflammatory polyarthritis patients with at least three tender joints and three swollen joints, who have failed at least two DMARDs.

Data on withdrawal rates after 3 months are from a meta-analysis of observational studies. In this model, withdrawal rates are assumed to be exogenous, i.e. independent of other variables in the model. In practice, withdrawal may depend on other factors, such as the biologic therapy used, obtaining a continuing response of both arthritis and psoriasis, and the options for switching to other biologics. Adverse events are not included in the model other than through their influence on withdrawal rates in the biologics register. In practice, there may be longer-term consequences and costs of adverse events, such as cancers and infections.

There is little good-quality data on the effect of arthritis and psoriasis on health-service costs in the UK. The base-case model uses UK data[176] on the effect of HAQ on costs, but is rather dated, the methods used to analyse the data are not clearly reported and are likely to underestimate the impact of very severe HAQ on health and Personal Social Services costs. The base-case model uses data from a UK study of 272 patients with mild-to-moderate psoriasis to estimate the health service costs if biologics are not used or patients do not respond to biologics.[192] The model uses data from the Netherlands to estimate the health service costs of treating moderate-to-severe psoriasis if biologics are not used or patients do not respond to biologics.[188]

It is assumed that there is no progression of HAQ for patients using biologics, based on elicitation of opinion from experts. There is considerable uncertainty about the 'rebound' of HAQ after withdrawal. The results of the expert elicitation seemed to indicate that experts believed that

HAQ would rebound by less than the initial gain. This scenario increased the cost-effectiveness of all biologics, but did not materially change the conclusions of the model compared with the base case.

There is uncertainty about how the results of RCTs should be generalised to clinical practice. The base-case model assumed that the results in the placebo arm of the trials represented 'non-pharmacological' aspects of medical care that might not be reproduced outside the trial setting. The results of the trials were adjusted to take out this 'placebo effect'. An alternative scenario that assumed these non-pharmacological aspects of medical care would be generalisable to general practice slightly increased the cost-effectiveness of all biologics, but did not materially alter the conclusions of the base-case analysis.

We compared the results from the current York model with those of other models and, in particular, the industry submissions to this appraisal. The current York model is essentially very similar in methods (and results) to the earlier York Assessment Group model reported by Bravo Vergel *et al.*[177] if there is no skin involvement, the time horizon is 40 years and the HAQ rebound after withdrawal from biologic is equal to initial gain. Adalimumab was not included in Bravo Vergel *et al.* model,[177] but the current York model finds that adalimumab would not be cost-effective in this subgroup.

Abbott[151] (manufacturers of adalimumab) found that adalimumab has an ICER of just below £30,000 per QALY compared with palliative care and other biologics are not cost-effective. The Abbott model[151] calculated the 'average' cost-effectiveness of the biologics over all patients with PsA, 40% of whom were assumed not to have psoriasis, and assumed a mean PASI of 6.9 in the 60% of the population with psoriasis. The York model found that for patients with PsA and mild-to-moderate psoriasis adalimumab is extendedly dominated and is therefore unlikely to be the most cost-effective treatment. The reasons for the differences between the York and the Abbott model[151] are difficult to pinpoint, not least because the sources of data for the Abbott[151] bivariate evidence synthesis are unclear. Abbott[151] estimate a higher response rate for PsARC and ACR with adalimumab than etanercept.

Schering-Plough[152] (the manufacturers of infliximab) found that infliximab was cost-effective for patients of 60 kg weight if vial sharing is allowed, or if patients use three vials per administration. If vial sharing is not allowed or patients require four vials per administration then Schering-Plough[152] concluded that etanercept was the most cost-effective strategy at a threshold of £20,000 per QALY in patients without psoriasis and with psoriasis. These conclusions are broadly consistent with those of the York model.

Wyeth[153] (the manufacturer of etanercept) found that etanercept was the most effective and cost-effective biologic, and dominated or extendedly dominated infliximab and adalimumab. This is not consistent with the results of the York model, which found infliximab to be the most effective and most costly biologic. The main differences between the models are likely to be:

- *The estimates of PsARC response* Wyeth[153] found that etanercept had the highest probability of PsARC response, whereas the York evidence synthesis (and those of the other manufacturers) found infliximab to be the most effective for PsARC.
- *The assumption made by Wyeth[153] that changes in HAQ are proportional to changes in PASI* This is a strong assumption and Wyeth[153] did not provide any clinical justification to support it.

Despite the differences in data and model structure outlined above (see *Comparison of the York Economic Assessment with the manufacturers' models*), the results of the York model are broadly

consistent with those of Schering-Plough,[152] taking account of assumptions about vial sharing. The Abbott model[151] appears to have overestimated the effectiveness of adalimumab in terms of PsARC and ACR responses. The Wyeth model[153] appears to have overestimated the effectiveness of etanercept, in terms of PsARC response, and makes strong and arguably unjustified assumptions about the relationship between HAQ and PASI.

Chapter 5

Assessment of factors relevant to the NHS and other parties

The results of this technology assessment have some implications for clinical practice. At present, most patients with PsA who receive biologic therapy are managed by a rheumatologist. However, patients with PsA primarily concerned with improvements in their skin may benefit from being managed by a dermatologist who can tailor any ongoing topical therapy appropriately. Some patients with severe skin and joint disease may need dual management of both specialties, although it has implications in terms of additional administration, costs and communication between the specialties and primary care.

For patients with joint disease who respond to biologic treatment, potential cost savings might include reduced need for contact with services (e.g. physiotherapy) and monitoring costs for certain DMARDs. For patients responding in terms of skin disease, there may be the potential for avoiding inpatient admissions resulting from severe psoriasis.

There is a choice of measures available for assessing joint response (ACR or PsARC). BSR guidelines currently recommend PsARC, but also suggest this is supplemented with measures of HAQ, ESR and CRP. The choice of outcome measure will therefore have resource use as well as methodological implications.

The mode of delivery varies among the biologics included in this evaluation. Provision of infliximab requires the treatment centre to have the appropriate capacity in terms of staff and facilities to delivered scheduled i.v. infusions of the agent. In contrast, etanercept and adalimumab are delivered by self-administered injection. This may have short-term implications for initial training of patients, although with potential cost savings in the longer term.

As the rate of serious adverse events for these biologic agents has yet to be well established, all patients should be monitored by a specialist. In addition, relevant data for the BSRBR should be collected and appropriate measures for infection screening should be used.

The potential benefits of these agents on physical function and QoL might result in reduced demand on social services and carers, and the potential (although not yet fully demonstrated) for slowing disease progression could potentially reduce the demand for joint replacement surgery and associated services.

Chapter 6

Discussion

Statement of principal findings

The systematic review of clinical efficacy found a limited amount of high-quality data suggesting that etanercept, infliximab and adalimumab all produce significant improvements in joint response measures relative to placebo. Some evidence suggesting beneficial effects for these agents in terms of skin response, although data on this outcome are sparse. Although short-term data on joint progression are promising, longer-term controlled data on this outcome are lacking. The range of incidences of serious adverse events did not appear to differ remarkably between agents.

An indirect comparison of the three drugs indicated that infliximab is associated with the highest probability of response on joint and skin outcomes. The response in joint disease appeared greater with etanercept than with adalimumab, whereas the skin response appeared greater with adalimumab than with etanercept, though these differences are not statistically significant. In those patients who achieve a PsARC response to treatment the highest mean reductions in HAQ are seen with infliximab and etanercept.

Under base-case assumptions the York economic model found that for patients with mild-to-moderate skin disease, the ICER of etanercept versus palliative care is about £18,000 per QALY, the ICER of infliximab versus etanercept is about £44,000 per QALY and adalimumab is extendedly dominated. On average, given these base-case assumptions, etanercept would be considered the most cost-effective strategy if the threshold for cost-effectiveness were £20,000 or £30,000 per QALY. The probability etanercept is the most cost-effective treatment is 0.44 at a threshold of £20,000 per QALY and 0.48 at a threshold of £30,000 per QALY. The expected lifetime prescription costs of biologic therapies is considerably greater than the offset cost savings elsewhere in the NHS. These results were sensitive to several of the scenarios tested in univariate sensitivity analyses

Strengths and limitations of the assessment

Strengths

We conducted a rigorous systematic review that addressed clear research questions using predefined inclusion criteria. Comprehensive literature searches were performed to locate all relevant published and unpublished studies without any language restrictions, thereby minimising both publication and language biases.[164,166] Efforts were also made to identify additional studies by hand-searching company submissions, clinical trial reports and reference lists of relevant publications. Compared with the previous review,[174] the current updated review has included a larger body of evidence (e.g. additional inclusion of two RCTs of adalimumab). In addition, data on serious adverse events of biologic treatment were also systematically reviewed. We are therefore confident that we have been able to include all the relevant studies in the evaluation of efficacy and adverse events of etanercept, infliximab and adalimumab.

Our review included RCTs to assess the efficacy of biologic agents in the treatment of PsA. That uncontrolled trials would be particularly unreliable for the purpose of evaluating treatments for PsA was demonstrated by the trials of treatment interventions for PsA in which the uniform improvement of symptoms was consistently observed in the placebo group.[54] It is important to note that all the included trials were rated as 'good' quality using the prespecified criteria, which ensured the internal validity of their research findings.

In the review process, sufficient attempts have been taken to reduce the potential for reviewer errors and biases. The study selection, data extraction and quality assessment were performed in duplicate. In particular, statistical heterogeneity was assessed and appropriate meta-analyses methods were adopted in the evaluation of efficacy. In terms of the evaluation of adverse events, the level of clinical heterogeneity between studies has been fully investigated. Owing to the high degree of clinical heterogeneity identified between included studies, a narrative synthesis was therefore appropriately adopted.

In the absence of head-to-head comparison evidence on the efficacy between the alternative biologic therapies, an indirect comparison was undertaken using Bayesian approaches to estimate the relative efficacy of these biologic agents in terms of both skin and joint symptom improvement. These estimates, together with other parameters were subsequently used to inform the independent economic model as an overall framework for the cost-effectiveness evaluation of biologic treatment.

This review has addressed many of the limitations of the previous economic assessment of biologic therapies for PsA. It is based on an updated evidence synthesis that includes infliximab, etanercept and adalimumab and includes responses of both psoriasis and arthritis. The model assesses the cost-effectiveness of biologic therapies for patients with different degrees of severity of psoriasis and arthritis at baseline. The model takes account of potential correlations between responses of arthritis and skin disease to biologic, and considers alternative rules about continuation on therapy beyond the initial 3 months. Withdrawal rates are estimated from a synthesis of data from several registers. The model takes account of the health-care costs associated with treating psoriasis if this is uncontrolled by biologics. The appraisal undertook an elicitation of expert clinical opinion to inform the estimate of the change in HAQ following withdrawal from biologic drugs. The economic analysis explores the potential for sequencing biologic drugs.

Limitations

The main limitation of this systematic review was that there were limited efficacy data available. Although all the included trials were judged as good quality, the analyses for each efficacy outcome were limited to only two RCTs. Some trials also recruited a small number of participants. Most trials had short follow-up period of either 12/14 or 24 weeks, which were often considered inadequate to assess radiographic changes in response to the treatment. There was a lack of controlled data on long-term outcomes, such as radiographic assessments. Given the fact that the treatment effect on the joint disease is more accurately reflected by the more objective radiographic measure, radiographic long-term data could provide more generalisable estimates of the biologic treatment effect. In addition, a lack of direct comparison evidence between biologic agents also made it difficult to draw firm conclusions on the relative effectiveness of these biological agents.

Another limitation of this systematic review resulted from the difficulties in assessing PsA activity and its response to the biologic therapy. Although a number of outcome measures were used in estimating the treatment effects, no outcome measure has been clearly identified as optimal for

PsA. In this review we have attempted to use the best available outcome measures. In the clinical evaluation, we used a number of efficacy outcome measures as reported in the various clinical trials including PsARC, ACR 20/50 /70, HAQ and PASI. These measures are not ideal but are the best available, especially when data for joint and skin are both used. We also used the outcome of radiological assessment to address the long-term joint disease progression despite the data being sparse in included trials.

Despite the fact that we have incorporated both joint and skin aspects of treatment effects in the clinical effectiveness and cost-effectiveness evaluation, the data of biologic efficacy on the skin condition were very sparse.

Limitations of the adverse event evaluation in this review reflected on the non-randomised design of the majority of included studies and its reliance on uncontrolled data. Although we also included the data from RCTs, the adverse event data from these RCTs were often limited by a very short-term follow-up. The majority of data in the evaluation of adverse events for the treatment with etanercept, infliximab and adalimumab were derived from the observational studies and open-label extension of RCTs; however, the reliability of these data was questionable due to lack of a control group.

The new York cost-effectiveness model measures the severity of skin disease using the PASI score. PASI may not be well correlated with HRQoL. BAD recommends that both DLQI and PASI are used to assess the severity of arthritis. DLQI was not recorded by many trials, and so could not be measured in the evidence synthesis or model. The model measures the severity of joint disease using the HAQ score and assumes initial changes in HAQ are a function of PsARC response and treatment. Changes in HAQ may be more accurately predicted by a richer set of clinical and demographic variables such as ACR response and age. ACR responses from the RCTs were synthesised in *Chapter 3* (see *Results of review of clinical effectiveness*), but incorporating PASI 75, PsARC and ACR responses in the model was considered to be very complex.

The cost-effectiveness model relied on observational data to estimate withdrawal rates and changes in HAQ for patients not using biologic therapy. However, it is unlikely that long-term randomised data would ever be available. The model uses observational data to estimate how the effectiveness of second-line therapy differs from first-line therapy. However, a randomised study comparing second-line use of biologics, depending on the reason for failing the first-line therapy, might be difficult to design. The model assumes patients withdraw to palliative care. If sequential use of biologics were included in the model this might change the estimate of the cost-effectiveness of first-line biologic therapy. The elicitation of expert opinion included only five experts and the results should be considered exploratory.

The model only includes adverse events to the extent that they influence the assessment of initial response and long-term withdrawal rates. Serious adverse events such as cancers and infections are rare, but may have long-term consequences. Biologics may have an effect on mortality, either for better (through reduced coronary events) or worse (through serious adverse events). Data on mortality attributable to the use of biologics in PsA is sparse and these effects therefore have been excluded.

There are few good quality data on the effect of arthritis and psoriasis on health-service costs in the UK. The model excludes productivity losses and private health-care expenditure in accordance with the NICE reference case, but these costs to society from PsA are likely to be substantial.

Uncertainties

- The treatment effect of each biologic agent for the joint and skin conditions in this systematic review is based on only two RCTs with limited sample size. In particular, few patients provided data on the psoriasis response to biologics.
- Bayesian indirect comparison analyses provide evidence of the relative effectiveness of these biological agents; however, those findings may be considered more uncertain than would be provided in head-to-head RCTs.
- The patients recruited in most trials are not precisely representative of the populations recommended for biologic therapy in current guidelines. It is unclear whether the observed beneficial effects are similar in those populations.
- The evidence of risk of serious adverse events (serious infection, malignancy and activation of latent TB) for treatment with these biologic agents remains uncertain because there are large uncertainties associated with these estimates, as well as the unreliable nature of the majority of the data.
- The adverse event data for etanercept, infliximab and adalimumab are derived primarily from patients with RA or other indications. The generalisability of these findings to patients with PsA remains unclear.
- The results of the York economic model are sensitive to several of the scenarios tested in univariate sensitivity analyses.
  - The model assumes that biologics are effective in treating joint disease in two ways: (1) for patients successfully maintained on treatment, biologics reduce symptoms and prevent the progression of arthritis; and (2) biologics are assumed to permanently delay the progress of joint disease in patients, even if they withdraw from treatment, relative to a patient who had never used biologics. Results are sensitive to these assumptions about the progression of HAQ on and off treatment and the length of time over which biologics are assumed to be effective.
  - The elicitation of expert opinion found that clinicians believed the change in HAQ following withdrawal from biologic drugs would be less than the initial gain on starting biologic therapy. This is an important parameter in the model and should be investigated further.
  - The estimate of the prescription cost of the therapies relies on BSR guidelines and expert opinion about the number of vials required. This should be supported with empirical evidence on actual resource use. Results are sensitive to alternative data about the costs of treating psoriasis of different levels of severity. Results are sensitive to alternative assumptions about the relationship between utility and the severity of arthritis and psoriasis.

Chapter 7

Conclusions

Implications for service provision

- The limited data available indicate that etanercept, infliximab or adalimumab are efficacious in the treatment of PsA compared with placebo, with beneficial effects on both joint and skin symptoms and on functional status. Short-term data suggest that these three biologic agents can delay joint disease progression.
- Despite the limited data in the evaluation of clinical effectiveness of etanercept, infliximab and adalimumab, the evidence to support their efficacy in the treatment of PsA is convincing given the size of treatment effect and quality of data.
- An indirect comparison of the three drugs indicated that infliximab is associated with the highest probability of response on PsARC, ACR and PASI outcomes. In those patients who achieve a PsARC response to treatment the highest mean reduction in HAQ are seen with infliximab and etanercept.
- This review cannot rule out concerns about increased risk of rare serious adverse events (serious infection, malignancy and activation of latent TB) of the biologic agents investigated. Until further data are available, appropriate measures for screening and monitoring of patients should be used.
- Under base-case assumptions, the York model indicated that etanercept would be considered the most cost-effective strategy if the threshold for cost-effectiveness were £20,000 per QALY or £30,000 per QALY. The expected lifetime prescription costs of biologic therapies are considerably greater than offset cost savings elsewhere in the NHS.
- For patients with PsA and mild-to-moderate psoriasis who have failed adalimumab or infliximab as first-line therapy for either adverse events or inefficacy, etanercept is cost-effective at a threshold of £20,000 per QALY. For patients who have failed etanercept as first-line therapy for either adverse events or inefficacy, adalimumab is cost-effective at a threshold of £20,000 per QALY, although infliximab is more likely to be cost-effective if the threshold is £30,000 per QALY.
- The present value prescription costs per person of biologic therapy over 40 years are estimated to be around £52,000 for infliximab, £33,000 for etanercept and £27,000 for adalimumab (at a discount rate of 3.5% per year). Most of these liabilities will accrue to NHS hospital trusts. Offset cost savings elsewhere in the NHS from less need for arthritis and psoriasis treatments are likely to be relatively modest. For patients with PsA with minimal psoriasis or mild-to-moderate psoriasis, who are thought to make up about 75% of the population, the present value of lifetime offset cost savings are expected to be no greater than about £5000.

Suggested research priorities

- Long-term observational studies with large sample sizes of patients with PsA are required to demonstrate that beneficial effects for joint and skin disease and improvement of function are maintained. In particular data on the effects of joint disease progression (e.g. radiographic assessment), long-term HAQ progression while responding to biologic agents

and HRQoL are required. Withdrawal rates due to lack of efficacy and adverse events should also be reported.

- Further monitoring of the safety profiles of the biologic agents (e.g. through the BSBR) is required. Future research should also establish whether long-term patterns of adverse events of these biologic agents in PsA are similar to those in RA.
- Further investigation is required to reduce uncertainties around the following parameters identified in the economic model:
  - The length of time over which biologics are assumed to be effective.
  - The change in HAQ following withdrawal from biologic drugs.
  - Evidence from general practice about the prescribing, administration and monitoring costs of biologic therapy.
  - The NHS costs of treating psoriasis of different levels of severity.
  - The progression of HAQ on and off biologic treatment.
  - The effectiveness and withdrawal rates of biologics used as second-line therapy.
- Future studies should assess how the biologic treatment of both arthritis and psoriasis affects patients' QoL using generic preference-based utility instruments.
- The cost effectiveness of sequential use of biologic therapies should be evaluated further.
- Although indirect analysis is useful, future trials comparing one biologic agent with another in the treatment of PsA are warranted.

The effectiveness and cost-effectiveness of biologics in patients who might not quite reach the current BSR/BAD criteria for either psoriasis or arthritis, but might nevertheless benefit from biologic therapy, should also be examined.

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Contribution of authors

Mark Rodgers was responsible for study selection, data extraction, validity assessment, data analysis and writing the report. David Epstein and Laura Bojke were responsible for the review of cost-effectiveness evidence and the overall development of the economic model. Huiqin Yang contributed to study selection, data extraction, validity assessment, data analysis and writing the report. Dawn Craig and Tiago Fonseca were responsible for the evidence synthesis section. Lindsey Myers devised the search strategy, carried out the literature searches and wrote the search methodology sections of the report. Ian Bruce and Robert Chalmers provided clinical advice and commented on drafts of the report. Sylwia Bujkiewicz was responsible for developing Transparent Interactive Decision Interrogator (TIDI) interface and wrote the chapter on TIDI development. Monica Lai contributed to programming of the TIDI interface and liaised between York and Leicester teams. Alex Sutton, Nicola Cooper, Keith Abrams and David Spiegelhalter contributed original ideas and oversaw the development of TIDI, commented on drafts of the chapter on TIDI and provided statistical advice on the decision model and evidence synthesis. Mark Sculpher contributed to all aspects of the economic sections, and Nerys Woolacott contributed to all aspects of the clinical effectiveness sections. All authors contributed to and commented on the final draft of the report.

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Appendix 23

Development of a Transparent Interactive Decision Interrogator to facilitate the decision-making process

Introduction

The aim of this report was to determine the clinical effectiveness, safety and cost-effectiveness of etanercept, infliximab and adalimumab for the treatment of active and progressive PsA in patients who have had an inadequate response to standard treatment. To allow readers to make fully informed decisions based on the available evidence, a range of different scenario analyses were presented in *Chapter 4* (see *Results of York Economic Assessment*) of this report. However, as the authors cannot anticipate every potential scenario that might be of interest to decision makers, NICE agreed to allow the development and use of interfaces in their appraisal process to be undertaken alongside this report.

Transparent Interactive Decision Interrogator has been developed to aid the decisions made by NICE committees during their consultations. The aim of the development of TIDI was to make the NICE decision process more transparent, by making the decision models more accessible to critique by a wider range of decision makers and also by using flexible and clear model components developed in R and WINBUGS. TIDI also aims to make the decision-making process more efficient by allowing the (re-)running of models potentially in real time during the NICE appraisal meetings.

This user friendly, EXCEL-based interface allows decision makers to have access to all components of a decision model developed in R and WINBUGS, without a need of knowledge of these specialised software programmes. It makes it possible not only to change model parameters and rerun models under different scenarios in real time, but also provides a control over the model assumptions. By allowing this, TIDI can make the process of evaluating uncertainty faster and more efficient, while avoiding arbitrary limitations of preprepared analysis of a restricted number of scenarios. TIDI also provides interactive access to supplementary analyses, such as meta-analyses and influence analysis, which can help to establish which parameters have most impact on the cost-effectiveness estimates. This interface has been developed for the York decision model, presented in *Chapter 4*.

Software

Transparent Interactive Decision Interrogator is an EXCEL-based interface, programmed in Visual Basic for Applications (VBA).[243,244] It allows all of the model parameters and options to be changed by using controls set out on the EXCEL spreadsheet. REXCEL,[245,246] which is an add-in to EXCEL, provides communication between EXCEL and R. All data used by the model components, stored in the EXCEL spreadsheets, can be transferred to R workspace and various actions, for example execution of the model or its components, can be activated also using controls located on the EXCEL spreadsheet. Having this possibility of running programs developed in R from

EXCEL allows the user also to execute (from EXCEL) additional model components, for example evidence syntheses, developed in WINBUGS (using R2WINBUGS).[247]

Interface capabilities: model building

The controls for the model parameters and actions are set out on the front page of TIDI, called 'SetupAndRun'. These controls allow for change of any parameters that inform the decision model. *Figure 12* shows the layout of these controls and scrolling down the spreadsheet will reveal more parameters and options of this complex model as shown in *Figure 13*. These controls allow for the parameter change, as well as switching between alternative options of modelling the cost-effectiveness and then further for the change of the parameters corresponding to these alternative options. This gives an in-depth access to the model parameters and assumptions leading to building new model scenarios.

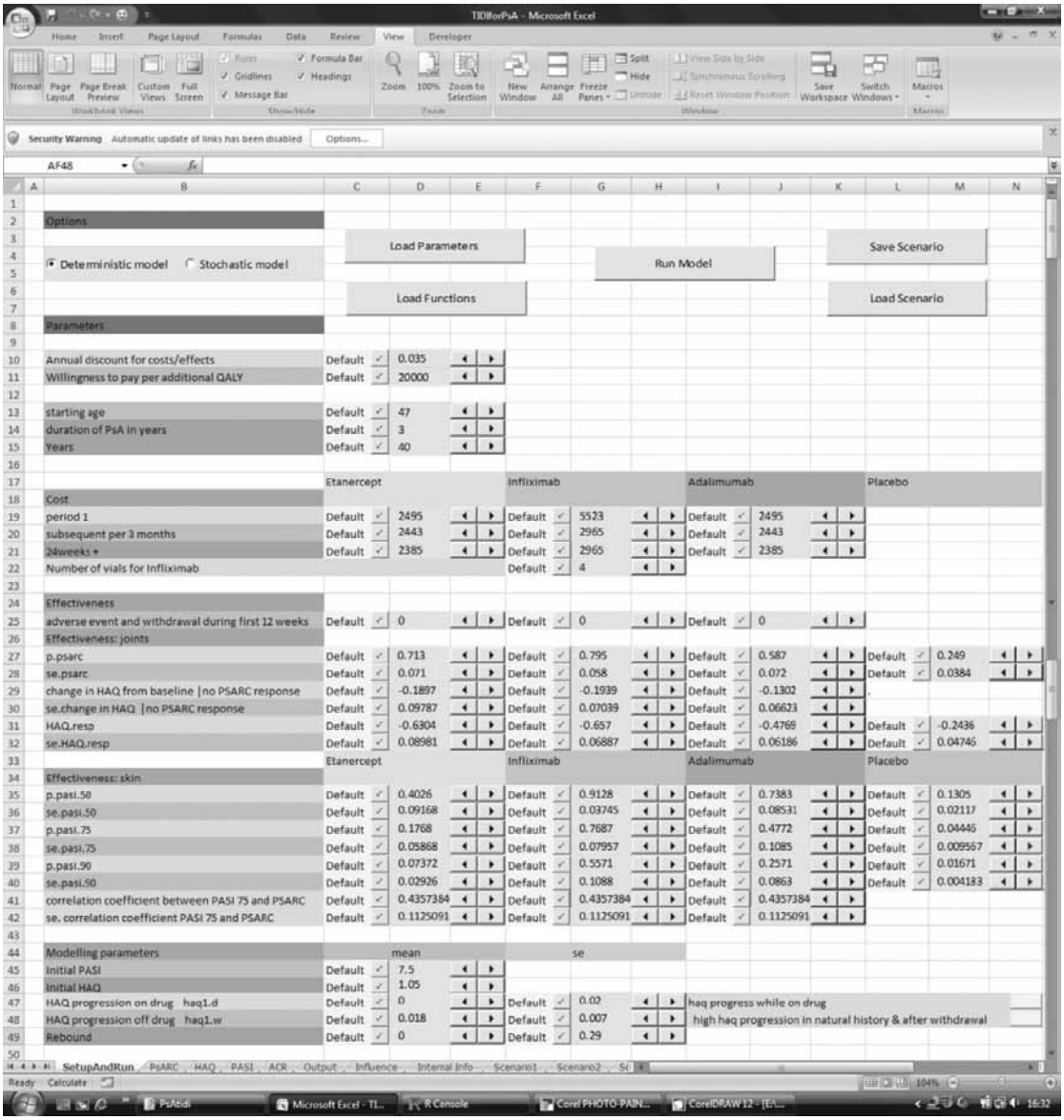

FIGURE 12 Layout of the parameter and action controls on the front page ('SetupAndRun') of TIDI.

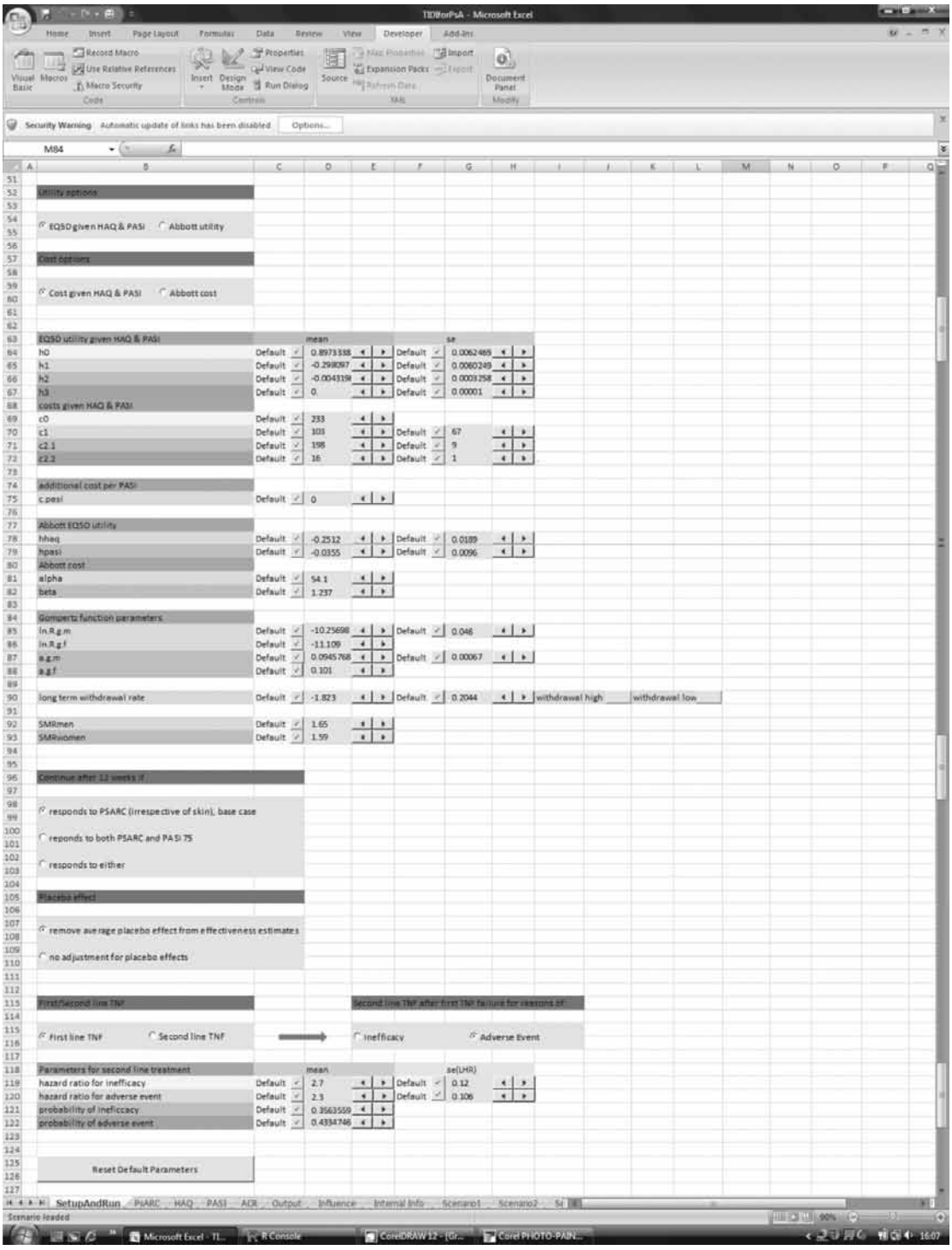

FIGURE 13 Further controls of model parameters and assumptions on the front page ('SetupAndRun') of TIDI.

For example, the radio buttons on top of *Figure 13* allow the user to choose how the utility and additional cost over time are modelled. The parameters that were used to fit utility and cost in the base-case model or those used by the Abbot submission to NICE (scenarios 4 and 9, results of which were shown in *Chapter 4*, *Results of York Economic Assessment*) can be further changed here, allowing for much wider range of scenarios to be considered in real time.

Further options are available to choose the stopping rule or whether or not to include placebo effect (scenarios 6–8 and base case). The possibility to switch between these options combined with any change of the model parameters give a lot more flexibility in considering the most appropriate scenarios.

The TIDI also allows for a change of the parameters used in the scenarios that consider second-line treatment. The controls allow the user to choose, for example between reasons for switching (inefficacy or adverse event as in scenarios 24 and 25) and then to adjust the parameters specific to these scenarios.

All the above options make TIDI a flexible tool that can run not only all the scenarios listed in *Chapter 4* (see *Results of York Economic Assessment*) of this report, but also, in addition, infinite numbers of new ones.

Model execution and results

Once a new model scenario is built, all model parameters are loaded to R workspace where the R code is executed and cost, QALYs and ICERs are being calculated. Note that to be able to execute the York economic model in real time, the model was run deterministically. The time required to run the full stochastic model was too long to allow running it during a committee meeting. However, the deterministic version gives a good approximation of the cost-effectiveness point estimates. The full analysis of agreement between deterministic and stochastic model for each scenario is presented in *Appendix 22*. The average differences between the stochastic and deterministic models were 2.16% (SD = 5.74%) for QALY, 0.02% (2.84%) for cost and 4.75% (9.95%) difference in ICER.

The results of the model are then displayed in the 'Output' spreadsheet. As shown in the example in *Figure 14*, the 'Output' spreadsheet lists QALYs, cost, ICERs relative to placebo, and, finally, ICERs resulting from the final selection of the most effective strategy (following exclusion of strategies being dominated or extendedly dominated). The results are shown along with the final ICERs from the base-case model listed below the main set of results for comparison. The final results of the decision model are also represented graphically. In the plot included in *Figure 14*, the circles denoted N, A, E and I represent each strategy on the cost-effectiveness plane ('Cost' vs 'QALY'), and the slopes of the lines linking these circles correspond to the ICERS. Dashed line marks the strategy (in this case adalimumab) that has been excluded as being extendedly dominated by another strategy (in this case etanercept).

The set of the scenario parameters and corresponding results can be saved in a separate spreadsheet 'ScenarioN', creating a library of scenarios considered by decision makers for later viewing. The whole set of parameters and settings of any saved scenario can also be uploaded back to the 'SetupAndRun' front page of the TIDI workbook for further considerations and amendments, after which the model can be rerun.

Further interface applications: meta-analysis

Effectiveness estimates that inform the decision model are obtained from the meta-analyses presented in *Chapter 3* of this report and these can also be accessed and adjusted from TIDI. The interface of meta-analysis is designed in such a way to allow selection of any subset of available studies for which pooled outcomes can be recalculated. The resulting estimates are then displayed in tabular form as well as using interactive forest plots. The outcome of the new meta-analysis

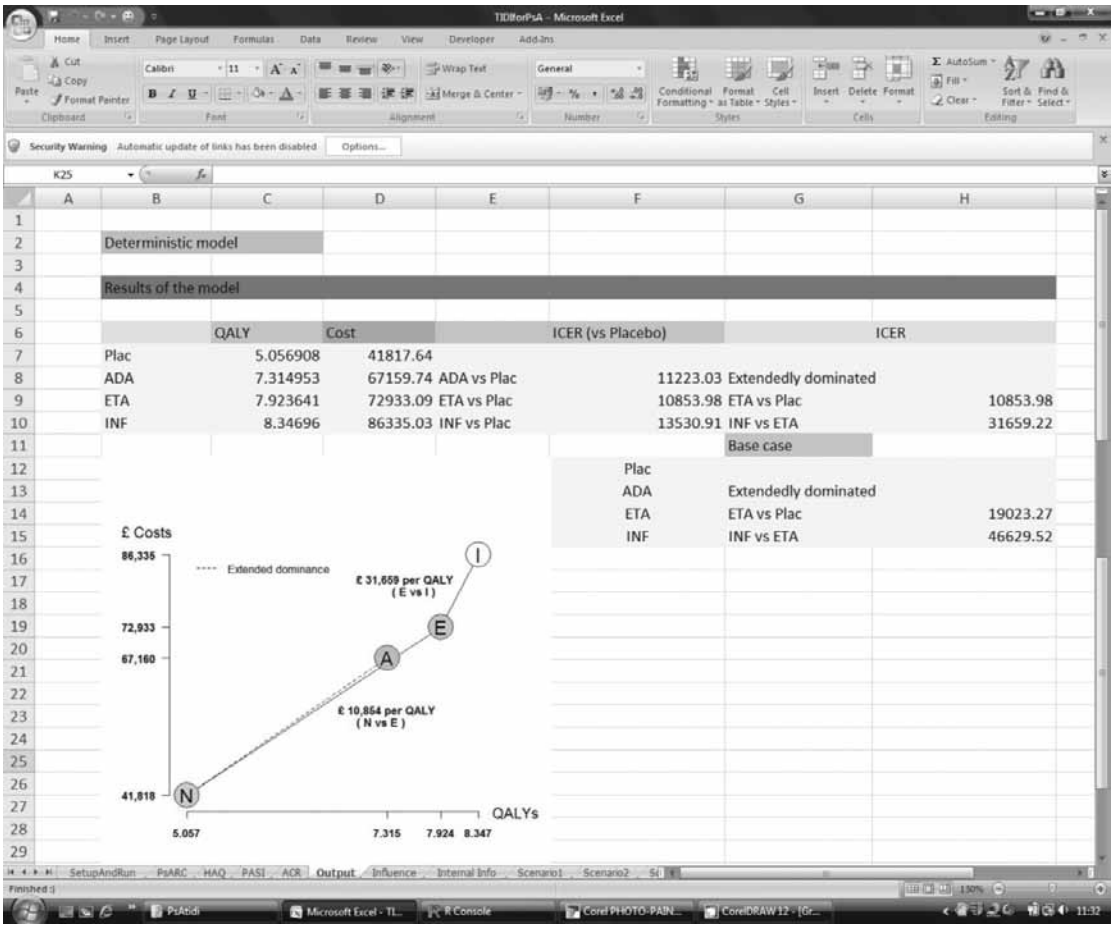

FIGURE 14 Results of the decision model in the 'Output' spreadsheet (results correspond to scenario 2).

can then be uploaded into the front spreadsheet containing the model parameters and the model can be rerun with the amended effectiveness estimates. This sensitivity analysis can be vital in situations when some of the available studies are, for example, of questionable quality or do not represent the considered population of patients.

An example of the PsARC meta-analysis is shown in *Figure 15*. This example shows how this tool can be used to carry out a sensitivity analysis adjusting for relevance. Here to demonstrate this, the Genovese *et al.*[83] study has been removed. By pressing the button 'Run' the user reruns the meta-analysis and new estimates are presented in tables below the 'Run' button, as well as in the forest plots. Now the estimates for Genovese *et al.* study have been greyed out as the study no longer contributes to the meta-analysis and the pooled result has now changed which is plotted alongside with the greyed out original pooled result of the meta-analysis (that includes all the available studies) for comparison. The first two forest plots show ORs of comparisons of each anti-TNF with placebo, and pooled probability of response in the placebo group. The resulting probability of response in treatment groups is showed in the final forest plot providing estimates for the decision model.

Apart from the option of uploading the new estimates to the decision model, the interface provides the pooled common effect estimates, which can also be uploaded and used to inform the decision model. Here the common effect was precalculated (using all six studies available) and saved on the spreadsheet holding the data. In the future applications this can be extended by

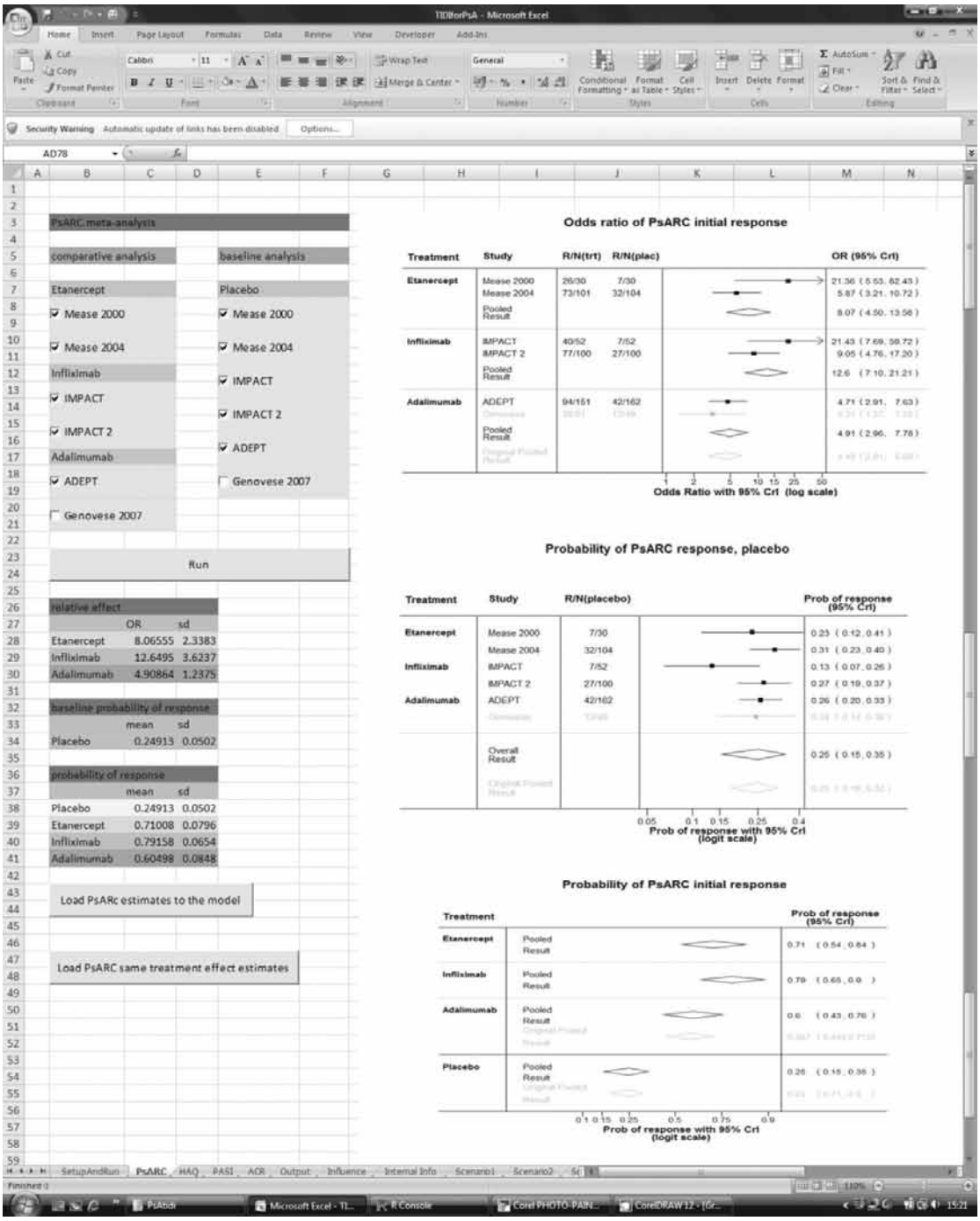

FIGURE 15 Interactive meta-analysis.

adding an interactive option allowing for the common treatment to be calculated in real time for chosen subsets of studies.

Influence analysis: tornado plots

Health economic models, such as the York model described in this report, are informed by a large number of parameters related to cost and effectiveness of treatments. It is infeasible to carry

out the sensitivity analysis that explores all possible scenarios, considering different values of all parameters. Influence analysis can help to identify those parameters that have highest impact on the cost-effectiveness estimates, such as ICERs or incremental net benefit. The influence analysis presented here was carried out by means of tornado plots. Each parameter of the decision model has a defined range of plausible values. This range can be simply a 95% CI if we know the SE of the parameter. The minimum and the maximum value of each parameter were used in the model one at a time, leaving the remaining parameters set to the same values as in the base-case scenario. This gives the ICERs corresponding to the minimum and maximum values of each parameter, and if those ICERs are far apart for a given parameter, it suggests that a change in this parameter will have an impact on the final result of the decision model.

Figure 16 shows the 'Influence' spreadsheet containing values and ranges of all the model parameters. Clicking on the 'Tornado Plot' button shows a user form that allows the choice of a tornado plot from six pair-wise comparisons of ICERs and additional differences in ICERs that can help in understanding the influence of all the parameters better. *Figure 17* shows an example of the tornado plot for ICERs of adalimumab compared with Infliximab. Ranges of ICERs for each parameter are sorted and plotted from the widest on top to the narrowest on the bottom (only the top 34 have been plotted for clarity) forming the tornado plot. The parameters most influential for this ICER are the cost of infliximab in period 2, the amount by which the patients progress in terms of HAQ while on treatment, and cost of adalimumab in period 3.

This analysis is limited because of more than two treatments being compared and in such cases tornado plots cannot provide definitive answers. Further development of adequate methodology is required to face these limitations. However, even these limited tools can shed some light on what is important in the decision model.

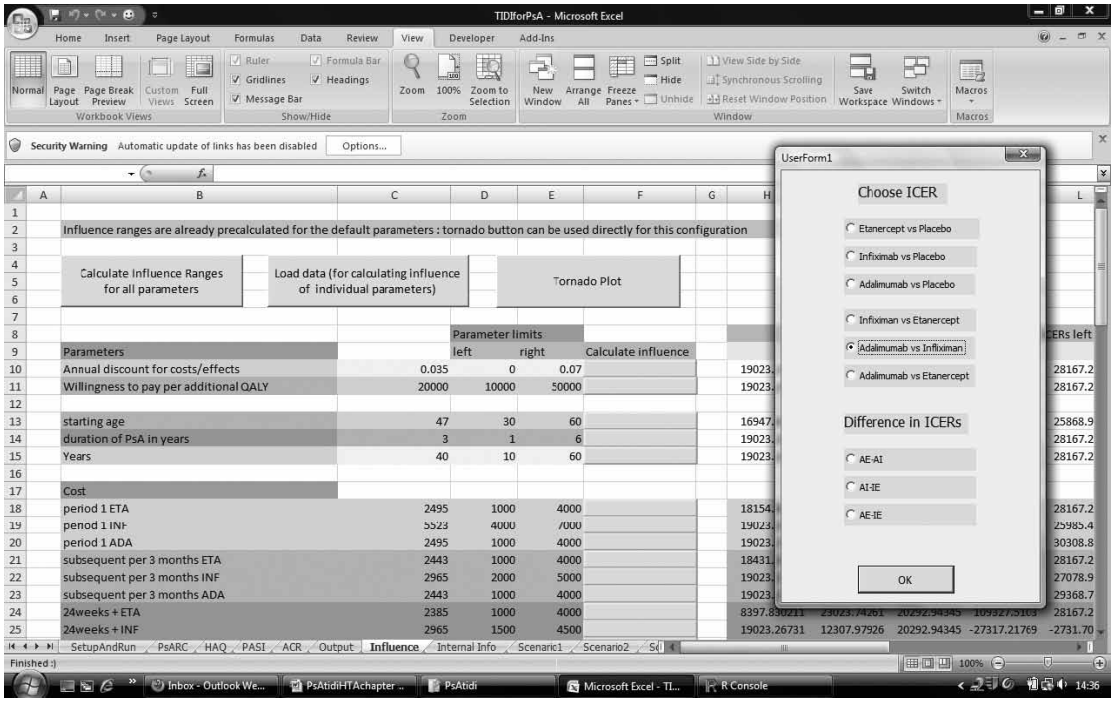

FIGURE 16 Influence analysis spreadsheet.

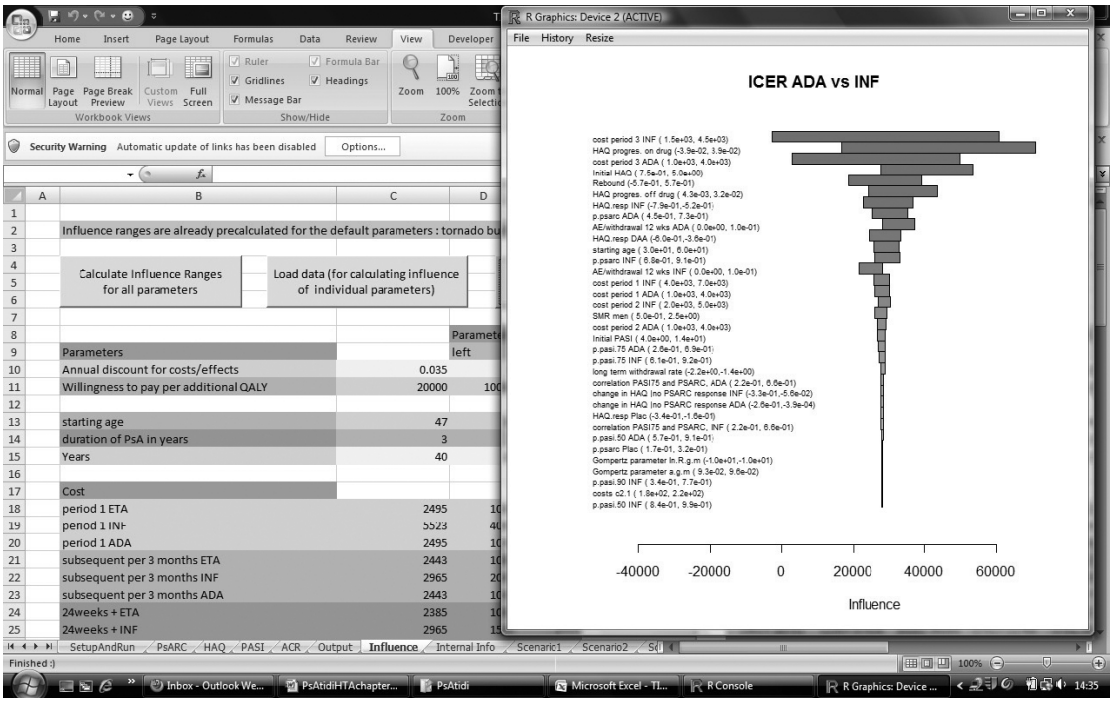

FIGURE 17 Influence analysis: tornado plot.

Summary and discussion

The TIDI has been created as a concept aiming to help the NICE decision process to be more transparent and efficient. It provides a tool to critique and explore further the decision models by a wider community of decision makers, not only those familiar with specialised software such as R and WINBUGS. It allows the user to have an in-depth access to, and control over, all model parameters and assumptions, and, at the same time, uses flexible, clear and hence transparent model components developed in R and WINBUGS. By making it possible to run models in real time, it makes the decision process to be more efficient. Being able to rerun a model under new scenarios in real time not only allows sensitivity analysis that potentially can change the final decision, but also can simply provide reassurance that, for example uncertainty of a parameter does not have much effect on the cost-effectiveness estimates. Any required additional model scenarios can be considered during the committee meetings without the need for the committee to delay a decision and having to reconvene. This interface, developed for the model presented in this HTA report, was used by NICE in the committee meeting to support their decision process.

The TIDI, as with every new concept, has some limitations and could be developed further. One of the disadvantages for this appraisal was that it was not possible to use it to run the full stochastic model in real time because it takes too long a time to run. However, it was possible to use deterministic model as an approximation. If any NICE committee decision was going to be influenced by the results of this simplified model, the decision could be later confirmed by the full stochastic analysis. Further work can be carried out to optimise complex models, such as the York model used here, so that it is possible to run them in real time during the committee meetings. Further considerations should also aim to develop tools equivalent to the tornado plots that will allow quantifying the influence of parameters on the model estimates that are based on comparisons of more than two strategies.

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