Etanercept, Infliximab and Adalimumab for the Treatment of Psoriatic Arthritis: a Systematic Review and Economic Evaluation

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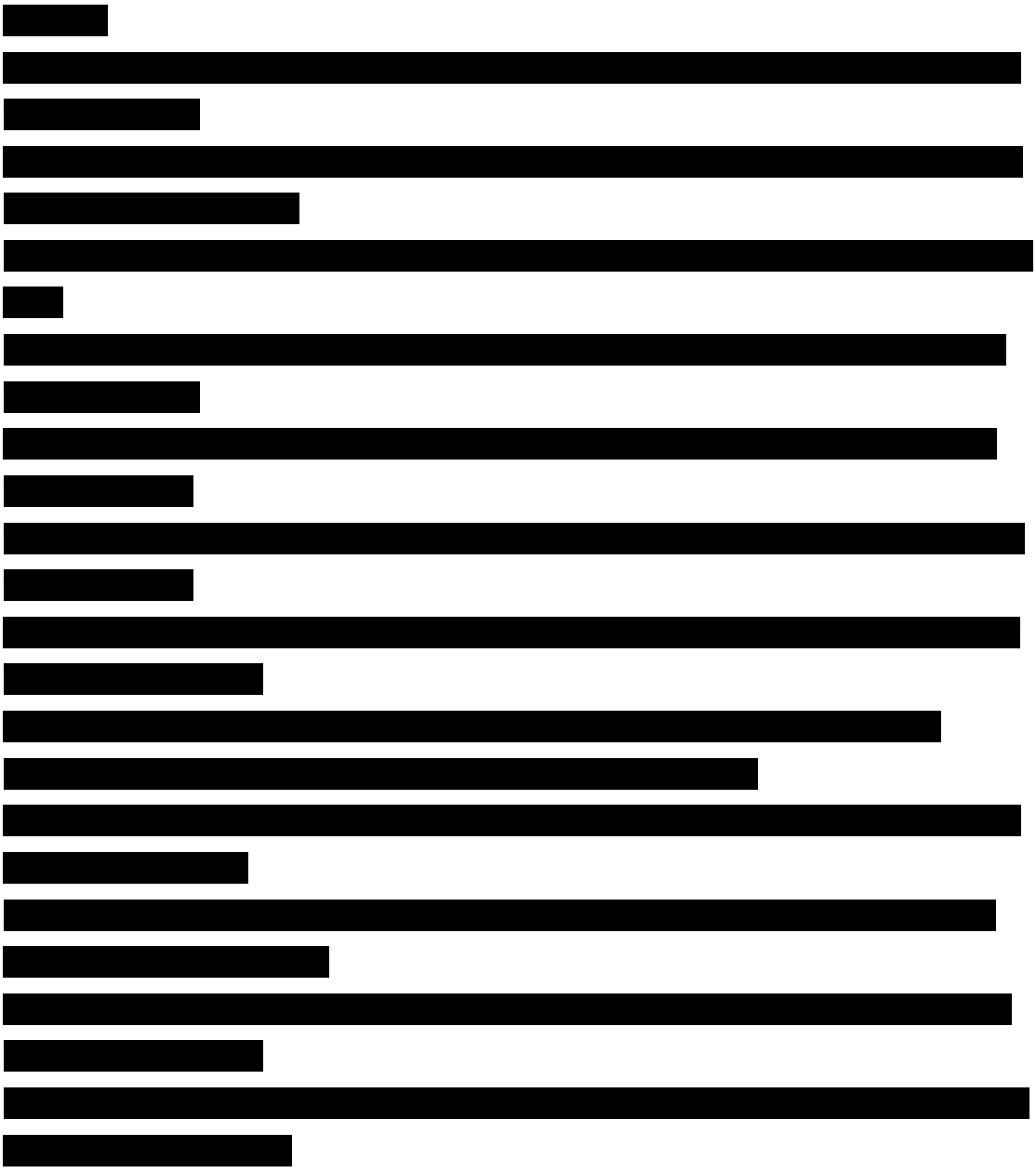

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Definition of Terms

Acitretin

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

American College of Rheumatology 20% improvement criteria (ACR 20)

ACR 20 is a response measure which requires a 20% reduction in the tender joint count, a 20% reduction in the swollen joint count, and a 20% reduction in at least 3 of 5 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 which requires a 50% reduction in the tender joint count, a 50% reduction in the swollen joint count, and a 50% reduction in at least 3 of 5 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 which requires a 70% reduction in the tender joint count, a 70% reduction in the swollen joint count, and a 70% reduction in at least 3 of 5 additional measures including patient and physician global assessment, pain, disability and an acute-phase reactant.

Adverse effect

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

Ankylosing spondylitis

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

Arthritis

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

Articular

Of or relating to the joints.

Autoimmune disease

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

Biologic therapies (biological)

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

Confidence interval (CI)

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

Corticosteroid

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

Cost-benefit analysis

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

Cost-effectiveness analysis

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

Cost-utility analysis

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

Credible Interval

In Bayesian statistics, a credible interval is a posterior probability interval estimation which 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.

Crohn's disease

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

C-reactive protein (CRP)

Concentrations of this protein in the blood can be measured as a test of inflammation or disease activity, for example in rheumatoid arthritis.

Ciclosporin

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

Disease-modifying anti-rheumatic 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 sulphasalazine, methotrexate and ciclosporin, as well as azathioprine, cyclophosphamide, antimalarials, penicillamine and gold. The newer agent leflunomide may be included as a DMARD. The biologics such as etanercept and infliximab are not generally referred to as DMARDS.

Effect size

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

Emollient

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

Erythrocyte sedimentation rate (ESR)

One of the tests designed to measure the degree of inflammation.

Fixed effect model

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

Health Assessment Questionnaire (HAQ)

HAQ is a validated, self-administered questionnaire which measures two dimensions of health status including physical disability and pain. The physical disability comprises eight subscales: dressing, grooming, arising, hygiene, reach, eating, walking, 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

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

Methotrexate

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

Mixed treatment comparison

Mixed treatment comparison is a form of meta-analysis used to strengthen inference concerning the relative efficacy of two treatments. It uses data based on direct comparisons (A 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 that recognizes only one antigen.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Consists 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.

PASI score

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

Placebo

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

Plaque psoriasis

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

Psoriatic Arthritis Response Criteria (PsARC)

PsARC is a composite response measure which incorporates patient global self-assessment, physician global assessment, tender and swollen joint scores.

Psoriasis

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

Psoriatic arthritis

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

Quality Adjusted Life Year (QALY)

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

Quality of Life

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

Random effects model

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

Randomised controlled trial (RCT) (Synonym: randomised clinical trial)

An experiment in which investigators randomly allocate eligible people into intervention groups to receive or not to receive one or more interventions that are being compared.

Relative Risk (RR) (synonym: risk ratio)

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

Remission

A lessening or abatement of the symptoms of a disease.

Rheumatoid arthritis

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

Sensitivity analysis

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

Statistical significance

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

Squamous cell carcinoma

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

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

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

Weighted mean difference (in meta-analysis)

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

List of abbreviations

ACR	American College of Rheumatology response criteria
ADEPT	Adalimumab Effectiveness in Psoriatic Arthritis Trial
ANA	Antinuclear Antibodies
BAD	British Association of Dermatologists
BNF	British National Formulary
BSA	Body surface area
BSR	British Society of Rheumatologists
BSRBR	British Society of Rheumatologists Biologics Register
CEAC	Cost effectiveness acceptability curve
CI	Confidence interval
CSA	Ciclosporin
DMARD	Disease modifying anti-rheumatic drug
dsDNA	Double stranded DNA
EULAR	European League Against Rheumatism
EQ-5D	EuroQol-5D
ESR	Erythrocyte sedimentation rate
FBC	Full blood count
FCE	Finished consultant episodes
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
GP	General Practitioner
HAQ	Health Assessment Questionnaire
HES	Hospital episode statistics
HODaR	Health Outcomes Data Repository
HRGs	Healthcare resource groups
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio (e.g. incremental cost per QALY gained)
IMPACT	Infliximab Multinational Psoriatic Arthritis Controlled Trial
INB	Incremental net benefit
i.m.	Intramuscular
IP	Inflammatory polyarthritis
i.v.	Intravenous
LFT	Liver function test
MIMS	Online and print prescribing database for health professionals
MTC	Mixed treatment comparison
MTX	Methotrexate
NH	Natural History

NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NOAR	Norfolk Arthritis Register
OLS	Ordinary Least Squares
OMERACT	Outcome Measures in Rheumatoid Arthritis (Rheumatology) Clinical trials
PASI	Psoriasis Area and Severity Index
PhGA	Physician Global assessment
PRESTA	Psoriasis Randomized Etanercept STudy in Subjects with Psoriatic Arthritis
PsA	Psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
PtGA	Patient global assessment
QALYs	Quality adjusted life years
QoL	Quality of life
RA	Rheumatoid Arthritis
RF	Rheumatoid factor
RR	Relative risk
SJS	Swollen joint score
SSZ	Sulphsalazine
STA	Single Technology Appraisal
MTA	Multiple Technology Appraisal
TB	Tuberculosis infection
THIN	The Health Improvement Network
TJS	Tender joint score
TSS	Total Sharp Score
UVB	Ultraviolet light, type B
U&E	Urea and electrolytes
VAS	Visual analogue scale
WMD	Weighted mean difference

2 Executive summary

2.1 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 and psychosocial disability. Due to the lack of a precise definition and diagnostic marker for PsA, it is difficult to gauge its exact prevalence. The United Kingdom (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 which target pathologic T cell 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 anti-rheumatoid drugs (DMARDs) has been inadequate.

2.2 Objectives

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).

2.3 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 ten electronic databases (including MEDLINE, EMBASE and 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 (PsARC, ACR 20), skin lesion response (PASI) and functional status (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 employed for adverse event data. Published cost-effectiveness studies and the economic analyses submitted to 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.

2.4 Results

Efficacy

Six RCTs were identified for the evaluation of clinical efficacy (43 publications). The six RCTs were comprised of 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 PsA patients 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 (RR 2.60, 95% CI: 1.96, 3.45), infliximab (RR 3.44, 95% CI: 2.53, 4.69), and adalimumab (RR 2.24, 95% CI: 1.74, 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 only observed 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, though 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 (-0.6275 for infliximab and -0.6235 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), and only those for infliximab achieved statistical significance.

Short-term radiographic measures indicate that these agents can slow disease progression in the short term (<24 weeks). The available follow-up data, though 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% to 13.2%, infliximab 0.8% to 13.8% and adalimumab 0.4% to 5.1%. The rates of malignancy were: etanercept 1% to 5.7 %, infliximab 0.16% to 5.1% and adalimumab 0.1% to 1.1%. The rates of activation of TB for the treatment were: etanercept 0% to 1.4%, infliximab 0.06% to 4.6% and adalimumab 0% to 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 the 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 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 concluded that the most cost-effective strategy depended on patient weight. Wyeth [redacted]

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 £16,000 per QALY, and the ICER of infliximab versus etanercept is about £54,000 per QALY. Adalimumab is extendedly dominated. The probability that etanercept is cost-effective is 0.524 at a threshold of £20,000 per QALY and 0.56 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, the ICER of adalimumab versus palliative care is about £15,000 per QALY, the ICER of etanercept versus adalimumab is about £16,000 per QALY and the ICER for infliximab versus etanercept is about £36,000 per

QALY. If the cost-effectiveness threshold were £20,000 per QALY etanercept has the greatest probability (0.432) of being cost-effective. Etanercept also has the highest probability of being cost-effectieeffective at a threshold of £30,000 per QALY (0.41). The probability that infliximab is cost-effective is 0.212 at a threshold of £30,000 per QALY.

For patients with PsA with negligible skin involvement, the ICER of etanercept versus palliative care is about £17,000 per QALY, and the ICER of infliximab versus etanercept is about £76,000 per QALY. Adalimumab is extendedly dominated in this group.

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 less than £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 less than £20,000 per QALY and the ICER for infliximab is less than £30,000 per QALY. Infliximab has a greater probability of being cost-effective if the threshold is £30,000 per QALY.

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

2.5 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, though 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, though 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 if the threshold for cost-effectiveness were £20,000 or £30,000 per QALY. In a secondary analysis, etanercept appeared most likely to be cost-effective for patients with PsA and mild-to-moderate psoriasis who have failed adalimumab or infliximab as first-line therapy. For patients with PsA and mild-to-moderate psoriasis who have failed etanercept as first-line therapy, adalimumab seems most likely to be cost-effective at a threshold of £20,000 per QALY, though infliximab is most likely to be cost-effective if the threshold is £30,000 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 RA or other indications. The generalisability of these findings to PsA patients 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 of varying severity

2.6 Conclusions

Implication for service provision

- The limited data indicate that etanercept, infliximab or adalimumab are efficacious in the treatment of PsA compared with placebo, with beneficial effects on joint symptoms, functional status and skin. Short-term data demonstrate 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, mild-

to-moderate or moderate-to-severe psoriasis if the threshold for cost-effectiveness were £20,000 to £30,000 per QALY.

- 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, though 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), long-term HAQ progression whilst 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 BSR Biologics Register) 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' quality of life, 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.

3 Background

3.1 Description of health problem

Epidemiology

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 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 GP practices in the Norwich Health Authority with 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

PsA 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. 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 joint and nail lesions. All joints of a single digit are thus more likely to be affected in PsA, whilst in RA the same joints on both sides tend to be affected.[1] Dactylitis, spondylitis and sacroiliitis are common in PsA whilst 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 enthesal 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 PsA patients.[1] Most patients with PsA develop psoriasis first, whilst 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 circa 10 years after the first signs of psoriasis.[1] In addition, rheumatoid factor (RhF) (an antibody produced by plasma cells) may be detected in about 13% of patients with PsA, whilst it can be detected in more than 80% of patients with RA.[1]

PsA is a progressive disorder ranging from mild synovitis to severe progressive erosive arthropathy.[11, 13] Research has found that PsA patients 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 DMARD treatment, radiological joint damage has been shown in up to 47% of PsA patients at a median interval of 2 years.[14 15] Untreated PsA patients 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 <1 score;[16]. Of those who can sustain clinical remission, only a small fraction of patients can discontinue medication with no evidence of damage.[17] Research has reported that the frequency of remission was 17.6% of PsA patients and the average duration of remission was 2.6 years from data of 391 patients with peripheral arthritis.[17] Joint damage can occur early in the disease often prior to functional limitation.[9, 18] 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.[19, 20]

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.[21] Each actively inflamed joint in PsA is associated with a 4% risk of increased damage within six 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.[22] Other risk factors for a more progressive course of PsA also include the presence of elevated erythrocyte sedimentation rate (ESR) and female sex.[1, 23]

A classification scheme for PsA on the basis of joint manifestations describes five patterns of disease [9, 24]:

- 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.
- Arthritis mutilans: it is a severe presentation of the disease with osteolysis of the phalanges, metatarsals, and metacarpals.
- 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.
- Oligoarthritis: this is the most common condition of PsA, which is characterised by asymmetric involvement of a small number of joints (less than four). Arthritis in a single knee might be the first symptom of oligoarthritis.
- 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 life-long disorder and its impact on patients' functional status and quality of life fluctuates over time.[25] As it involves both skin and joints, PsA can result in significant impairment of quality of life and psychosocial disability[7, 10] compared with a healthy population. PsA patients score significantly worse in HRQoL assessment on physical mobility, pain, energy, sleep, social isolation, and emotional reaction.[26] A comparison of health-related quality of life (HRQoL) between PsA patients and RA patients found that both patient populations had lower physical health compared with healthy controls.[27] PsA patients 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 quality of life between RA and PsA patients; this study reported that despite greater peripheral joint damage in RA patients the function and quality of life scores were similar for both groups.[28] [29] 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, PsA patients may also suffer from other psychological consequences such as embarrassment, self-consciousness and even depression. Because of a significant reduction in a patient's health-related quality of life, ideally PsA should be diagnosed early and treated aggressively in order to minimise joint damage and skin diease.[18]

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.[25, 30, 31] 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 PsA patients is approximately three years.[32]

The economic costs of PsA have not been well quantified. In the United States (US), the mean annual direct cost per patient with PsA is estimated as $3,638 according to data from Medstat MarketScan in 1999-2000.[33] In Germany, the mean annual direct cost per patient with PsA is estimated as €3,162, with the mean indirect cost (time lost from work and normal activities) per patient of €11,075.[34] Studies of RA[35-37] and psoriasis [38] have shown that costs increase with the severity of both diseases, and productivity losses are significant, [39, 40] largely as a consequence of extensive work disability.[36] 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 healthcare costs represented about one-quarter of all costs and these were dominated by inpatient and community day care,[41] with DMARD drugs representing a minor proportion: 3-4% of total costs and 13-15% of direct costs.[42] Evidence from the US suggests that expenditure on biologics might represent 35% of direct cost,[43] but similar data are not yet available for the UK. Increasing expenditure on biologics might be at least partly offset by cost savings elsewhere,[44] though as yet the evidence for this is only suggestive.

3.1.1 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). 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'.[45] In recent years the compound response criterion, the 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, PsARC, was developed specifically for a trial in PsA and has been adopted by the BSA.[46]

ACR response criteria

The ACR response criteria were developed after the identification of a set of core disease activity measures. ACR 20 requires a 20% reduction in the tender joint count, a 20% reduction in the swollen joint count, and a 20% reduction in 3 of 5 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.[47, 48] It is unclear whether the ACR 20 has the same discriminatory validity in PsA.[49] 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 patients' 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 distal interphalangeal joints (DIP joints) are included.

PsARC

PsARC was developed for a trial of sulphasalazine in PsA,[50] and incorporates 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 developed for assessment of PsA, it does not incorporate an assessment of psoriasis. The Working Group producing the British Society of Rheumatologists (BSR) guidelines for the use of anti-TNF drugs in PsA[51] 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 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, which 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 MTP joints of the feet and IP joint of the first toe, has been used in the trials of etanercept and adalimumab.[52, 53] None of these methods that were developed for RA score additional radiographic changes specific to PsA. A new score has been tested by Wassenberg et al, [54] 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.

HAQ

The HAQ score is a well validated tool in the assessment of patients with RA.[49] It focuses on two dimensions of health status: physical disability (8 scales) and pain, generating a score of 0 (least disability) to 3 (most severe disability). A modification of the HAQ for spondylarthropaties (HAQ-S) and for psoriasis (HAQ-SK) have been developed but when tested against HAQ, their scores were almost identical[55] suggesting either can be used in PsA.[49] The HAQ is one component of the ACR 20 (50 or 70) response criteria.

HAQ has been tested in patients with PsA, showing a moderate to close correlation with disease activity as measured by the actively inflamed joint count and some measures of clinical function (including the ACR functional class).[56] 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.[57]

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 anti-TNF drugs and DMARDs in RA.[58-60]

PASI

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.[49] In clinical trials of patients with psoriasis, assessment of the response to treatment is usually based on the Psoriasis Area and Severity Index (PASI). PASI is also used in trials of PsA; 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 has to be affected by the skin disease in order for the PASI measure to be used.[49] 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 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 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 body surface area which 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 (above 36) are not common even in severe psoriasis. Furthermore, it fails to capture the disability which 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 body surface area.

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 quality of life. 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 RCTs.

3.2 Current service provision

The effective treatment for PsA needs to consider both skin and joint conditions, especially if both are affected significantly. In current services it is rheumatologists who manage the majority of PsA patients. Although dermatologists focus principally on the cutaneous expression of psoriasis they frequently use drugs such as methotrexate 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, 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, methotrexate and sulphasalazine are considered the DMARDs of choice, despite the largely empirical evidence for methotrexate and the modest effects of sulphasalazine.[13] A review of the experience of 100 PsA patients treated with DMARDs [61] reported that of those treated with sulphasalazine,

gold, methotrexate or hydroxychloroqine, over 70% of patients had discontinued due to a lack of efficacy or adverse events (range 35% with methotrexate to 94% with hydroxychloroqine).

Another DMARD (leflunomide) has, in addition to being licenced 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[62] and PsA.[63] Evidence also suggests that clinical responses in RA patients with leflunomide treatment are equivalent to those with methotrexate treatment. [64] Unlike methotrexate, 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.[55] Ciclosporin and penicillamine are also sometimes used in clinical practice[65].

Costs of current service

Based on prices from the BNF[66] weekly treatment costs with the most commonly used DMARDs in PsA, sulphasalazine and methotrexate are approximately £2 and less than 50p respectively. The cost of ciclosporin is approximately £40 to £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 £2 million per quarter year to nearly £4.5million during this period. In addition to the cost of DMARDs the cost of NSAIDs was almost £4 million per quarter year in December 2008, though the number of prescriptions and expenditure on NSAIDS has fallen sharply in recent years.[67]

Expenditure on biologic therapies in England is now considerable. For all indications, the cost of prescribing in 2008 was £152.2 million for etanercept, £102.7 million for adalimumab and £77.1 million for infliximab, with over 95% of these prescriptions dispensed by hospitals.[68] Expenditure for biologic drugs increased during 2008 by 15% for etanercept, 55% for adalimumab and 25% for infliximab. Among the drugs appraised by NICE, etanercept and adalimumab are now ranked in the top five by estimated cost of prescribing in England.

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 in the delivery of care amongst rheumatologists, 29% of whom failed to diagnose PsA, mainly due to their failure to enquire about skin lesions.[69] Of those who did correctly diagnose PsA only 43% referred patients to a dermatologist and 66% ordered laboratory tests. The median costs for imaging and laboratory investigations were higher in those patients correctly diagnosed with PsA compared with the remaining patients who were incorrectly diagnosed.

3.3 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 that result in the migration and activation of T cells which then release tumour necrosis factorα (TNFα). TNFα is one of several pro-inflammatory cytokines that have been implicated in the pathogenesis of both psoriasis and PsA.[70, 71] 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.[72] 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 antiTNF monoclonal gamma immunoglobulin that inhibits the binding of TNF to its receptor.[10] Adalimumab is a fully humanised monoclonal IgG1 antibody and TNF antagonist.[73] 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 £2145.12, and the annual cost thereafter is £8580.48. The recommended dose for infliximab is 5 mg/kg is given as an intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter, each dose corresponding to 3 or 4 vials of infliximab depending upon the patient's body weight. The initial 3-month acquisition cost of infliximab is estimated to be £5035.44 assuming 4 vials, and the annual cost thereafter is £11539.55. In addition, based on the recommended dose

regimen (40 mg subcutaneous injections administered every other week), the estimated initial 3-month acquisition cost of adalimumab is £2145, with an average annual drug cost of £8580.

4 Definition of decision problem

4.1 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,[74] and adalimumab was separately evaluated more recently.[75] There is a need for an up-to-date evaluation of all three biological agents licensed for use in PsA.

It is important to establish how well these three licenced 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 effectiveness and cost-effectiveness.

4.2 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).

5 Assessment of Clinical Effectiveness

5.1 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 CRD's guidance [76] and the QUOROM statement.[77]

5.1.1 Search strategy

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

- MEDLINE
- EMBASE
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Science Citation Index
- Conference Proceedings Citation Index - Science (CPCI-S)
- ClinicalTrials.gov
- metaRegister of Controlled Trials (mRCT)
- 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 (01 April 2004 to date) updating the searches undertaken for the 2006 HTA report.[74] 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 the review remained up-to-date and covers 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.

5.1.2 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 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 (RCTs) (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 (FDA, 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 has responded inadequately to previous DMARD therapy excluding TNF-α 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, quality of life assessments (e.g. 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 section) 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 IV antibiotic therapy and/or hospitalisation or cause death) and reactivation of latent tuberculosis. 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 is clinically appropriate to do so.

5.1.3 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 9.2 and 9.3 of data extraction). 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.

5.1.4 Quality assessment strategy

The quality of RCTs and other study designs were assessed using standard checklists.[76] 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 less than 500 patients receiving biologics were excluded from the review. The assessment was performed by one reviewer, and independently checked by a second. Disagreements were resolved through consensus, or by consulting a third reviewer if necessary.

5.1.5 Data analysis

Where sufficient clinically and statistically homogenous 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-effect 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.[78] 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, 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 and 70 responses and PASI 50, 75 and 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 10.5

5.2 Results of Review of Clinical Effectiveness

5.2.1 Quantity and quality of research available

A total of 1320 records were identified from both the clinical effectiveness and adverse event searches (see Figure 5.1). Details of studies excluded at the full publication stage are provided in Appendix 10.4

5.2.1.1 RCTs and extensions in PsA

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.[52, 53, 79-119] Two placebo-controlled RCTs in patients with PsA were found for each of the three agents: etanercept,[53, 79, 98, 100, 106, 108, 111] infliximab[80-83, 90-92, 96, 97, 99, 107, 110, 112-119] and adalimumab.[52, 84, 89, 93, 94, 101-105] Baseline characteristics from all six RCTs are presented in Table 5.1

5.2.1.2 Additional adverse event studies

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 5.1).[90, 98, 100, 120-149]

Figure 5.1: Flow chart showing number of studies identified and included

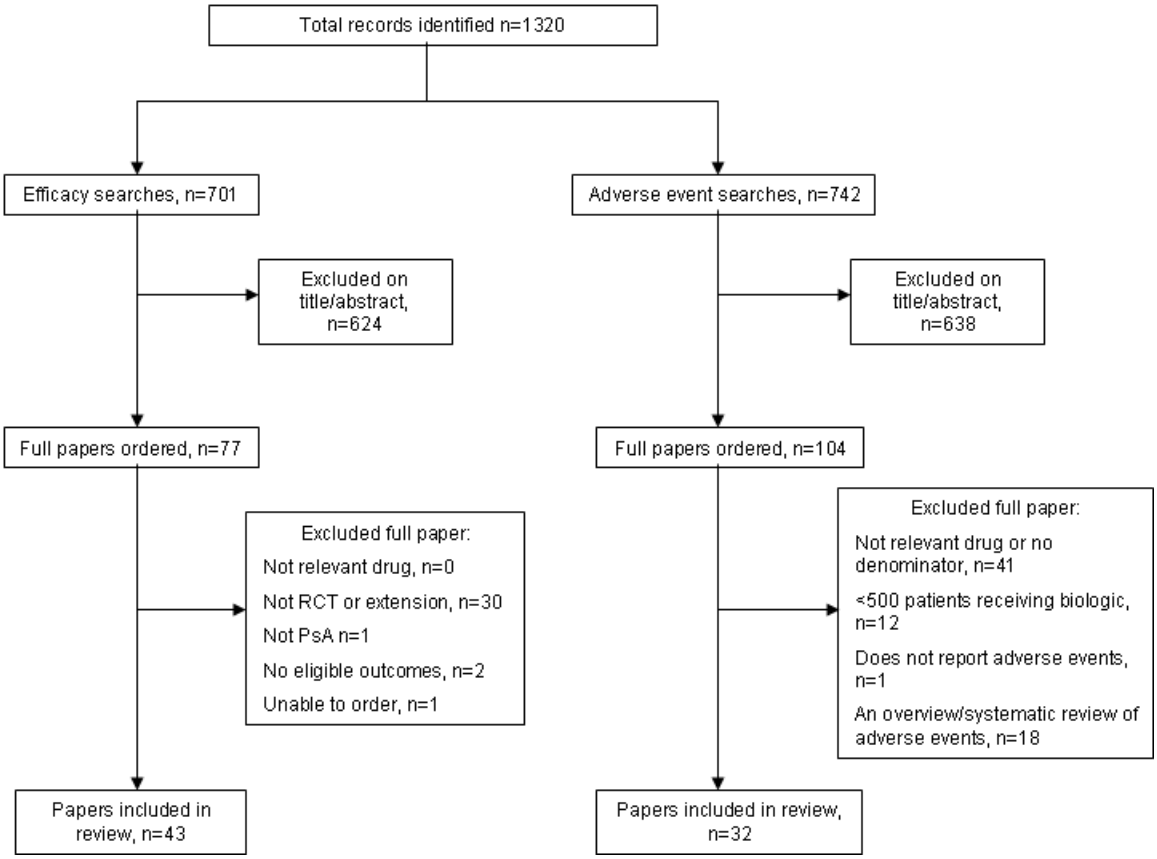


Table 5.1 Summary of trial population characteristics

	Etancercept				Infliximab				Adalimumab			
	Mease 2000[79]		Mease 2004[53, 98, 100, 106, 108, 111]		IMPACT[80-82, 90, 97, 110, 112, 114-116, 118, 119]		IMPACT 2[83, 91, 92, 96, 99, 107, 113, 117]		ADEPT[52, 89, 93, 94, 101-105]		Genovese 2007[84]	
	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 in years Mean (SD)	46.0 (30.0-70.0)†	43.5 (24.0-63.0)†	47.6 (18-76)†	47.3 (21-73)†	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)†	9.5 (1-30)†	9.0 (-)†	9.2 (-)†	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)†	17.5 (2-43)†	18.3 (-)†	19.7 (-)†	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*	-	-	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
Methotrexate	47	47	45	49	46	65	47	45	51	50	47	47
Hydroxycloroquine	-	-	-	-	-	-	-	-	-	-	16	16
Sulfasalazine	-	-	-	-	-	-	-	-	-	-	8	14
Leflunomide	-	-	-	-	-	-	-	-	-	-	6	4
Other DMARD	-	-	-	-	-	-	-	-	-	-	2	6
Type of PsA (%)												
DIP joints in hand and feet	-	-	51	50	-	-	-	-	-	-	-	-
Arthritis mutilans	-	-	1	2	-	-	-	-	1	0	0	0
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
Tender Joint Count	22.5 (11,	19.0 (10,	20.4 (-)*	22.1 (-)*	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)

Mean (SD)	32)*	39)*										
Swollen Joint Count Mean (SD)	14.0 (8, 23)*	14.7 (7, 24)*	15.9 (-)*	15.3 (-)*	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)*	1.2 (0.8, 1.6)*	1.1 (-)*	1.1 (-)*	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)
Number (%) of patients evaluable for PASI at baseline	19 (63%)♦	19 (63%)♦	[redacted]	[redacted]	22 (42%)‡	17 (33%)‡	83 (83%)♦	87 (87%)♦	70 (46%)♦	70 (43%)♦	-	-
PASI (0-72) at baseline among patients evaluable for PASI Mean (SD)	10.1 (2.3-30.0) †	6.0 (1.5-17.7) †	[redacted]	[redacted]	8.6 (6.6)	8.1 (6.6)	11.4 (12.7)	10.2 (9.0)	7.4 (6.0)	8.3 (7.2)	-	-

†median (range)
* median (25th, 75th percentile)
♦ Patients with ≥3% BSA psoriasis at baseline
‡Patients with a baseline PASI score ≥2.5

5.2.2 Assessment of effectiveness

5.2.2.1 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 (see Table 5.2).[53, 79, 98, 100, 106, 108, 111] Both trials were available as industry trial reports and journal publications.

Table 5.2: Results of quality assessment for trials of etanercept

Quality assessment criteria	Study	
	Mease 2000[79]	**Mease 2004[53, 98, 100, 106, 108, 111]**
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 co-interventions?	Y	Y
Compliance with treatment adequate?	Y	Y
All randomised patients accounted for?	Y	Y
Valid ITT analysis?	Y	Y
$\geq$ 80% patients in follow-up assessment?	Y	Y
Quality rating	Good	Good

Y=yes; N=no; NR=not reported

The baseline characteristics of the trial population are summarised in Table 5.1. Both trials were of adults (aged 18 to 70 years), with active PsA (defined in both trials as $\geq$3 swollen joints and $\geq$3 tender or painful joints although only the more recent trial[53, 98, 100, 106, 108, 111] specified stable plaque psoriasis). Patients in both trials had demonstrated an inadequate response to NSAIDs. Over 70% of the patients in the larger trial (Mease 2004)[53, 98, 100, 106, 108, 111] had previously used at least one DMARD. Over 80% of patients in the Mease 2004[53, 98, 100, 106, 108, 111] 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 (tender joint count, swollen joint count, HAQ at baseline and baseline and previous medication) significant differences

between the populations in terms of overall disease severity are unlikely. Patients taking stable doses of methotrexate or corticosteroids were permitted to continue with that dose and randomisation was stratified for methotrexate 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 patients for whom etanercept is licenced for use: these patients would, according to the British Society of Rheumatology have demonstrated a lack of response to at least two DMARDS.[150]

In both trials etanercept was administered by subcutaneous (SC) injection twice weekly at a dose of 25 mg. Treatment with active drug or placebo was administered for 12 weeks in the smaller trial (Mease 2000)[79] and for 24 weeks in the larger trial (Mease 2004).[53, 98, 100, 106, 108, 111] 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, ACR 50 and ACR 70 and HAQ at week 12. The primary outcome variable in the Mease 2000 trial[79] was PsARC whilst in Mease 2004[53, 98, 100, 106, 108, 111] it was ACR 20. Data on PASI at week 12 are available from the small (Mease 2000)[79] trial only. RCT outcome data for PsARC, ACR 20, ACR 50 and ACR 70, HAQ, PASI and radiographic assessment of progression at week 24 are available from the larger (Mease 2004) trial[53, 98, 100, 106, 108, 111] (n=205). In addition, a sub-group analyses by concomitant methotrexate use provided additional PsARC, ACR 20, 50 and 70 data at weeks 12 and 24. As sub-group analyses in already fairly small trials the findings generated must be interpreted with some caution. They are however, useful to explore the influence concomitant methotrexate has on the main treatment effect. All outcome data are summarised in Table 5.3, with pooled 12 week data in table 5.4.

Uncontrolled data on all outcomes are also available at 36 weeks or 12 months (uncontrolled follow-up data). These data are summarised in Table 5.4.

Table 5.3: Etanercept efficacy outcomes – RCT data

Trial	Duration	Outcomes	Etanercept	Placebo	RR or mean difference (95% CI)
Mease 2000[79]	12 weeks	PsARC*	26/30 (87%)	7/30 (23%)	3.71 (1.91, 7.21)
		ACR 20	22/30 (73.0%)	4/30 (13%)	5.50 (2.15, 14.04)
		ACR 50	15/30 (50.0%)	1/30 (3%)	15.00 (2.11, 106.49)
		ACR 70	4/30 (13%)	0/30 (0%)	9.00 (0.51, 160.17)
		HAQ % change from baseline (mean (SD))	(n=29) 64.2 (38.7)	(n=30) 9.9 (42.9);	[redacted]
		PASI 50	8/19 (42%)	4/19 (21%)	2.00 (0.72, 5.53) p=0.295
		PASI 75	5/19 (26%)	0/19 (0%)	11.00 (0.65, 186.02) p=0.0154
Mease 2004[53, 98, 100, 106, 108, 111] 12 weeks		PsARC			
		All pts	73/101 (72%)	32/104 (31%)	2.35 (1.72, 3.21) p<0.001
		+*MTX*	32/42 (76%)	14/43 (33%)	2.34 (1.47, 3.72)
		-*MTX*	41/59 (69%)	18/61 (30%)	2.35 (1.54, 3.60)
		ACR 20*			
		All pts	60/101 (59%)	16/104 (15%)	3.86 (2.39, 6.23) p<0.001
		+*MTX*	26/42 (62%)	8/43 (19%)	3.33 (1.70, 6.49)
		-*MTX*	34/59 (58%)	8/61 (13%)	4.39 (2.22, 8.7)
		ACR 50			
		All pts	38/101 (38%)	4/104 (4%)	9.78 (3.62, 26.41) p<0.001
		+*MTX*	17/42 (40%)	1/43 (2%)	17.40 (2.42, 124.99)
		-*MTX*	21/59 (36%)	3/61 (5%)	7.24 (2.28, 22.98)
		ACR 70			
		All pts	11/101 (11%)	0/104 (0%)	23.68 (1.41, 396,53) p<0.001
		+*MTX*	4/42 (10%)	0/43 (0%)	9.21 (0.51, 165.93)
		-*MTX*	7/59 (12%)	0/61 (0%)	15.5 (0.91, 265.46)
		HAQ % change from baseline (mean (SD))	(n=96) 53.5 (43.4)	(n=99) 6.3 (42.7)	[redacted]
24 weeks		PsARC			
		All pts	71/101 (70%)	24/104 (23%)	3.05 (2.10, 4.42) p<0.001
		+*MTX*	31/42 (74%)	11/43 (26%)	2.89 (1.68, 4.95)
		-*MTX*	40/59 (68%)	13/61 (21%)	3.18 (1.90, 5.32)
		ACR 20			
		All pts	50/101 (50%)	14/104 (13%)	3.68 (2.17, 6.22) p<0.001
		+*MTX*	23/42 (55%)	8/43 (19%)	2.94 (1.49, 5.83)
		-*MTX*	27/59 (46%)	6/61 (10%)	4.73 (2.10, 10.63)
		ACR 50			
		All pts	37/101 (37%)	4/104 (4%)	9.52 (3.52, 25.75) p<0.001
		+*MTX*	16/42 (38%)	3/43 (7%)	5.46 (1.72, 17.37)
		-*MTX*	21/59 (36%)	1/61 (2%)	21.71 (3.02, 156.30)
		ACR 70			
		All pts	9/101 (9%)	1/104 (1%)	9.27 (1.20, 71.83) p=0.009
		+*MTX*	2/42 (5%)	0/43 (0%)	5.12 (0.25, 103.50)
		-*MTX*	7/59 (12%)	0/61 (0%)	15.50 (0.91, 265.46)
		HAQ % change from baseline (mean (SD))	(n=96) 53.6 (55.1)	(n=99) 6.4 (49.6)	47.20 (32.47, 61.93) p<0.001
		PASI 50	31/66 (47%)	11/62 (18%);	2.65 (1.46, 4.80) p<0.001
		PASI 75	15/66 (23%)	2/62 (3%)	7.05 (1.68, 29.56) p=0.001
		PASI 90	4/66 (6%)	2/62 (3%)	1.88 (0.36, 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, -0.26) p=0.0006
		+*MTX*	(n=42) 0.06 (0.76)	(n=43) 0.48 (1.00)	-0.42 (-0.80, -0.04) p=0.12345
		-*MTX*	(n=59) -0.09 (0.71)	(n=61) 0.57 (1.62)	-0.66 (-1.11, -0.21) p=0.0014

Note* Primary outcome variable in the respective trials

Efficacy after 12 weeks treatment

The individual trial results (Table 5.3) and pooled estimates of effect (Table 5.4) 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 2004[53, 98, 100, 106, 108, 111] data revealed that the effect of etanercept was not dependent upon patients' concomitant use, or not, of methotrexate. The PASI results from Mease 2000[79] indicate some beneficial effect on psoriasis at 12 weeks, however the data are too sparse (38 patients in total) to establish statistical significance. The statistically significant reduction in HAQ score with etanercept compared to placebo indicates a beneficial effect of etanercept on functional status.

Table 5.4: Meta-analysis of etanercept efficacy data – outcomes at 12 weeks

Trial	Outcomes	Etanercept	Placebo	RR or mean difference (95% CI)
	PsARC			
Mease 2000		26/30 (87%)	7/30 (23%)	3.71 (1.91, 7.21)
Mease 2004		73/101 (72%)	32/104 (31%)	2.35 (1.72, 3.21) p<0.001
	Pooled RR (95% CI), p I^2			***2.60 (1.96, 3.45) p<0.00001 I^2=34%***
	ACR 20			
Mease 2000		22/30 (73.0%)	4/30 (13%)	5.50 (2.15, 14.04)
Mease 2004		60/101 (59%)	16/104 (15%)	3.86 (2.39, 6.23) p<0.001
	Pooled RR (95% CI), p I^2			***4.19 (2.74, 6.42) p<0.00001 I^2=0%***
	ACR 50			
Mease 2000		15/30 (50.0%)	1/30 (3%)	15.00 (2.11, 106.49)
Mease 2004		38/101 (38%)	4/104 (4%)	9.78 (3.62, 26.41) p<0.001
	Pooled RR (95% CI), p I^2			***10.84 (4.47, 26.28) p<0.00001 I^2=0%***
	ACR 70			
Mease 2000		4/30 (13%)	0/30 (0%)	9.00 (0.51, 160.17)
Mease 2004		11/101 (11%)	0/104 (0%)	23.68 (1.41, 396,53) p<0.001
	Pooled RR (95% CI), p I^2			***16.28 (2.20, 120.54) p=0.006) I^2=0%***
	HAQ% change from baseline (mean (SD))			
Mease 2000		(n=29) -64.2 [redacted]	(n=30) -9.9 [redacted]	-54.3 (33.47, 75.13)
Mease 2004		(n=96) -53.5 [redacted]	(n=99) -6.3 [redacted]	-47.20 (35.11, 59.29)
	Pooled WMD (95% CI), p I^2			***-48.99 (38.53, 59.44) p<0.00001 I^2=0%***

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, though this data was only available for one trial (see Table 5.3). As at 12 weeks the subgroup analyses conducted on the Mease 2004[53, 98, 100, 106, 108, 111] data revealed that the effect of etanercept was not dependent upon patients' concomitant use, or not, of methotrexate. The size of treatment effect did not appear greater at 24 weeks than at 12 weeks.

At 24 weeks TSS annualised rate of progression was statistically significantly lower in etanercept treated patients compared to placebo patients. This treatment difference did not

vary with or without concomitant methotrexate use. However, this duration of follow-up is to be considered short and barely adequate for this outcome.

At 24 weeks the treatment effect on psoriasis favoured etanercept with RRs for PASI 75 of 7.05 (95% CI: 1.68, 29.56), PASI 50 of 2.65 (95% CI: 1.46, 4.80) and PASI 90 of 1.88 (95% CI: 0.36, 9.90). The result for PASI 75 and PASI 50 was statistically significant despite there being only 66 patients on etanercept evaluable for psoriasis.[53, 98, 100, 106, 108, 111]

Longer-term follow-up

The results for long-term follow-up are summarised in Table 5.5. 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 one year the mean annualised rate of progression TSS for all patients was –0.03 (SD 0.87) indicating that on average no clinically significant progression of joint erosion had occurred. Limited two year data indicated little change in mean TSS, though data on patient numbers or variability were not reported.

Table 5.5 Etanercept efficacy outcomes – uncontrolled follow-up data

Trial	Type of data	Duration	Outcomes	Etanercept/placebo
Mease 2000[79]	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))	[redacted]
			PASI 75	7/19 (37%)
			PASI 50	11/19 (58%)
Mease 2004[53, 98, 100, 106, 108, 111]	Uncontrolled	12 months	ACR results etc only as brief text	Maintained as at 24 wks
			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

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 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 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 one year; however these data may not be reliable.

5.2.2.2 Efficacy of infliximab

The literature search identified two RCTs of infliximab for the treatment of PsA.[80-83, 90-92, 96, 97, 99, 107, 110, 112-119] Both were rated as Good by the quality assessment (Table 5.6). The trials were reported in published papers, abstracts and the industry trial report was made available.

Table 5.6: Results of quality assessment for trials of infliximab

Quality assessment criteria	**Study**	
	IMPACT[80-82, 90, 97, 110, 112, 114-116, 118, 119]	IMPACT 2[83, 91, 92, 96, 99, 107, 113, 117]
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 co-interventions?	Y	Y
Compliance with treatment adequate?	Y	Y
All randomised patients accounted for?	Y	Y
Valid ITT analysis?	Y	Y
$\geq$ 80% patients in follow-up assessment?	Y	Y
Quality rating	*Good*	*Good*

Y=yes; N=no; NR=not stated

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 rheumatoid factor and active disease including 5+ swollen/tender joints. All patients must have had an inadequate response to at least one DMARD.[80-83, 90-92, 96, 97, 99, 107, 110, 112-119] One trial required patients to have active plaque psoriasis with at least one

qualifying target lesion (≥2cm diameter).[83, 91, 92, 96, 99, 107, 113, 117] 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).[80-82, 90, 97, 110, 112, 114-116, 118, 119] 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 5.1. These demonstrate that the trial populations are 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 half in IMPACT and possibly even fewer in IMPACT 2 having failed to respond to two or more DMARDs (Failure to respond to DMARDs as defined by the BSR).[150]

In the RCT phase of the IMPACT trial infliximab (5 mg/kg) or placebo was infused at weeks 0, 2, 6 and 14 with follow-up at week 16. Further infusions of infliximab were administered to all patients in an open label fashion at eight-week intervals, with further follow-up at week 50. Patients in the IMPACT 2 trial were randomized 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 weeks 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 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 and IMPACT 2, respectively). All data are summarised in Table 5.7, with pooled data presented in Table 5.8.

Table 5.7: Infliximab efficacy outcomes – RCT data

Trial	Duration	Outcomes	Infliximab	Placebo	RR or mean difference (95% CI)
IMPACT (randomised period[80-82, 90, 97, 110, 112, 114-116, 118, 119]	14 weeks	PsARC	40/52 (76.9%)	7/52 (13.5%)	5.71 (2.82, 11.57)
		ACR 20			
		All pts	35/52 (67.3)	6/52 (11.5%)	5.83 (2.68, 12.68)
		+*MTX*	NR	NR	-
		-*MTX*	NR	NR	-
		ACR 50	19/52 (36.5%)	1/52 (1.9%)	19.00 (2.64, 136.76)
		ACR 70	11/52 (21.2%)	0/52 (0%)	23.00 (1.39, 380.39)
	16 weeks	PsARC	39/52 (75.0%)	11/52 (21.2%)	3.55 (2.05, 6.13) p<0.01.
		ACR 20			
		All pts	34/52 (65.4%)	5/52 (9.6%)	6.80 (2.89, 16.01) p<0.01.
		+*MTX*	15/24 (62.5%)	4/34 (11.8%)	5.31 (2.01, 14.03) p<0.01.
		-*MTX*	19/28 (67.9%)	1/18 (5.6%)	12.21 (1.79, 83.46) p<0.01
		ACR 50	24/52 (46.2%)	0/52 (0%)	49.00 (3.06, 785.06) (p<0.01
		ACR 70	15/52 (28.8%)	0/52 (0%)	31.00 (1.90, 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, -28.3); p<0.01.
		PASI 50*	22/22 (100%)	0/16 (0%)	33.26 (2.17, 510.71)
		PASI 75*	15/22 (68.2%)	0/16 (0%)	22.91 (1.47, 356.81)
		PASI 90*	8/22 (36.4%)	0/16 (0%)	12.57 (0.78, 203.03)
		PASI mean (SD) change from baseline**	(n=42) -4.1 (3.9)	(n= 38) 0.9 (3.7)	–5 (–6.8, -3.3); p<0.01
IMPACT 2(randomised)[83, 91, 92, 96, 99, 107, 113, 117]	14 weeks	PsARC	77/100 (77%)	27/100 (27%)	2.85 (2.03, 4.01)
		ACR 20			
		All pts	58/100 (58%)	11/100 (16%)	5.27 (2.95, 9.44)
		+*MTX*	NR	NR	-
		-*MTX*	NR	NR	-
		ACR 50	36/100 (36%)	3/100 (3%)	12.00 (3.82, 37.70)
		ACR 70	15/100 (15%)	1/100 (1%)	15.00 (2.02, 111.41)
		HAQ mean (SD) % change from baseline	(n=100) -48.6 (43.3)	(n=100) 18.4 (90.5)	-67.00 (-86.66, -47.33)
		[redacted]	[redacted]	[redacted]	[redacted]
		PASI mean (SD) % change from baseline	NR	NR	-
	24 weeks	PsARC	70/100 (70%)	32/100 (32%)	2.19 (1.60, 3.00)
		ACR 20			
		All pts	54/100 (54%)	16/100 (16%)	3.38 (2.08, 5.48)
		+*MTX*	NR	NR	-
		-*MTX*	NR	NR	-
		ACR 50	41/100 (41%)	4/100 (4%)	10.25 (3.81, 27.55)
		ACR 70	27/100 (27%)	2/100 (2%)	13.5 (3.30, 55.26)
		[redacted]	[redacted]	[redacted]	[redacted]
		HAQ mean (SD) % change from baseline	(n=100) -46.0 (42.5)	(n=100) 19.4 (102.8)	-65.40 (-87.20, -43.60)
		PASI mean (SD) % change from baseline	NR	NR	-

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

**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, 4.69; Table 5.8). There was some 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, 8.71), with an overall response of 61% in infliximab treated patients, demonstrating a clear degree of efficacy of infliximab in 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, though the limited number of observations mean that there is considerable uncertainty around these pooled estimates, as reflected by their confidence intervals (see Table 5.8). 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 indicated no significant difference in ACR 20 response at 16 weeks between patients with and without concomitant methotrexate, though 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, 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, though it should be noted that PASI outcomes were only recorded for those patients with a score of at least 2.5 at baseline. 42% of infliximab patients achieved the highest level of skin response (PASI 90), though again there is considerable uncertainty around the estimates (see Table 5.7).

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

Table 5.8: Meta-analysis of infliximab efficacy data - outcomes at 14 weeks

Trial	Outcomes	Infliximab	Placebo	RR or mean difference (95% CI)
	PsARC			
IMPACT		40/52 (76.9%)	7/52 (13.5%)	5.71 (2.82, 11.57)
IMPACT 2		77/100 (77%)	27/100 (27%)	2.85 (2.03, 4.01)
	Pooled RR (95% CI), p ***I^2***			*3.44 (2.53, 4.69), p<0.0001* ***I^2=68%***
	ACR 20			
IMPACT		35/52 (67.3%)	6/52 (11.5%)	5.83 (2.68, 12.68)
IMPACT 2		58/100 (58%)	11/100 (11%)	5.27 (2.95, 9.44)
	Pooled RR (95% CI), p ***I^2***			*5.47 (3.43, 8.71)* ***I^2=0%***
	ACR 50			
IMPACT		19/52 (36.5%)	1/52 (1.9%)	19.00 (2.64, 136.76)
IMPACT 2		36/100 (36%)	3/100 (3%)	12.00 (3.82, 37.70)
	Pooled RR (95% CI), p ***I^2***			*13.75 (5.11, 37.00), p<0.0001* ***I^2=0%***
	ACR 70			
IMPACT		11/52 (21.2%)	0/52 (0%)	23.00 (1.39, 380.39)
IMPACT 2		15/100 (15%)	1/100 (1%)	15.00 (2.02, 111.41)
	Pooled RR (95% CI), p ***I^2***			*17.67 (3.46, 90.14), p=0.001* ***I^2=0%***
	PASI 50			
IMPACT		22/22 (100%)	0/16 (0%)	33.26 (2.17, 510.71)
IMPACT 2		[redacted]	[redacted]	[redacted]
	Pooled RR (95% CI), p ***I^2***			*10.58 (5.47, 20.48) , p<0.0001** ***I^2=0%***
	PASI 75			
IMPACT		15/22 (68.2%)	0/16 (0%)	22.91 (1.47, 356.81)
IMPACT 2		[redacted]	[redacted]	[redacted]
	Pooled RR (95% CI), p ***I^2***			***26.68 (7.79, 91.44), p<0.0001**** ***I^2=0%***
	PASI 90			
IMPACT		8/22 (36.4%)	0/16 (0%)	12.57 (0.78, 203.03)
IMPACT 2		[redacted]	[redacted]	[redacted]
	Pooled RR (95% CI), p ***I^2***			*40.01 (5.93, 270.15), p<0.0001** ***I^2=0%***
	HAQ % change from baseline (mean (SD))			
IMPACT		(n=48) –49.8 (56.8)	(n=47) 1.6 (56.9)	-51.4 (-74.27, -28.54)
IMPACT 2		(n=100) -48.6 (43.3)	(n=100) 18.4 (90.5)	-67.00 (-86.66, -47.33)
	Pooled WMD (95% CI), p ***I^2***			***-60.37 (-75.28, -45.46)*** ***I^2=3%***

*combined 14 and 16 week data

Efficacy after 24 weeks

The IMPACT 2 trial 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 5.7).

Longer-term follow-up

The data for longer-term follow-up (50/54 weeks) from the two IMPACT trials are summarised in Table 5.9. 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 (vdH-S) 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.

Table 5.9: Infliximab efficacy outcomes – uncontrolled follow-up data

Trial	Duration	Outcomes	Infliximab/placebo
IMPACT[80-82, 90, 97, 110, 112, 114-116, 118, 119]	50 weeks	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*	19/22 (86.3%)
		PASI 75*	13/22 (59%)
		PASI 90*	9/22 (40.9%)
		PASI mean (SD) change from baseline*	(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[83, 91, 92, 96, 99, 107, 113, 117]	54 weeks	PsARC	67/90 (74.4%)
		PASI 50*	57/82 (69.5%)
		PASI 75*	40/82 (48.8%)
		PASI 90*	32/82 (39%)
		Total modified van der Heijde-Sharp score – mean (SD) change from baseline	Infliximab/inflimab -0.94 (3.4) Placebo/infliximab 0.53 (2.6)

* PASI 50/75/90 outcomes are for subgroup of patients with ≥3% BSA psoriasis

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

- 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, though these data are not of high quality.

5.2.2.3 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 (see Table 5.10).[52, 84, 89, 93, 94, 101-105]

Table 5.10: Results of quality assessment for trials of adalimumab

Quality assessment criteria	Study	
	ADEPT[52, 89, 93, 94, 101-105]	**Genovese 2007**[84]
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 co-interventions?	Y	Y
Compliance with treatment adequate?	Y	Y
All randomised patients accounted for?	Y	Y
Valid ITT analysis?	Y	Y
$\geq$ 80% patients in follow-up assessment?	Y	Y
Quality rating	Good	Good

Y=yes; N=no; NR=not reported

Both trials were of adults (aged 18 to 70 years), with active PsA (defined in both trials as $\geq$3 swollen joints and $\geq$3 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 methotrexate.[52, 89, 93, 94, 101-105] All patients in the smaller trial received concomitant DMARDs or had a history of DMARD therapy with inadequate response.[84]

The baseline characteristics of the trial populations are summarised in Table 5.1. In both trials, around half of the randomised patients received concomitant methotrexate. Other DMARDs and NSAIDs were used concomitantly by patients in the smaller trial[84] but not by those in the larger trial.[52, 89, 93, 94, 101-105] The mean number of prior DMARDs used was similar between the trials, though 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 among 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 (tender joint count, swollen joint count, and HAQ at baseline) suggests 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.

In both trials adalimumab was administered by SC 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)[84] and for 24 weeks in the larger trial (ADEPT).[52, 89, 93, 94, 101-105] 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 Total Sharp Score (TSS).[52, 89, 93, 94, 101-105] All randomised outcome data are summarised in Table 5.11, with pooled data presented in table 5.12.

ADEPT reported longer-term open-label follow-up of patients at 48, 104, and 144 weeks. These data are summarised in Table 5.13.

Table 5.11: Adalimumab efficacy outcomes – RCT data

Trial	Duration	Outcomes	Adalimumab	Placebo	RR or mean difference (95% CI)
ADEPT[52, 89, 93, 94, 101-105]	12 weeks	PsARC	94/151 (62%)	42/162 (26%)	2.40 (1.80, 3.20) p<0.05
		ACR 20			
		All pts	88/151 (58%)	23/162 (14%)	4.10 (2.75, 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, 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, 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, -0.19), p<0.001
		PASI 50*			
		All pts	50/69 (72%)	10/69 (14%)	5.00 (2.77, 9.03) p<0.05
		+*MTX*	17/29 (76%)		
		-*MTX*	28/40 (70%)		
		PASI 75*			
		All pts	34/69 (49%)	3/69 (4%)	11.33 (3.65, 35.17) p<0.05
		+*MTX*	17/29 (59%)		
		-*MTX*	17/40 (43%)		
		PASI 90*			
		All pts	21/69 (30%)	0/69 (0%)	43.00 (2.66, 696.04) p<0.05
		+*MTX*	11/29 (38%)		
		-*MTX*	10/40 (25%)		
	24 weeks	PsARC	91/151 (60%)	37/162 (23%)	2.64 (1.93, 3.60) p<0.05
		ACR 20			
		All pts	86/151 (57%)	24/162 (15%)	3.84 (2.59, 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, 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, 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, -0.20), p<0.001
		PASI 50*			
		All pts	52/69 (75%)	8/69 (12%)	6.50 (3.34, 12.64) p<0.05
		+*MTX*	25/29 (86%)		
		-*MTX*	27/40 (68%)		
		PASI 75*			
		All pts	41/69 (59%)	1/69 (1%)	41.00 (5.80, 289.75) p<0.05

		+MTX	21/29 (72%)		
		-MTX	20/40 (50%)		
		PASI 90*			
		All pts	29/69 (42%)	0/69 (0%)	59.00 (3.68, 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
Genovese 2007[84]	12 weeks	PsARC	26/51 (51%)	14/49 (24%)	1.78 (1.06, 3.00) p<0.05
		ACR 20	20/51 (39%)	8/49 (16%)	2.40 (1.17, 4.94) p<0.05
		ACR 50	13/51 (25%)	1/49 (2%)	12.49 (1.70, 91.90) p<0.05
		ACR 70	7/51 (14%)	0/49 (0%)	14.42 (0.85, 5.26) p=n.s
		HAQ change from baseline (mean (SD))	-0.3 (0.5)	-0.1 (0.3)	-0.2 (-0.36, -0.04), p=0.015
	24 weeks (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)	-

*reported for patients with at least 3% BSA psoriasis

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, 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, 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, though as with other estimates of these outcomes their related confidence intervals were wide (see Table 5.12). Again, the large relative differences on these higher response thresholds reflect some response with biologic therapy versus virtually none with placebo (e.g. 18% versus 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 methotrexate.[52, 89, 93, 94, 101-105]

12-week PASI response measures were reported by only one trial, in patients with psoriasis of at least 3% BSA at baseline.[52, 89, 93, 94, 101-105] Response was significantly greater for adalimumab than placebo at all three PASI thresholds (PASI 50, PASI 75 and PASI 90; see Table 5.11). As with the ACR outcomes, there was little evidence of any differential PASI response between patients receiving and not receiving concomitant methotrexate, though the number of patients in each subgroup was small.

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

Table 5.12: Meta-analysis of adalimumab efficacy data – outcomes at 12 weeks

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

Efficacy after 24 weeks treatment

The ADEPT trial maintained randomisation for 24 weeks.[52, 89, 93, 94, 101-105] 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 up to 24 weeks of treatment (see Table 5.12).

In addition, this trial reported a statistically significant difference in mean change in TSS score from baseline (-0.2 versus 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.

The smaller of the two trials allowed patients to enter an open-label follow-up period from weeks 12-24. The pattern of reported joint disease outcomes appear 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 two years (see table 5.13).[52, 89, 93, 94, 101-105] 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, though the open-label observational nature of these open-label data make it difficult to reliably determine any clear changes in TSS over time.

Table 5.13: Adalimumab efficacy outcomes – uncontrolled follow-up data

Trial	Type of data	Duration	Outcomes	Adalimumab	Adalimumab/placebo
ADEPT[52, 89, 93, 94, 101-105]	Uncontrolled	48 weeks	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 weeks	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 weeks	Mean (sd) TSS change from baseline	(n=115) 0.5 (4.20)	(n=128) 0.9(6.36)

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.
- 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 two 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.

5.2.2.4 Efficacy of all three biologics

As described in section 5.1.5, 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 the trials identified in the systematic review were used in the analysis; although not all trials provided data for of all outcomes analysed. Full details of the methods used are given in Appendix 10.5

PsARC response

The results of the evidence synthesis for PsARC response are in the form of probability of response (Table 5.14). 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. Whilst the credible intervals for all three biologics overlap each other, none overlap placebo.

Table 5.14: Probability of PsARC response to biologics

		Credible intervals	
	Mean	2.50%	97.50%
Placebo	0.249	0.178	0.317
Etanercept	0.741	0.566	0.832
Infliximab	0.797	0.672	0.886
Adalimumab	0.568	0.444	0.713

Changes in HAQ

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 5.15) and those who did not achieve a PsARC response (Table 5.16).

Table 5.15: Change in HAQ in patients who responded to treatment

		Credible intervals	
	Mean	2.50%	97.50%
Placebo	-0.218	-0.314	-0.128
Etanercept	-0.624	-0.815	-0.438
Infliximab	-0.653	-0.796	-0.509
Adalimumab	-0.423	-0.539	-0.296

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 -0.2179, which is below the minimum clinically significant threshold for PsA of -0.3.[151] Patients who responded to etanercept and infliximab achieved similar mean changes in HAQ (-0.6235 and -0.6275, respectively) whilst responders to adalimumab achieved a lower mean change in the HAQ score of -0.423 with credible intervals that do not overlap those of the other two treatments.

Table 5.16: Change in HAQ in patients who did not respond to treatment

		Credible intervals	
	Mean	2.50%	97.50%
Placebo	0	0	0
Etanercept	-0.185	-0.390	0.015
Infliximab	-0.191	-0.337	-0.046
Adalimumab	-0.064	-0.188	0.065

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

PASI

The results of the evidence synthesis for a PASI response are in the form of probability of response (Table 5.17). 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.

Table 5.17: Probability of PASI response to biologics

			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

ACR model

The results of the evidence synthesis for a ACR response are in the form of probability of response (Table 5.18). 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 5.18: Probability of ACR response to biologics

			Credible intervals	
		mean	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, 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.

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 have been presented in Table 5.19 and are discussed below.

Two of the company submissions, Abbott and Schering-Plough, conducted evidence syntheses to derive estimates that would allow the relative efficacy of the drugs to be compared. Wyeth chose not to conduct this synthesis themselves but to use the results of a previously published STA relating to Abbott Laboratories' adalimumab.[75]

Full details of the evidence synthesis model used by Wyeth were not provided in the Wyeth submission. Further, the methodology of the evidence synthesis from which these results were obtained was not presented in the original report.[152] The synthesis was conducted by Abbott 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, Abbott and by the Assessment Group in this report.

PsARC response

For PsARC response all of the evidence synthesis models used a fixed effect meta-analysis to synthesise the evidence. Both the Assessment Group and Schering-Plough identified and included 6 RCTs in their synthesis. Abbott, with slightly broader inclusion criteria, identified and included 10 RCTs. Abbott included RCTs where the drug golimumab was administrated to the comparator arm of the RCT and, whilst 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 estimated PsARC response using slightly different data. The Assessment Group used the closest follow-up outcome to 12 weeks, whilst Schering-Plough used the latest available endpoints. This meant that with the exception of the adalimumab data the data inputs were principally the same. Abbott Laboratories 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 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.

As can be seen from the results presented for the probability of response to the biologics under appraisal (and placebo) (Table 5.20), 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 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 based their evidence synthesis on a previous York report[74] which linked two meta-analyses, one estimating PsARC the other HAQ conditional on PsARC.

HAQ conditional on a PsARC response

The economic models developed by both the Schering-Plough 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. The two modelling approaches were based on fixed effects meta-analysis. The Schering-Plough approach uses two linked meta-analysis 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 used the latest available endpoints for HAQ, in contrast to the Assessment Group who elected to use the 12-16 week HAQ data to reflect short-term benefits. Long-term benefits are considered explicitly in the economic model.

The results obtained (see Table 5.21) 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 only included the five trials which reported HAQ outcomes for responders and non-responders. To enable them to include all six trials Schering-Plough assumed that for the one trial where the data were not stratified by responder/non-responder [79] that 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 which reported in a manner that facilitated modelling. The Schering-Plough 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. Whilst they state that this was only used to inform relationships between variables, the coding and appendix do not make this clear.

Abbott 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) which change during the trial and affect both PsARC response and, independently, the change in HAQ.

PASI 50/75/90 response

The PASI outcomes were synthesised by Abbott, Schering-Plough and the Assessment Group. Schering-Plough 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 results, both of whom 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 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 5.23 are similar. As previously stated, the Abbott model was complex and (the assessment team felt) difficult to fully understand. As such it is not clear if data from all ten included trials were used in the Abbott PASI model. The data inputs for the Assessment Group model are reported in Appendix 10.5. Due to a lack of reporting in some trials, the Assessment Group model included data from five trials, one of which only provided data on two of the outcomes (PASI 50/75).

ACR 20/ 50/70 response

Schering-Plough did not synthesise for this outcome. Both the Assessment Group and Abbott did, but again elected to use two differing modelling approaches, ordered logit and bivariate probit. The comparative results are presented in table 5.24. The results are again similar, with the ranking of the drugs being maintained.

Abbott's model 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 economic model required 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 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 all been presented for all models used by the Assessment Group. Whilst 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.

Table 5.19: Comparison of industry and Assessment Group evidence syntheses

	Abbott	**Schering-Plough**	**Wyeth**	**Assessment team (York)**
Interventions	Etanercept, Infliximab, Adalimumab	Etanercept, Infliximab, Adalimumab	Etanercept, Infliximab, Adalimumab	Etanercept, Infliximab, Adalimumab
Studies used in the analysis	Mease, 2000, Antoni, 2003, Mease, 2004, Antoni, 2005, Kaltwasser, 2004, Mease, 2005, Mease, 2006, Genovese, 2007, Kavanaugh, 2008, Gottlieb, 2009.	IMPACT, IMPACT 2, Mease 2000, Mease 2004, ADEPT, Genovese 2007, York HTA, GO-REVEAL.	Mease 2004, PRESTA, ADEPT, IMPACT 2, STA ADL.	IMPACT, IMPACT 2, Mease 2000, Mease 2004, ADEPT, Genovese 2007
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.[75]	12 weeks
HAQ	12 weeks (dependent on ACR response type, via Multivariate regression).	Week 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[75] 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-analysis: PsARC/HAQ and PASI.	Model used not reported. The results were taken from a published evidence synthesis[75]	Fixed effect meta-analysis (PsARC, HAQ|PsARC, 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.[152]	

Table 5.20 Key Assumptions in the Synthesis Models

Abbott	Schering-Plough	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 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 conditional 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 ≥ 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 ≥ 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 fixed across trials.

Table 5.21: PsARC model results

	Current assessment		Abbott		Schering-Plough		Wyeth	
Probability of Response	**mean**	**credible interval**	**mean**	**credible interval**	**mean**	**credible interval**	**mean**	**credible interval**
Placebo	0.249	[0.1779, 0.3169]	0.258	not reported	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	0.713	[0.5665, 0.8317]	0.743		[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	0.795	[0.6725, 0.8855]	0.76		[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	0.587	[0.4441, 0.713]	0.591		[redacted]	[redacted]	[redacted]	[redacted]

Table 5.22: HAQ conditional on response. Different treatment effects (common baseline)

Treatment	**Current assessment**		**Abbott**	**Schering-Plough**		**Wyeth**
Changes in HAQ | Response	**mean**	**credible interval**	**NC**	**mean**	**credible interval**	**NC**
Etanercept	-0.6235	[-0.8153, -0.4375]	**NC**	[redacted]	[redacted]	**NC**
Infliximab	-0.6527	[-0.7962, -0.509]	**NC**	[redacted]	[redacted]	**NC**
Adalimumab	-0.423	[-0.5392, -0.2955]	**NC**	[redacted]	[redacted]	**NC**
Changes in HAQ | No-Response	**mean**	**credible interval**	**NC**	[redacted]	[redacted]	**NC**
Etanercept	-0.1854	[-0.39, 0.01543]	**NC**	[redacted]	[redacted]	**NC**
Infliximab	-0.1907	[-0.3373, -0.0463]	**NC**	[redacted]	[redacted]	**NC**
Adalimumab	-0.0642	[-0.1878, 0.0652]	**NC**	[redacted]	[redacted]	**NC**
Placebo			**NC**	[redacted]	[redacted]	**NC**
Changes in HAQ | Response	**mean**	**credible interval**	**NC**	[redacted]	[redacted]	**NC**
All treatments	-0.2179	[-0.3139, -0.1278]	**NC**	[redacted]	[redacted]	**NC**

Table 5.23: PASI common Effects Model

	Current assessment		Abbott		Schering-Plough	Wyeth	
Placebo	**mean**	**credible interval**	**mean**	**credible interval**		**mean**	**credible interval**
Probability of response to PASI 50	0.1305	[0.09173, 0.1747]	0.151	not reported	**NC**	[redacted]	[redacted]
Probability of response to PASI 75	0.04446	[0.02811, 0.06535]	0.049	not reported	**NC**	[redacted]	[redacted]
Probability of response to PASI 90	0.01671	[0.0098, 0.0261]	0.009	not reported	**NC**		
Etanercept				not reported			
Probability of response to PASI 50	0.4026	[0.2361, 0.5916]	0.393	not reported	**NC**	[redacted]	[redacted]
Probability of response to PASI 75	0.1768	[0.085, 0.313]	0.189	not reported	**NC**	[redacted]	[redacted]
Probability of response to PASI 90	0.07372	[0.0317, 0.145]	0.057	not reported	**NC**		
Infliximab				not reported			
Probability of response to PASI 50	0.9128	[0.823, 0.968]	0.915	not reported	**NC**	[redacted]	[redacted]
Probability of response to PASI 75	0.7687	[0.5943, 0.901]	0.774	not reported	**NC**	[redacted]	[redacted]
Probability of response to PASI 90	0.5571	[0.347, 0.767]	0.515	not reported	**NC**		
Adalimumab				not reported			
Probability of response to PASI 50	0.7383	[0.5518, 0.881]	0.732	not reported	**NC**	[redacted]	[redacted]
Probability of response to PASI 75	0.4772	[0.275, 0.693]	0.5	not reported	**NC**	[redacted]	[redacted]
Probability of response to PASI 90	0.2571	[0.119, 0.4524]	0.239	not reported	**NC**		

Table 5.24: ACR model common effects

	Current assessment		Abbott		Schering-Plough	Wyeth
Placebo	**mean**	**credible interval**	**mean**	**credible interval**		
Probability of response to ACR 20	0.1369	[0.108, 0.168]	0.132	not reported	**NC**	**NC**
Probability of response to ACR 50	0.05347	[0.04, 0.07]	0.048	not reported	**NC**	**NC**
Probability of response to ACR 70	0.01806	[0.013, 0.025]	0.012	not reported	**NC**	**NC**
Etanercept				not reported		
Probability of response to ACR 20	0.6093	[0.459, 0.75]	0.578	not reported	**NC**	**NC**
Probability of response to ACR 50	0.362	[0.231, 0.516]	0.362	not reported	**NC**	**NC**
Probability of response to ACR 70	0.1583	[0.088, 0.26]	0.174	not reported	**NC**	**NC**
Infliximab				not reported		
Probability of response to ACR 20	0.6775	[0.533, 0.81]	0.615	not reported	**NC**	**NC**
Probability of response to ACR 50	0.4333	[0.288, 0.59]	0.398	not reported	**NC**	**NC**
Probability of response to ACR 70	0.2028	[0.1138, 0.326]	0.199	not reported	**NC**	**NC**
Adalimumab				not reported		
Probability of response to ACR 20	0.5595	[0.429, 0.686]	0.537	not reported	**NC**	**NC**
Probability of response to ACR 50	0.3146	[0.209, 0.438]	0.323	not reported	**NC**	**NC**
Probability of response to ACR 70	0.1313	[0.077, 0.205]	0.148	not reported	**NC**	**NC**

5.2.3 Review of adverse events

5.2.3.1 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 DARE database inclusion criteria.[76] The searches (see Appendix 9.1 of Search Strategies) resulted in 16 potentially relevant reviews. Ten were excluded because of a failure to meet the DARE criteria or to report relevant data on adverse events of biologics. Six systematic reviews (see Table 5.25) were therefore included in this overview.

All the six systematic reviews were published between 2006 and 2009. Three reviews [153-155] included patients with RA and three reviews [156-158] 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 randomised controlled trials (RCTs) to assess the safety of biologics whilst only one review[155] 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.[159, 160] However, in the majority of these reviews[153-156, 158] it was unclear whether any language restrictions on study inclusion were made, which may have introduced the possibility of language bias.[161]

There were variations in methods of pooling the adverse event data in these reviews. Five reviews [153, 154, 156-158] used meta-analyses to synthesise the evidence of adverse event data of biologics, whilst one review used a narrative synthesis.[155] 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 [154] also used the individual patient data 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.[153, 157] Statistical heterogeneity [162, 163] was adequately assessed in most reviews. In addition, three reviews assessed the adverse events for more than two biologics combined,[153, 156, 157] whilst the other reviews evaluated them for each biologic respectively. [154, 155, 158]

A range of adverse events of biologics were evaluated in these reviews. Three reviews [155, 157, 158] evaluated both common and serious adverse events of biologics, whilst two reviews exclusively focused on serious adverse events such as malignancy. [153, 154] Two reviews [156 157] 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 2008[158] reported that there were no significant increased incidences of one or more adverse events or serious adverse events for patients receiving etanercept. Brimhall 2008 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 2008[155] which principally evaluated the common adverse events of biologics showed similar results based on the data from 18 experimental and observational studies for RA patients. This review reported that biologics appeared to be 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 RA patients.

Both the review by Ravindran 2008[156] and the review by Saad 2008[157] used the withdrawal rate due to toxicity/adverse events as the outcome measure to assess the safety of biologics. These are two reviews of exclusively PsA patients. The review by Ravindran 2008[156] reported that biologic treatment for PsA patients 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 2008[157] on the basis of the pooled results of five RCTs (including the same four RCTs as Ravindran 2008), which also reported a non-significant difference between biologics and placebo in the proportion of PsA patients 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 infection of TB) of biologics for PsA patients.

Two reviews assessed the serious adverse events of malignancy and/or serious infections due to use of biologics for RA patients.[153, 154] Bongartz 2006[153] reported that malignancies were significantly more common in patients treated with biologics compared with placebo: the pooled OR for malignancy in patients receiving infliximab and adalimumab compared with

placebo was 3.3 (95% CI: 1.2, 9.1) and for serious infection was 2.0 (95% CI: 1.3, 3.1). Malignancies were also significantly more common in patients receiving higher doses of biologics compared with patients receiving lower doses of biologics. However, some inconsistent findings were reported in the review by Bongartz 2009[154] 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 individual patient data was not statistically significant (HR 1.84, 95% CI: 0.79, 4.28) in patients using etanercept compared with placebo or mixed controls 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.[147, 164-166] 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 IV 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.

Table 5.25: Published systematic reviews of adverse events of biologics

Study details	Intervention and patients	Searching and included studies	Analyses	Outcomes
Bongartz 2006[153]	Infliximab & Adalimumab 5014 RA patients	Data sources: MEDLINE, EMBASE, the Cochrane Library were searched from inception to December 2005. The abstract databases of annual scientific meetings of European League Against Rheumatism and the American College of Rheumatology were searched from 1996 to 2005. Included studies: 9 RCTs (4 RCTs of Infliximab; 5 RCTs of Adalimumab)	Studies were combined using a fixed-effects model of Mantel-Haenszel method. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated, with a continuity correction method for sparse data. The effects for high and low doses of antiTNFs 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 non-melanoma skin cancers.	The pooled OR for malignancy was 3.3 (95% CI: 1.2, 9.1) and for serious infection was 2.0 (95% CI: 1.3, 3.1). Malignancies were significantly more common in patients received higher doses of anti-TNFs compared with patients received lower doses of anti-TNFs. For patients with anti-TNF treatment in included RCTs, the number needed to harm was 154 (95% CI: 91, 500) for 1 additional malignancy within a treatment period of 6 to 12 months. For serious infections, the number needed to harm was 59 (95% CI: 39, 125) within a treatment period of 3 to 12 months.
Bongartz 2009[154]	Etanercept 3316 RA patients	Data sources: MEDLINE, EMBASE, the Cochrane library, Web of Science were searched from inception to December 2006. Pharmaceutical companies were contacted for unpublished trials. Included studies: 9 RCTs	Studies were combined using a random-effects model of DerSimonian and Laird model. Pooled hazard ratios (HRs) with 95% CIs were calculated using individual patient data (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 non-melanoma skin cancers (NMSC) from case definition. Subgroup analyses were performed for three non-overlapping periods of follow-up time (<6 months, 6–12 months, >24 months). In	The pooled HR for malignancies based on IPD data was 1.84 (95% CI: 0.79, 4.28) in patients using etanercept compared with controls. The random effects model resulted in a similar estimate of an HR of 1.82 (95% CI: 0.78, 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, 4.38). When using a random-effects DerSimonian and Laird model, the pooled HR malignancies in patients receiving etanercept compared with patients receiving control

			addition, pooled odds ratios (ORs) with 95% CIs were calculated using the Mantel–Haenszel model with a continuity correction method.	treatment was 1.71 (95% CI: 0.73, 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, 4.62). With the exclusions of all NMSC from analyses, similar results were found (HR 1.86, 95% CI: 0.62, 5.59). When the data were stratified according to three different time points: 0–6 months; 6–12 months and more than 12 months, it did not show a particular time period in which the risk of cancer was significantly increased.
Brimhall 2008[158]	Etanercept & 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 biological agent. The safety of biological agents was assessed by relative risk of one or more adverse events and serious adverse events for all doses. All dosages were combined for comparison. The number needed-to -treat (NNT) and the number needed- -to-harm (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, 1.16, p=0.28). Similar results were observed for the incidence of SAEs (RR 1.17, 95% CI: 0.59, 2.33, p=0.66). The most common reported AEs reported were injection-site reaction, headache and upper respiratory tract infection. 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 (RR1.18, 95% CI: 1.07, 1.29, *P* <0.001), with NNH of 9 (95% CI: 5.99, 19.61). The most common reported AEs were upper respiratory tract infection, headache, increased hepatic enzymes and infection. Infliximab was not associated with a significant increase in SAEs (RR 1.26, 95% CI: 0.56, 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 2006[155]	Etanercept , Infliximab and Adalimumab The review included RA patients 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 adverse events.	Studies were combined in meta-analyses using random-effects models. Subgroup analyses were conducted for the population who had remained symptomatic despite the methotrexate 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 meta-regression. Publication bias was assessed using funnel plots and Kendall's tests. Where there were no direct head-to-head studies comparing an antiTNF with another, an indirect comparison was undertaken using placebo as the common comparator. For the adverse event data, the evidence was summarised qualitatively.	When the studies were pooled, adalimumab was associated with weighted mean incidence of diarrhoea (8.16, 95% CI: 4.44, 11.88), headache (18.23, 95%CI: 6.51, 29.95), infection site (18.98, 95% CI: 9.21, 28.76), nausea (8.84, 95% CI: 5.55, 12.13), rhinitis (14.8, 95% CI: 7.26, 22.35), and upper respiratory tract infection (17.05, 95% CI: 9.5, 24.59). Etanercept was associated with weighted mean incidence of diarrhoea (18.14, 95% CI: 3.45, 32.84), headache (17.54, 95%CI: 1.9, 33.18), infection site (24.67, 95% CI: 11.21, 38.13), nausea (20.86, 95% CI: 2.65, 39.08), rhinitis (18.42, 95% CI: 6.97, 35.71), and upper respiratory tract infection (20.89, 95% CI: 6.97, 34.82).

				Infliximab was associated with weighted mean incidence of diarrhoea (9.31, 95% CI: 7.94, 10.68), headache (17.7, 95% CI: 3.03, 33.36), rhinitis (7.77, 95% CI: 0, 18.12), upper respiratory tract infection (24.05, 95% CI: 0, 49.81). In addition, rare but serious adverse events (e.g. serious infections, lymphoma or neutropenia) were of concern in the included trials but could not be reliably assessed.
Ravindran 2008[156]	Etanercept , Infliximab & Adalimumab 2039 PsA patients in total receiving the treatment of antiTNFs, Sulfasalzaine, gold salts, Leflunomide and DMARDs. (882 PsA patients receiving antiTNFs)	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 risk ratios (RRs) with 95% CIs for dichotomous outcomes were calculated. The pooled Peto odds ratios (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 number-needed-to- treat (NNT) to number-needed-to harm (NNH) was calculated to assess the benefit versus risk of each treatment.	When the studies (2 RCTs of etanercept, 2 RCTs of infliximab and one RCT of adalimumab) were pooled, antiTNF treatment was associated with a non-significant increase of withdrawal rate due to toxicity compared with placebos (RR 2.2, 95%CI; 0.82, 5.91, p=0.12; 5 RCTs). AntiTNFs were associated with a high ratio (0.25) of numbers needed to treat (NNT) to numbers needed to harm (NNH).
Saad 2008[157]	Etanercept , Infliximab & Adalimumab 982 PsA patients	Data sources: MEDLINE, EMBASE, CINAHL, and the Cochrane controlled trials register were searched from inception to May 2007. The US food and drug administration and European Medicines Evaluation Agency websites were searched. Reference lists of relevant publications were also screened. Included studies:	Studies were combined in meta-analyses using random-effects models. The pooled relative risks (RRs) and risk differences (RDs) for dichotomous outcomes, with 95% CIs, were calculated. The weighted mean differences (WMDs) for continuous outcomes, with 95%CIs were also calculated. Statistical heterogeneity was measured using Chi^2 and I^2 statistics. Where there were no direct head-to-head studies comparing an	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, 1.18), withdrawal due to adverse events (RR 2.14, 95% CI: 0.73, 6.27), serious adverse events (RR 0.98, 95% CI: 0.55, 1.77), and upper respiratory tract infections (RR 0.91, 95% CI: 0.65, 1.28). The pooled rate

		6 RCTs	antiTNF with another, an indirect comparison was undertaken using placebo as the common comparator.	for injection site reactions were significantly higher for adalimumab and etanercept compared with placebos (RR 2.48, 95% CI: 1.16, 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, 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 serious adverse events. 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.

RA: Rheumatoid arthritis. PsA: Psoriatic arthritis.

5.2.3.2 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

RCTs in PsA

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%).[79] 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.[53, 98, 100, 106, 108, 111] 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%), though 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 RCTs 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, though outcomes for PsA, juvenile idiopathic arthritis, ankylosing spondylitis and patients with other chronic inflammatory conditions were also reported (see table 5.26). Average length of follow-up ranged from 48 weeks to seven years.

Table 5.26: Adverse events reported for etanercept

Study	Total infections	Serious infections	Cancers	TB	Mortality	Withdrawals to AE
Brassard 2006[136]	-	-	-	1.40%	-	-
Carmona 2005[142]	-	-	-	0.00%	-	-
Dixon 2006[137]	-	5.80%	-	0.06%	-	-
Dixon 2007[148]	-	11.20%	-	-	-	-
Favalli 2009[130]	-	4.50%	-	0.40%	-	-
Feltelius 2005[143]	11%	2.60%	1%	-	0.30%	5.50%
Fleischmann 2006[100]	54.40%	4.90%	-	0%	0.90%	6.50%
Gomez-Reino 2003[147]	-	-	-	0%	-	-
Gomez-Reino 2007[133]	-	-	-	0%	-	-
Horneff 2009[126]	9.60%	4.30%	-	-	0%	-
Klareskog 2006[121]	26.50%	16.20%	1.30%	0%	1.80%	4.60%
Listing 2005[123]	21.30%	6.10%	-	0%	-	-
Mease 2006[98]	1.80%	0.60%	-	-	0%	0%
Moreland 2006[122]	-	13.20%	5.70%	0%	3.10%	13.60%

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 three studies clearly reported cancer, with rates ranging from 1% to 5.7%. Seven of eleven studies reporting rates of tuberculosis 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.[100, 123] One cohort study reported significantly more infections in RA patients receiving etanercept than control patient (22.6 vs. 6.8 infections per 100 patient years, $p<0.01$; 6.4 vs. 2.3 serious infections per 100 patient years, $p<0.01$).[123] 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%, $P>0.05$).[100]

Infliximab

RCTs in PsA

Two placebo controlled RCTs evaluated infliximab in patients with PsA.[80-83, 90-92, 96, 97, 99, 107, 110, 112-119] 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.[80-82, 90, 97, 110, 112, 114-116, 118, 119] 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%), though as with other RCTs, the study was not powered to detect differences in adverse events.[83, 91, 92, 96, 99, 107, 113, 117] One patient in the placebo group developed basal cell carcinoma of the skin, though no deaths or withdrawals due to adverse events were reported.

Table 5.27: Adverse events reported for infliximab

Study	Total infections	Serious infections	Cancer	TB	Mortality	Withdrawals to AE
Antoni 2008[90]	URTI: 38.5% Diarrhoea 9.0% Pharyngitis: 9.0% Sinusitis: 5.1% UTI: 5.1%	2.6%	5.1%	0%	-	6.4%
Brassard 2006[136]	-	-	-	1.8%	-	-
Caspersen 2008[129]	-	10.1%	0.6%	0.3%	2.0%	-
Carmona 2005[142]	-	-	-	4.6%	-	-
Colombel 2004[125]	9.6%	3.0%	1.8%	-	2.0%	-
Dixon 2006[137]	-	8.9%	-	0.2%	-	-
Dixon 2007[148]	-	13.8%	-	-	-	-
Favalli 2009[130]	-	8.1%	-	0.6%	-	-
Fidder 2009[120]	-	6.5%	2.9%	0.1%	1.6%	-
Gomez-Reino 2003[147]	-	-	-	1.1%	-	-
Gomez-Reino 2007[133]	-	-	-	0.4%	-	-
Listing 2005[123]	26.6%	5.8%		0.3%		
Oka 2006[138]	-	3.1%	-	0.3%	0.06%	-
Schnitzler 2009[128]	-	0.8%	0.16%	-	1.6%	12.8%
St. Clair 2004[144]	URTI: 26.7% Sinusitis: 9.7% Pharyngitis: 13.8%	5.3%	0.5%	0.5%	0.27%	9.6%
Takeuchi 2008[131]	8.7%	Bacterial pneumonia: 2.2% Interstitial pneumonitis: 0.5%	0.16%	0.3%	-	-
Westhovens 2006[140](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%
Westhovens 2006[140] (22-54 weeks)	35.4%	3.1%	2.6%	0.4%	0.4%	8.0%
Wolfe 2004[145]	-	-	-	0.06%	-	-

Non-randomised studies/large RCTs 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, though the vast majority of patients had RA (see Table 5.27). Average length of follow-up ranged from 22 weeks to six 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 upper respiratory tract infections (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 tuberculosis 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.[120, 123, 140, 144] Two of these were RCTs of infliximab versus placebo plus MTX in RA,[140, 144] of which one found no difference in serious infections between groups at 22 weeks (3.3% vs. 1.7%, $p>0.05$),[140] and one reported significantly more serious infections associated with infliximab at around 54 weeks (5.3% vs. 2.1%, $p<0.05$).[144] 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 RA patients receiving infliximab,[123] the second reported no significant differences in serious infections (1.6 per 100 patient-years vs. 1.1 per 100 patient years), 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).[120]

Adalimumab

RCTs in PsA

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.[84] 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%).[52, 89, 93, 94, 101-105] Serious infections were reported in three patients; two receiving adalimumab and one receiving placebo. No deaths were reported.

Table 5.28: Adverse events reported for adalimumab

Study	Total infections	Serious infections	Cancers	TB	Mortality	Withdrawals to AE
Breedveld 2006[141]	9.12%	2.20%	1.10%	0.18%	0.90%	10.70%
Burmester 2007[132]	-	3.10%	0.70%	0.30%	0.50%	10.30%
Carmona 2005[142]	-	-	-	0%	-	-
Dixon 2006[137]	-	5.10%	-	0.08%	-	-
Dixon 2007[148]	-	7.30%	-	-	-	-
Colombel 2007[134](0-4 weeks)	15.20%	1.20%			0.20%	6.30%
Colombel 2007[134](4-56 weeks)	45.30%	2.70%	0.20%	0.40%		5.80%
Favalli 2009[130]	-	6.60%	-	0.30%	-	-
Gomez-Reino 2007[133]	-	-	-	0.20%	-	-
Rudwaleit 2009[127]	-	0.40%	-	-	-	-
Schiff 2006[139]	-	6.30%	0.10%	0.30%	-	-

Non-randomised studies/large RCTs 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 though - as for the other agents – most patients had RA (see Table 5.28).Average length of study follow-up ranged from 12 weeks to five 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 tuberculosis 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.[134, 141] One RCT of adalimumab alone or in combination with MTX against MTX alone in RA patients, 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, $p<0.05$).[141] 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%).[134]

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 ten of these uncontrolled studies (see Table 5.29)

Table 5.29: Studies reporting adverse events for more than one biologic

Study	Total infections	Serious infections	Cancers	TB	Mortality	Withdrawals to AE
Brassard 2006[136]	-	-	-	Etanercept: 1.4% Infliximab: 1.8%	-	-
Carmona 2005[142]	-	-	-	Infliximab: 4.6% Etanercept: 0% Adalimumab: 0%	-	-
Curtis 2007[135]	-	2.70%	-	-	-	-
Dixon 2006[137]	-	Etanercept: 5.8% Infliximab: 8.9% Adalimumab: 5.1%	-	Etanercept: 0.06% Infliximab: 0.2% Adalimumab: 0.08%	-	-
Dixon 2007[148]	-	Etanercept: 11.2% Infliximab: 13.8% Adalimumab: 7.3%	-	-	-	-
Dreyer 2009[149]	-	-	0.76%	-	-	-
Favalli 2009[130]	-	Etanercept: 4.5% Infliximab: 8.1% Adalimumab: 6.6%	-	Etanercept: 0.4% Infliximab: 0.6% Adalimumab: 0.3%	0.40%	-
Gomez-Reino 2003[147]	7.60%	0.65%	-	Etanercept: 0 (0%) Infliximab: 17 (1.1%)	0.10%	-
Gomez-Reino 2007[133]	-	-	-	Etanercept: 2 (0.1%) Infliximab: 5 (0.4%) Adalimumab: 1 (0.2%)	-	-
Listing 2005[123]	Etanercept: 21.3% Infliximab: 26.6%	Etanercept: 6.1% Inflixmab: 5.8%	-	Etanercept: 0 (0%) Infliximab: 1 (0.3%)	0.50%	-

RA patients predominated and average length of study follow-up (where reported) ranged from one to five 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.[123] 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%).

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

One large prospective cohort study of reported that 0.76% of patients treated with biologic agents developed cancer during follow-up.[149] None of the studies provided adequate data on rates of withdrawal, and none provided separate mortality data for each agent.

Summary of serious adverse events across all three agents

Table 5.30: 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%

Table 5.30 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.

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

5.2.4 Discussion of Clinical Evaluation

5.2.4.1 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 the trials appeared to deal with withdrawals appropriately by using intention-to-treat analyses. The completeness of follow-up was fairly good in all trials with losses to follow-up of less than 20%, thereby minimising attrition bias.[167] 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, whilst 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 confidence intervals 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, though 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 (HAQ)

All three agents appeared to have beneficial effects on functional status as measured by HAQ. The estimates with relatively high precision indicated that all the biologic therapies significantly improved the functional status of patients with PsA at around 3 months follow-up. The clinical significance of these effects is not entirely clear e.g. adalimumab was associated with a significant absolute mean reduction of HAQ score from baseline of -0.27 (95% CI: -0.36, -0.18). However, only changes greater than -0.3 have been considered as clinically meaningful improvement in PsA.[151]

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.[74] 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 of adalimumab and demonstrated its beneficial treatment effects compared to 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, though confidence intervals 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 psoriasis patients lay outside the scope of this evaluation.[168, 169]

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 amongst 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,[151] and only those for infliximab achieved statistical significance. A comparison of the indirect comparison undertaken by the Assessment Group with those of the manufactuers shows similar mean estimates of treatment effect despite the rather different methods employed.

5.2.4.2 Safety

Study design and quality

For the evaluation of adverse events of these biological agents, this review included a range of study types including randomised controlled trials, 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 PsA patients remains unclear. Overall, the limited evidence prevents firm conclusions about the comparative safety of the three biologic agents being drawn from our systematic review.

6 Assessment of cost-effectiveness evidence

6.1 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.

6.1.1 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, Health Economic Evaluations Databases (HEED), MEDLINE, National Research Register (NRR), NHS Economic Evaluation Database (NHS EED), PsycINFO, and Science Citation Index. Full details of the main search strategy for this review are presented in Appendix 10.1.

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.[170]

6.1.2 Results

6.1.2.1 Identified studies

The systematic literature of published literature identified three studies [171-173] 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).[74]. In

addition there were three industry submissions to NICE from: Abbott Laboratories[174], Schering-Plough[175] and Wyeth Pharmaceuticals[152].

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.

6.1.2.2 Available data

Table 6.1 summarises the data available from each of the six cost-effectiveness studies. The studies by Olivieri [173] and Bansback[171] are only available as journal articles. The study by Bravo Vergel [172] is available as a journal article but also as a full assessment report with an accompanying electronic model[74]. The three industry submissions included full reports and electronic models. Where an electronic model has been made available it has been possible to provide some validation of the model by ensuring 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 AG requested that each manufacturer provide new utility estimates using a common methodology (see Appendix 10.17) 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 10.6). Wyeth clarified that 12 week 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 section 6.3.2). Abbott clarified how many DMARDs were sequenced in the model, how withdrawal rates were calculated (see section 6.3.2) and clarified the degree of correlation between arthritis and skin outcomes. No further clarifications were sought from Schering-Plough other than the additional utility regressions.

Table 6.1: Summary of information sources available for the cost-effectiveness studies

	Journal article	Full report	Electronic model	Additional utility regression	Clarifications
Oliviera	✓				
Bansback	✓				
Bravo Vergel	✓	✓	✓		
Abbott submission		✓	✓	✓	✓
Schering-Plough submission		✓	✓	✓	
Wyeth submission		✓	✓	✓	✓

6.1.2.3 Summaries of cost-effectiveness studies

A full description of each of the six cost-effectiveness studies along with a quality assessment checklist is presented Appendix 10.7. Table 6.2 below summarises the key features and data sources for each of the studies.

Table 6.2: Summary of cost-effectiveness evidence identified in the review

	Oliviera	Bansback	Bravo Vergel	Abbott	Schering-Plough	Wyeth
Comparators	Biologics (as a group) compared to no 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 and 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 horizon.	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 a lifetime 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 2004[53]).	Baseline HAQ is assumed to be average from the three trials (Mease 2000[79], Mease 2004[53] and Antoni 2005[82]).	Individual sampling model using baseline patient characteristics from the ADEPT trial[89] used to determine the distribution of patients	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.	

				characteristics in the model.		
Sources of effectiveness evidence	Effectiveness from a single trial.	Mease et al[53]) used to determine response rates and HAQ.	Short term trial data (Mease, et al 2000[79], Mease et al, 2004[53] and IMPACT[82]was 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[172] along with IMPACT[82], IMPACT 2[83], Mease 2000[79], Mease 2004[53], GO-REVEAL[176], Genovese 2007[84] and ADEPT[52] were used in the evidence synthesis model.	[redacted]
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 3 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, 3) 24 week ACR response conditional on the 12 week ACR response. Patient level data from ADEPT[89] 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.	[redacted]

Sources of cost data	Resource use collected retrospectively from patients. DRG costs were used to cost of 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 the MIMS. Resource use associated with monitoring and administering drugs was estimated according to BSR guidelines. 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, 2002 study[42]. [redacted]	[redacted] (reference not given).
Utilities	EQ-5D utility scores were used in the cost-effectiveness analysis. These were collected directly from patients at 6 months proceeding biologics treatment, baseline, 6-	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[89] of adalimumab was used. SF-36 was converted to EQ-5D.	Two alternative methods to generate utilities were explored: the Gray algorithm (selected as the base-case) and the Brazier algorithm.	[redacted]

	months and 12-months.					
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 to ciclosporin and £38,000 compared to 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 NH 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 to 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 60kg patient for all patients and for psoriatic patients. For a 70kg patient etanercept is the most cost-effective strategy for all patients and for psoriatic patients. For an 80kg patient etanercept is the most cost-effective strategy for all patients and for psoriatic patients, with ICERs of £12,696 and £12,606 compared to adalimumab. For all patient weights, etanercept is the most cost-effective with an ICER of £12,432 compared to adalimumab for non-psoriatic patients.	
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	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 to palliative care, apart from changing the algorithm for estimating QoL.	

			response test and withdrawal rates from BSRBR and the rebound assumption.			

As shown in Table 6.2, the six cost-effectiveness studies produce different costs and QALYs, resulting in different ICERs for the various options being compared. The study by Oliviera is difficult to compare with the others as all biologics were considered as a group compared to DMARDs. This produced an ICER of around €40,000 for biologics. Bansback produced an ICER of around £38,000 for etanercept compared to the next best strategy, leflunomide. Bravo Vergel 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 generates an ICER for adalimumab of £29,827 with etanercept dominated by adalimumab and infliximab with an ICER over £199,000. Schering-Plough report results for all patients, psoriasis patients and non-psoriasis patients. For all patients etanercept is the most cost-effective strategy assuming a patient weight of 70 or 80kg (ICER = £12,606 compared to adalimumab). For a 60kg patient etanercept is the most cost-effective strategy for patients without psoriasis (ICER = £12,432 compared to adalimumab) and infliximab the most cost-effective for psoriasis patients and all patients, dominating etanercept. Wyeth produces a base-case ICER for etanercept of £12,480 compared to DMARDs. All other biologics are dominated or extendedly dominated.

It is difficult to disentangle exactly why the six studies produce, in some cases, 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. The choice of comparator

All biologics were grouped together in Oliviera, although the majority of patients were taking etanercept. It is, therefore, not possible to estimate any differences in cost-effectiveness between the biological agents. Bansback only compares etanercept with DMARDs, omitting all other biologics; whereas Bravo Vergel only compares infliximab and etanercept with palliative care. The models from Abbott, Schering-Plough and Wyeth all include the three biologics etanercept, infliximab and adalimumab. However, Abbott and Wyeth compare these to DMARDs, whereas Schering-Plough use palliative care as the comparator. The patient group specified by the decision problem (see Section 2.2) are those who have previously 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

Oliviera uses 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-and-after study, so there may be a problem of selection bias. Bansback similarly uses 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, Abbott, Schering-Plough and Wyeth 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 and Schering-Plough models, some of these data sources relate to treatments not included as comparators in the model, such as golimumab (see Section 5.2). 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 and Bravo Vergel do not include the effect of treatments on the skin component of PsA, whereas the models by Abbott, Wyeth and Schering-Plough all include the effect of both conditions. In the Wyeth model, however,

[redacted]

4. Model structure

Oliviera 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, Bravo Vergel and Schering-Plough all determine response according to PsARC and then model the associated HAQ score. Schering-Plough includes PASI change from baseline to 12 weeks, but estimates this for weeks for PsARC responders/non-responders. Wyeth similarly

[redacted]Abbott 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 assumes changes in HAQ in the first 3 months are a function of PsARC response and the biologic used, while Abbott and Wyeth assume 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 individual patient data from trials (Bansback, Abbott and Wyeth). Bravo-Vergel and Schering-Plough 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 to run probabilistic sensitivity analysis. They are also difficult to audit and so there may be differences in methodology employed in these models that are not possible to determine in the constrained time scale.

6. Sources of cost data

In their trial-based evaluation Oliviera 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 Section 6.3.2), reflecting different methodology and sources of data.

7. Sources of utility data

Oliviera collected utilities directly from patients enrolled in the trial using the EQ-5D questionnaire. These were collected for the 6 months proceeding biologic treatment, baseline, 6-months and 12-months after starting treatment. The other studies use different external datasets 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 and Bravo Vergel both use the Leeds cohort study as a source of utility estimates. Abbott use the ADEPT trial[89] of adalimumab, which reports SF-36 data, which are then converted to EQ-5D to generate utilities. Schering-Plough use the same approach but use the GO-REVEAL[176]

trial dataset. [redacted]

6.1.2.4 Relevance of cost-effectiveness evidence for NICE decision making

The evidence provided from the cost-effectiveness study conducted alongside a single trial [173] 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 section 6.3.2 but can be summarised as:

- The use of DMARDs as a comparator to biologics used in the Wyeth and Abbott 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[150], to receive a third DMARD.
- In estimating the treatment effect, the Abbott and Schering-Plough 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 [redacted]
  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 assume this is the case and adjust the expected effectiveness of biologics, while [redacted] and Abbott [redacted]

- Withdrawals after 3-months due to adverse events and lack of efficacy were estimated from a single dataset (BSR register) in all of the industry models. There are other potential biologic registry datasets available which could have been synthesised.
- The prediction of [redacted] 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 employed in each of the three industry models (see Section 6.3.2). 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 which considers and addresses each of these limitations. This model is presented in Section 6.2.

6.2 York Economic Assessment

6.2.1 Methods of York Economic Assessment

Introduction

The review in Section 6.1 of models detailed in published literature (including the earlier one by the York Assessment Group) and those in the company submissions to this appraisal indicates 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[180, 181]. 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 patients' 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 [150] and BAD [168] guidelines for the use of biologics in PsA (see Box 6.1).

Box 6.1. 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 psoriatic arthritis in adults when the response of previous DMARD therapy has been inadequate. Infliximab should be administered in combination with methotrexate or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated.
BSR guidelines for commencing biologics in PsA Anti-TNF therapy, within its licensed indications, is recommended for the treatment of adults with active psoriatic arthritis only when the following criteria are met: (a)The person has peripheral arthritis with three or more tender joints and three or more swollen joints on two separate occasions at least one month apart, based on a 78-tender and 76-swollen joint count (b)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 (a) Severe disease defined as a PASI score of 10 or more and a DLQI >10. AND (b) have contraindications to, have developed, or are at risk of developing, clinically important drug-related toxicity and where phototherapy and alternative standard therapy cannot be used; or are intolerant or unresponsive to standard systemic therapy; have significant, coexistent, unrelated co-morbidity which precludes use of systemic agents such as ciclosporin or methotrexate; or have severe, unstable, life-threatening disease Eligibility criteria for patients with SKIN and JOINT disease (i) have active psoriatic arthritis or skin disease that fulfils defined BSR or BAD guideline criteria, respectively (ii) patients with severe skin psoriasis and psoriatic arthritis who have failed or cannot use methotrexate may need to be considered for biologic treatment given the potential benefit of such treatment on both components of psoriatic disease

The parameters of the model were obtained from published literature, manufacturers' parameter estimates, the results of the evidence synthesis in Section 5.2.2.4 and a structured elicitation of expert opinion. The model adopts the perspective of the UK NHS and personal social services. The price year is 2008/2009 and the annual discount rate 3.5%[182]. 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 (Table 5.1). The body weight is assumed to be 70 kilograms, based on the mean weight in the UK general population (69.7 kg in women and 83.5 kg in men[183]). Patients are assumed to have failed at least two DMARDS. In the base-case, patients are assumed to fulfil BSR criteria (see Box 6.1 above). In the base-case the HAQ at the start of the model is 1.05, based on the average in the RCTs (Table 5.1). Although the mean HAQ when patients start biologics in the BSR register was 1.8[184], 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 (less than 3% body surface area (BSA) or a PASI score of less than 2.5), 25% have mild-to-moderate psoriasis (a baseline PASI score between 2.5 and 10), and 25% have moderate-to-severe psoriasis (a PASI score greater than 10) (Ian Bruce, personal communication 20th November 2009). Approximately 50% of patients in the RCTs had less than 3% BSA psoriasis or a baseline PASI of less than 2.5 (Table 5.1), 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 homogenous baseline population. The model has a Markov structure (see Figure 6.1). Patients enter the model either i) commencing therapy with etanercept, infliximab or adalimumab or ii) with no therapy (assumed to be palliative care only).

Initial response at 3 months

Table 6.3 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 BSR[150] and BAD guidelines[168] (see Box 6.2). These parameters were estimated by the evidence synthesis (Section 5.2.2.4)

Box 6.2 BSR and BAD guidelines for treatment response in patients with psoriatic arthritis 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 (i) a 50% or greater reduction in baseline PASI (or % BSA where the PASI is not applicable) and a 5 point or greater improvement in DLQI or (ii) a 75% reduction in PASI score compared to 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 psoriatic arthritis, 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 psoriatic arthritis).

The BAD guidelines highlight that the recommended time points for assessing the initial response vary between drugs and between guideline-making bodies. The licenses 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 an assessment is made for all drugs at 'around three months' or between 12 and 16 weeks. The assessment of effectiveness in Section 5.2.2 did not find any appreciable differences in the biologics' response rates for joint disease or psoriasis between approximately 12 weeks compared with 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 Section 5.2.2.4. 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 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 10.5, the mean change in HAQ in the first 3 months for PsARC responders, across all biologic drugs, is -0.5688 (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 Section 5.2.2.4. 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 10.18. Patients who do not achieve a PASI 75 response will also have some proportionate gain in PASI while they continue taking a biologic, though this will be less than a 75% improvement (Appendix 10.18).

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

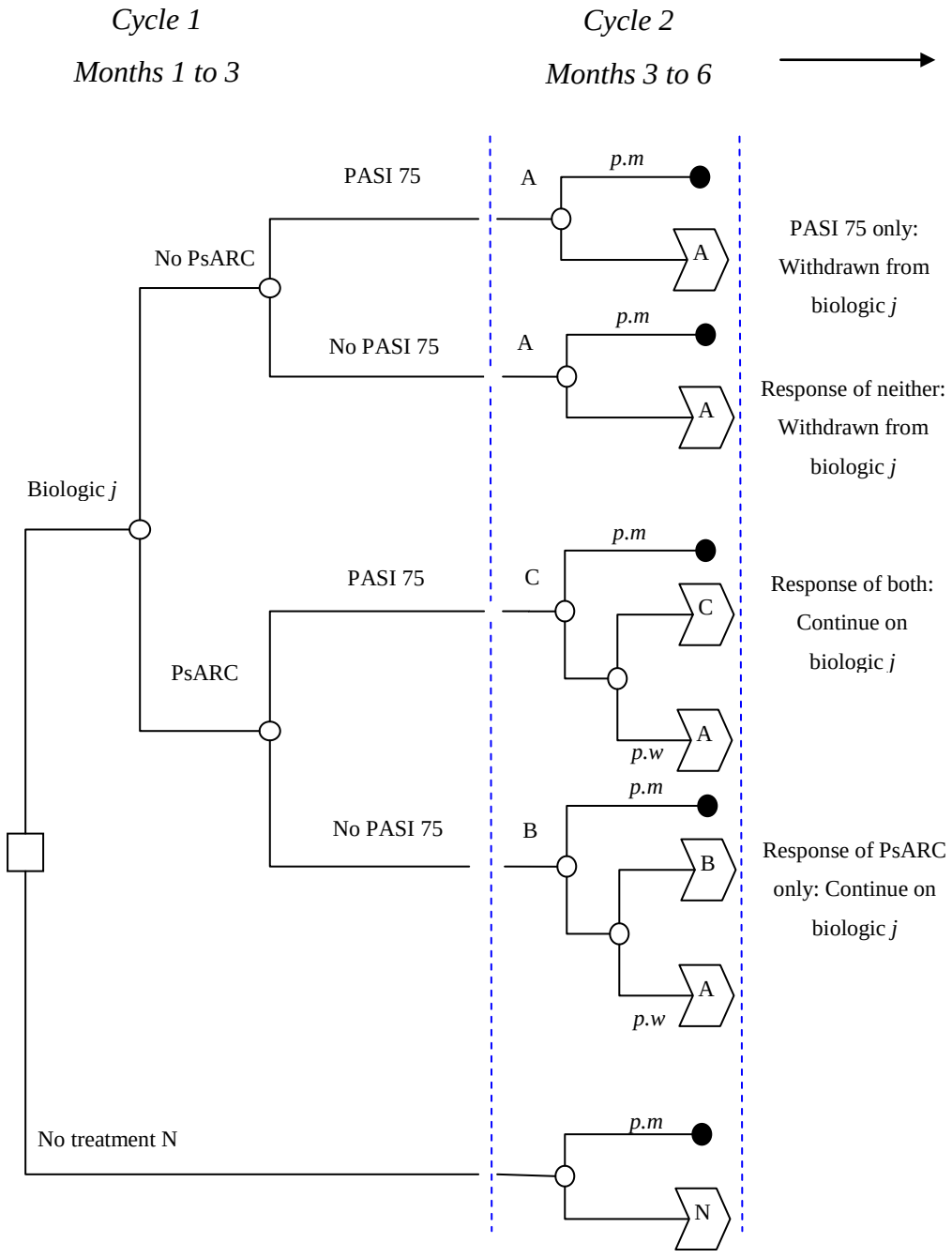
would be reproducible in general practice[185]. In the base-case we assume that part of the predicted response for treatment observed in the trial is attributable to the controlled trial setting and would not be reproducible in general practice. The change in HAQ in patients using biologics is reduced 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 10.9 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 4 possible outcomes at 3 months: skin response only, joints response only, response of both, response of neither (Figure 6.1). The base-case model assumes that the responses to psoriasis and arthritis might be correlated. Appendix 10.10 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 intention-to-treat 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 6.1: Structure of the decision model, assuming patients continue beyond 3 months if they achieve a PsARC response



Key: A – Withdrawn from biologic *j*. B – Continue on biologic *j* with response of arthritis but not of psoriasis. C – Continue on biologic *j* with response of both arthritis and psoriasis. N – No treatment.
P.m – Probability of mortality (any cause).
P.w – Probability of withdrawal from biologic after first 3 months.
Nodes: White circle – chance node. Black circle – terminal node (death from any cause). Arrow - Markov node

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[184, 186]. Appendix 10.11 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 Section 6.1).

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 three 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 $exp(-1.823 + 0.5*0.2044^2) = 0.165$ per year (Appendix 10.12). 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.[187] Therefore the decision model assumes the same withdrawal rates for all biologics. Appendix 10.12 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.[172] These scenarios are explained in more detail in Appendix 10.11. The current model is informed by the expert opinion elicitation exercise conducted with five experts, described in Appendix 10.11. 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 natural history) in sensitivity analyses.

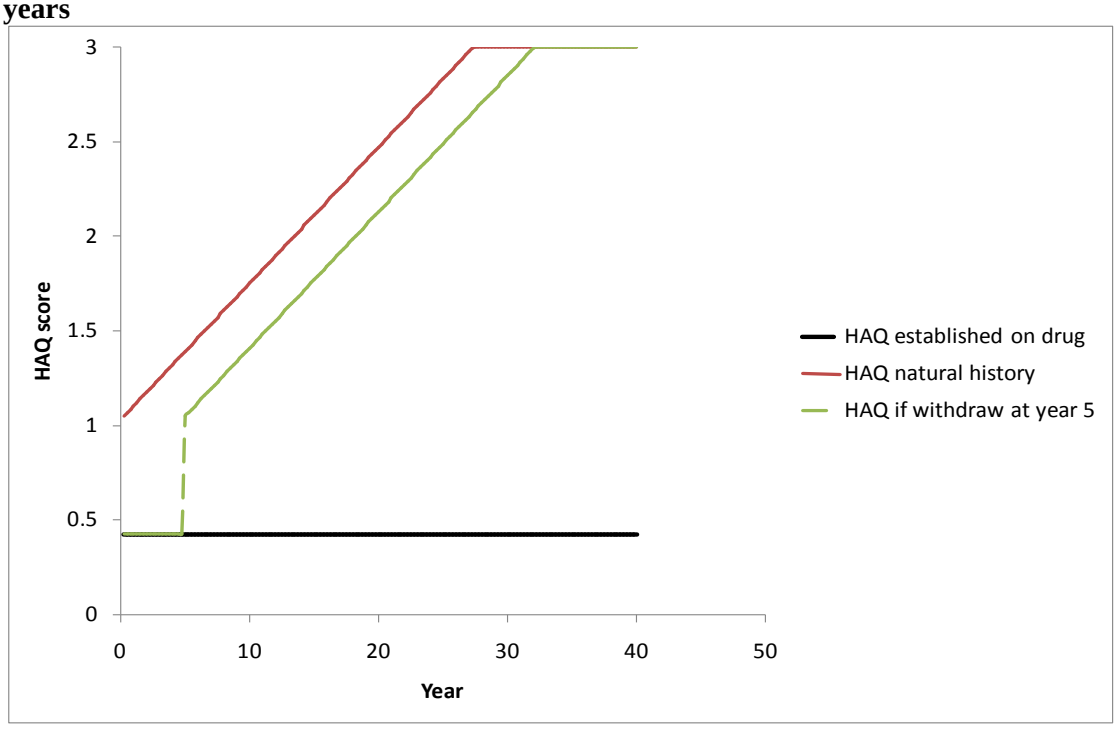
Outcomes for patients on palliative care

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 NOAR register (see details in Appendix 10.14).

Illustration of progression of HAQ in the model

Figure 6.2 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 this scenario ('rebound equal to initial gain') the five-year delay in progression obtained while on biologic drugs is permanently maintained after withdrawal.

Figure 6.2: 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

Utility

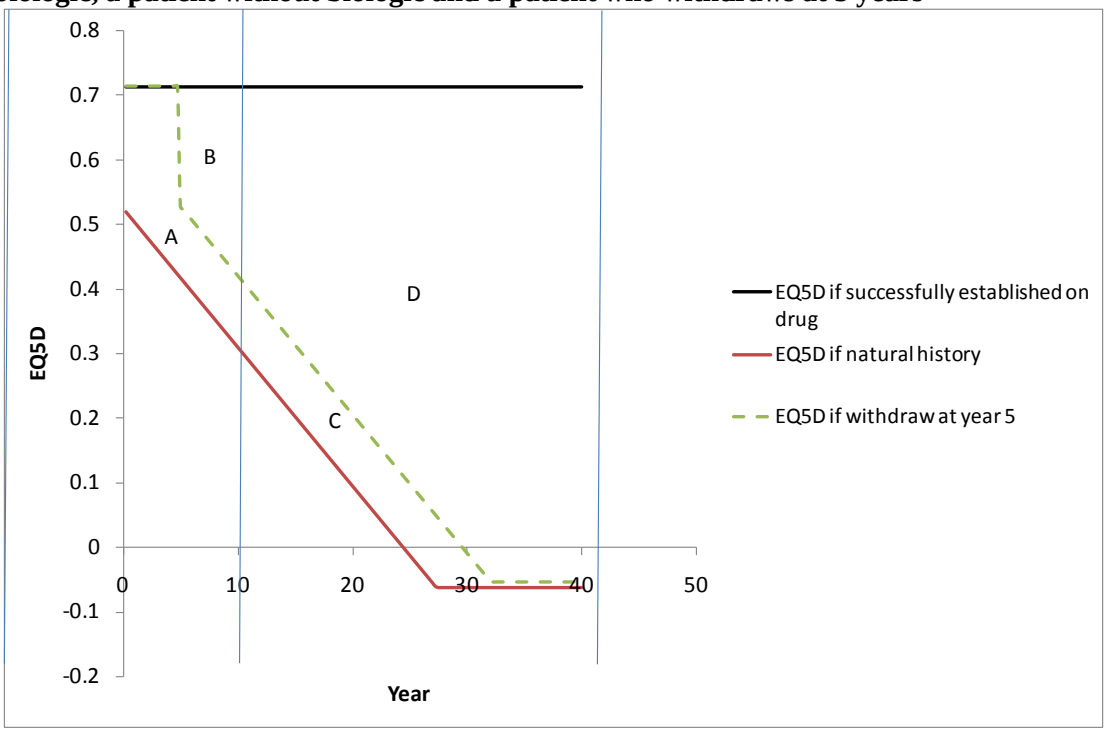
Health utility is measured as a function of HAQ and PASI. This relationship was estimated from analyses provided by the manufacturers, who carried out linear regressions of EQ5D utility versus HAQ and PASI in participants in key RCTs (Appendix 10.17). The base-case utility function is:

Expected utility = 0.897 – 0.298 x HAQ -0.004 x PASI
(SE) (0.006) (0.006) (0.0003)

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

Figure 6.3 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 (Figure 6.1 and Appendix 10.10). 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 which is less than zero, 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 natural history. The area between these curves (area 'A+C' in Figure 6.3) represents the difference in lifetime QALYs between a patient who withdraws at 5 years and a patient who never uses biologic therapy.

Figure 6.3: Illustration of utility (HRQOL) of a patient successfully maintained on biologic, a patient without biologic and a patient who withdraws at 5 years



Note: EQ5D utility takes a maximum value of one, indicating full health. Values less than zero correspond to health states that are considered worse than death by the general population

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 biologic therapy at 10 years, and all gains in HAQ with respect to natural history are lost at this point[172]. Figure 6.3 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 natural history, is area A+B+C+D. However, if is assumed that treatment effects only last 10 years, the difference in QALYs over 10 years between being on a biologic and natural history is only area A+B. For a patient who withdraws from a biologic at 5 years, the difference in lifetime QALYs compared with natural history 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 (BMA 2008[66]) (Appendix 10.13). The base-case assumes that vial sharing is not permitted.

Health care costs increase with severity of both arthritis[37] and psoriasis[38]. 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 (Kobelt 2002[42, 188]) (Appendix 10.15). 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[189] and a UK RCT[190]. No UK studies based on prospective individual patient data 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 (Hartman et al [191]) (Appendix 10.16).

All cause mortality

All cause mortality was estimated from UK life tables. A Gompertz function was fitted to these data (Appendix 10.19). The base-case uses a published estimate of the additional mortality risk in PsA .[30] The effect of biologics on mortality in PsA is uncertain. The US VA study of methotrexate in psoriasis and RA patients found that MTX was associated with significantly reduced incidence of vascular disease[192]. Long-term control of chronic inflammation may reduce mortality. However, biologics might increase other mortality risks. The decision model assumes 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 PsA patients with baseline HAQ of 1.05, the mean of HAQ across the RCTs (Table 5.1), 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 BSR biologics register[184]
- No skin involvement, with PASI of zero. Clinical opinion suggests 50% of PsA patients starting biologics in clinical practice would have mild or no skin involvement (Ian Bruce, personal communication 20 November 2009)

- A baseline PASI of 12.5, corresponding to moderate-to-severe psoriasis[193, 194]. Clinical opinion suggests 25% of PsA patients starting biologics in clinical practice would have a baseline PASI greater than 10 (Ian Bruce, personal communication 20 November 2009)

The review described in Section 5 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 sub-groups in baseline severity.

The base-case model assumes patients have failed at least two DMARDS but are naïve 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 2.1-3.4). 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 (1.9-2.9)[195]. Appendix 10.20 describes how these data were used to estimate the probability of initial response and later withdrawal for biologic therapies used as second line.

Table 6.3. 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 5.1)
Baseline PASI	PASI0	7.5			Clinical opinion
Baseline age	Age	47			Mean of RCTs (Table 5.1)

Description	**Variable name**	**Mean**	**SE**		**Source / appendix**
Model time horizon years	Years	40			Clinical opinion
Discount rate (per year)	r	0.035			[182]
Utility function intercept	h0	0.897	0.006		A10.17
Change in utility for 1 unit change in HAQ	h1	-0.298	0.006		A10.17
Change in utility for 1 unit change in PASI	h2	-0.004	0.0003		A10.17
Interaction term HAQ PASI	h3	0	10xE-5		A10.17
Cost function intercept (per 3 month period)	c0	233			A10.15
Change in cost for 1 unit change in HAQ	c1	187	21		Kobelt[42]A10. 15
3 month cost for mild-to-moderate psoriasis if uncontrolled by biologics	c2.1	198	9		Ref costs[189] A10.16
3 month cost for psoriasis in remission	c2.2	16	1		Hartman [191] A10.16
Change in HAQ while on treatment per 3 month period	HAQ1.d	0	0.02		Experts A10.11
Change in HAQ while not on treatment per 3 month period	HAQ1.w	0.018	0.007		NOAR A10.14
Rebound in HAQ in 3m after withdrawal (compared to HAQ at baseline) (Zero means 'rebound equal to initial gain')	loss.w	0	0.3		Experts A10.11
Intercept of regression of log-mortality versus age in men	ln.R.g.m	-10.25	0.046		England and Wales life table/ A10.19
Intercept of regression of log-mortality versus 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/A 10.12
Probability of PsARC response on placebo	p.psarc.plac	0.249	0.0384		Section 5.2
Change in HAQ given a PsARC response on placebo	HAQ.resp.plac	-0.218	0.0465		
Probability of PASI 50 response on placebo	p.pasi.50.plac	0.130	0.021		Section 5.2
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		
Standardised mortality ratio for PsA vs general population	SMRmen	1.65			[30] /A10.19
	SMRwomen	1.59			
generalisability of trial (1=no, 2 = yes)	plac.effect	1			A10.9
rules on continuation (1 - 5)	continue	1			BSR & BAD
		Etan	Inflix	Adal	
Cost of drugs (first 3 months)	c.drug1	2317	5523	2317	BSR/A 10.13

Description	Variable name	Mean	SE		Source / appendix
Cost of drugs for months 4-6	c.drug2	2150	3649	2150	
Cost of drugs, subsequent three months	c.drug3	2149	2965	2149	
Probability of PsARC response on biologic	p.psarc	0.713	0.795	0.587	Section 5.2
	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	-0.185	-0.190	-0.064	Section 5.2
	HAQ.no.resp_SE	0.102	0.073	0.064	
Change in HAQ in first 3 months given PsARC response of biologic	HAQ.resp	-0.623	-0.652	-0.423	Section 5.2
	HAQ.resp_SE	0.095	0.072	0.061	
Probability of PASI 50 response on biologic	p.pasi.50	0.4026	0.9128	0.7383	Section 5.2
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 [52]/A 10.10
	rho_SE	0.112	0.112	0.112	

Analytic methods

The uncertainty in each parameter was represented using a probability distribution. The probabilities in Table 6.3 were assigned beta distributions. If $p \sim Beta(\alpha,\beta)$, then $\alpha = E(p)*E(p)*(1-E(p))/Var(p)$ and $\beta = E(p)*(1-E(p))*(1-E(p))/Var(p)$. 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 $a = E(x)*E(x)/Var(x)$ and $s = Var(x)/E(x)$. All other uncertain parameters were assigned normal distributions with the mean and SE shown in Table 6.3. Probabilistic sensitivity analysis was carried out using Monte Carlo simulation.

The results of the model are presented in two ways. Firstly, mean lifetime costs and QALYs for the three strategies are reported and their cost-effectiveness compared, estimating incremental cost-effectiveness ratios (ICERs) using standard decision rules[196]. 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 less than £20,000 per QALY, and less likely to be considered cost-effective if the ICER were greater than £30,000 per QALY[182] . Secondly, 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.

6.2.2 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 Section 5.2.2, and an estimate of the correlation between PsARC and PAS I75 outcomes in biologic therapy from an RCT[52], 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 6.4).

Table 6.4. The probabilities of PsARC and PASI 75 responses at 3 months

Positive correlation

Response	Etanercept	Infliximab	Adalimumab
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)

Response	Etanercept	Infliximab	Adalimumab
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

Results of the base-case cost-effectiveness analysis

Table 6.5 Results of the base-case analysis

Strategy	QALY	Cost £	Inc QALY	Inc cost	ICER	PCE 20K	PCE 30K
N	5.241	42205				0.414	0.282
A	6.642	66408	1.401	24202	Ex dom	0.044	0.020
E	7.115	72172	0.473	5763	15986	0.524	0.566
I	7.430	89107	0.315	16935	53750	0.018	0.132

PCE 20K/30K: Probability that the treatment is cost-effective at a threshold of £20,000/£30,000 per QALY
ICER: Incremental cost-effectiveness ratio. QALY: Quality-Adjusted Life Year
N: Palliative care, A: Adalimumab, E:Etanercept, I:Infliximab
Ex dom: Extenedly dominated

The results of the base-case cost-effectiveness analysis are shown in Table 6.5, and univariate sensitivity analyses in Table 6.6. The base-case analysis suggests the 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 ICER of etanercept compared with palliative care is about £16,000 and the ICER of infliximab compared with etanercept is about £54,000 per QALY. Of the three biologic therapies, etanercept has the highest probability of being cost-effective at a threshold between £20,000 and £30,000 per QALY. Etanercept is the most cost-effective strategy in 52% of simulations of the base-case model at a threshold ICER of £20,000 and in 57% of simulations at a threshold of £30,000 per QALY.

Adalimumab is extendedly dominated by palliative care and etanercept. This means that it would be more cost-effective to treat a proportion of the population with etanercept than all the population with adalimumab. The expected discounted QALYs per patient using adalimumab are 6.64 and the expected total lifetime costs per patient are £66,000. However, if 81% of the population used etanercept (and the remainder offered only palliative care) then the expected total QALYs per patient would be 6.75 (5.42 x 0.19 + 7.12 x 0.81) while the expected total costs per patient would be the same as adalimumab (£42,000x0.19 + £72,000x0.81=£66,000). The probability that adalimumab is the most cost-effective strategy is 0.04 at a threshold ICER of £20,000 and 0.02 if the threshold ICER is £30,000 per QALY.

Expected QALYs are low in this model. The total lifetime discounted health associated with palliative care is about 5.24 QALYs. This is because the base-case scenario assumes that utility declines fairly rapidly in patients with uncontrolled arthritis, and may be less than zero in later years (Figure 6.3). For comparison, if HAQ and PASI could be reduced to zero for the complete time horizon of the model (40 years), the model predicts that this cohort would expect 15 quality-adjusted life years, given the rate of mortality, the intercept of the utility

function and the discount rate. Figure 6.5 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 6.4 partitions the total lifetime discounted health care costs of the strategies between costs associated with the acquisition, monitoring and administration cost of the biologic drugs, the cost savings associated with treating arthritis (that is, the reduction in HAQ score), and the cost savings associated with treating psoriasis (that is, 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, of etanercept is about £33,000 and of adalimumab is about £27,000. These prescribing costs are much greater than any offset health care cost savings elsewhere. Infliximab is associated with 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.

Figure 6.4. Lifetime discounted costs of biologic drugs, and cost savings for arthritis and psoriasis, relative to non-biologic treatments for PsA

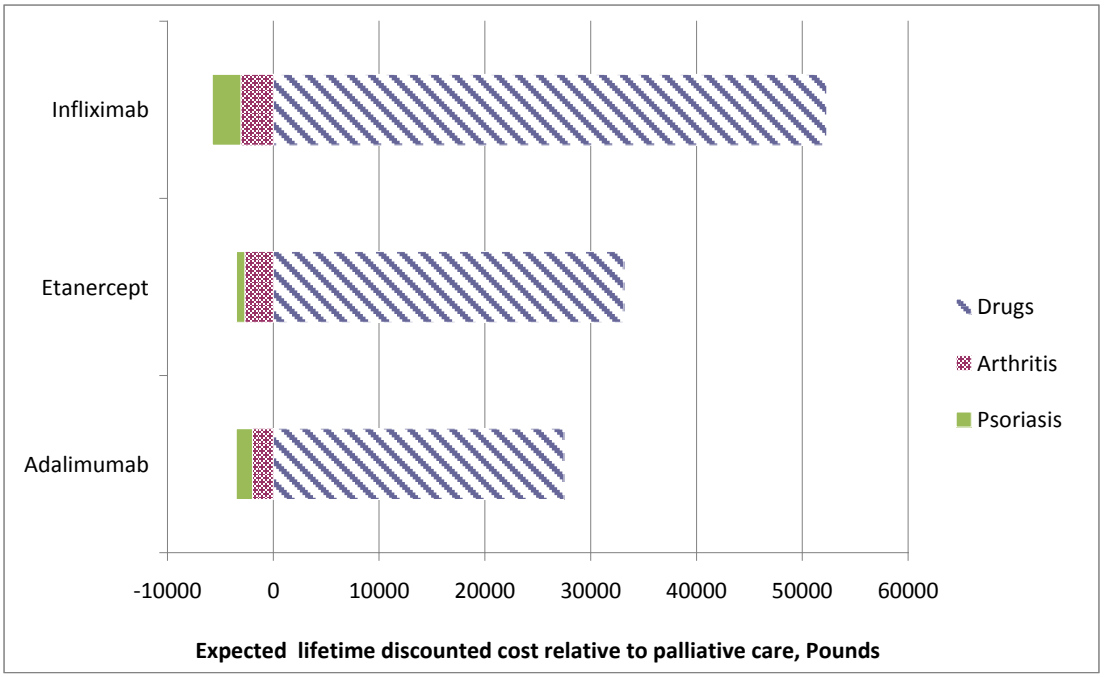


Figure 6.5. Gains in lifetime discounted QALYs associated with treating arthritis and psoriasis in PsA with biologic therapies, relative to palliative care

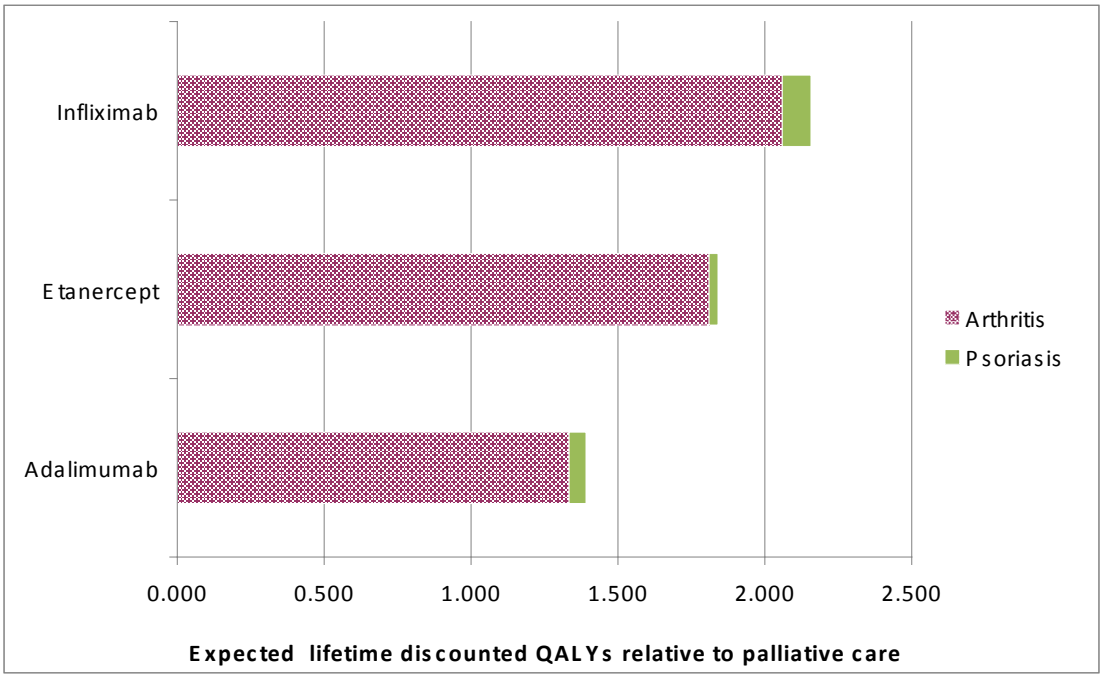


Table 6.6 Univariate sensitivity analyses

Scenario	Description	Trt	QALY	Cost £	ICER	p.20	p.30
1	Base-case	N	5.241	42205		0.414	0.282
1		A	6.642	66408	Ex dom	0.044	0.020
1		E	7.115	72172	15986	0.524	0.566
1		I	7.430	89107	53750	0.018	0.132
2	Rebound in HAQ is small after withdrawal (base-case =initial gain)	N	5.241	42205		0.204	0.112
2		A	7.227	65559	Ex dom	0.034	0.024
2		E	7.830	71138	11174	0.712	0.616
2		I	8.231	87949	41946	0.050	0.248
3	Rapid worsening in HAQ with no treatment (upper 95% of CI)	N	3.346	44423		0.316	0.176
3		A	4.974	68497	Ex dom	0.038	0.024
3		E	5.503	74237	13824	0.614	0.638
3		I	5.851	91211	48696	0.032	0.162
4	Log-PASI utility function (Abbott[174])(Base-case linear)	N	4.641	42205		0.408	0.272
4		A	6.075	66408	Ex dom	0.072	0.040
4		E	6.512	72172	16014	0.496	0.506
4		I	6.902	89107	43516	0.024	0.182
5	No correlation between PASI 75 and PsARC (base-case = 0.4)	N	5.241	42205		0.416	0.284
5		A	6.633	66741	Ex dom	0.036	0.016
5		E	7.111	72323	16106	0.530	0.570
5		I	7.425	89306	53968	0.018	0.130
6	RCT results fully generalisable to clinical practice (no adjustment for placebo effect)	N	5.241	42205		0.390	0.254
6		A	6.694	66339	Ex dom	0.044	0.030

Scenario	Description	Trt	QALY	Cost £	ICER	p.20	p.30
6		E	7.175	72091	15450	0.548	0.584
6		I	7.496	89019	52752	0.018	0.132
9	Exponential HAQ-cost function (Abbott [174])(base-case linear)	N	5.241	62036		0.342	0.240
9		A	6.642	78915	Ex dom	0.036	0.026
9		E	7.115	82756	11053	0.570	0.550
9		I	7.430	98643	50423	0.052	0.184
12	Inpatient treatment for uncontrolled psoriasis	N	5.241	151513		0.234	0.162
12		A	6.642	162995	8192	0.174	0.056
12		I	7.430	175719	16146	0.548	0.718
12		E	7.115	175778	Dominated	0.044	0.064
13	Cost per 3 month per 1 unit change in HAQ is £183 (US data)[43] (Base-case £103)	N	5.241	52405		0.390	0.270
13		A	6.642	75133	Ex dom	0.040	0.024
13		E	7.115	80344	14904	0.548	0.566
13		I	7.430	97007	52887	0.022	0.140
14	Change in utility per 1 unit change in HAQ is -0.45 (Wyeth[152]) (base-case -0.29)	N	0.939	42205		0.286	0.184
14		A	2.992	66408	Ex dom	0.012	0.008
14		E	3.755	72172	10644	0.598	0.556
14		I	4.132	89107	44881	0.104	0.252
15	HAQ improves while on drug (lower 95% of CI) (base-case no change)	N	5.241	42205		0.038	0.004
15		A	7.872	64586	Ex dom	0.072	0.034
15		E	8.553	70050	8405	0.800	0.622
15		I	9.026	86751	35367	0.090	0.340
16	High rate of withdrawal (upper 95% of CI)	N	5.241	42205		0.414	0.284
16		A	6.364	60416	Ex dom	0.040	0.022
16		E	6.739	64608	14955	0.524	0.560
16		I	6.986	77962	54033	0.022	0.134
17	Low rate of withdrawal (lower 95% of CI)	N	5.241	42205		0.424	0.282
17		A	6.951	73662	Ex dom	0.044	0.028
17		E	7.533	81331	17068	0.522	0.572
17		I	7.925	102588	54207	0.010	0.118
18	All treatments have the same probability of PsARC response at 3 months	N	5.251	41280		0.452	0.296
18		A	7.073	74072	Ex dom	0.114	0.124
18		E	7.264	74985	16741	0.434	0.578
18		I	7.337	88157	181439	0.000	0.002
19	All treatments have the same probability of psoriasis responses (PASI 50, 75 and 90) at 3 months	N	5.204	41651		0.386	0.276
19		A	6.628	65581	Ex dom	0.010	0.012
19		E	7.135	70092	14731	0.600	0.650
19		I	7.365	88464	80055	0.004	0.062
20	Cost of drugs as in Wyeth submission[152]	N	5.241	42205		0.400	0.270
20		A	6.642	65835	Ex dom	0.044	0.040
20		E	7.115	71476	15615	0.548	0.632
20		I	7.430	92771	67587	0.008	0.058
22	All biologics have the same change in	N	5.241	42205		0.392	0.278

Scenario	Description	Trt	QALY	Cost £	ICER	p.20	p.30
22	HAQ at 3 months for a PsARC responder	A	6.766	66226	15747	0.198	0.170
22		E	7.070	72239	19794	0.400	0.470
22		I	7.347	89230	61368	0.010	0.082
23	3 vials of infliximab (base-case: 4 vials)	N	5.241	42205		0.400	0.260
23		A	6.642	66408	Ex dom	0.004	0.000
23		E	7.115	72172	12183	0.146	0.146
23		I	7.430	77044	15911	0.450	0.594
26	Rebound to natural history after withdrawal (Base-case: rebound to initial gain)	N	5.241	42205		0.958	0.572
26		A	5.887	67513	Ex dom	0.002	0.018
26		E	6.188	73528	33057	0.040	0.408
26		I	6.395	90621	82777	0.000	0.002
31	No costs of psoriasis (base-case: UK data[189, 190])	N	5.241	28933		0.420	0.288
31		A	6.642	54556	Ex dom	0.022	0.014
31		E	7.115	59534	16325	0.548	0.606
31		I	7.430	78368	59777	0.010	0.092
32	Schering-Plough estimates of cost per PASI point excluding phototherapy[175]	N	5.241	55499		0.398	0.266
32		A	6.642	78255	Ex dom	0.066	0.032
32		E	7.115	84565	15505	0.514	0.536
32		I	7.430	100079	49240	0.022	0.166
33	Schering-Plough estimates of cost per PASI point including phototherapy[175]	N	5.241	112643		0.332	0.228
33		A	6.642	129230	11836	0.164	0.054
33		E	7.115	138404	19394	0.300	0.292
33		I	7.430	146778	26578	0.204	0.426
34	The effectiveness of biologic therapy lasts no longer than 10 years, compared with palliative care	N	5.241	42205		0.794	0.456
34		A	5.917	64136	Ex dom	0.012	0.028
34		E	6.211	69270	27882	0.194	0.506
34		I	6.410	84468	76510	0.000	0.010

P.20/P.30: Probability that the treatment is cost-effective at a threshold of £20,000/£30,000 per QALY
ICER: Incremental cost-effectiveness ratio. QALY: Quality-Adjusted Life Year. Ex dom: Extended-dominated.
N: Palliative care, A:Adalimumab, E:Etanercept, I:Infliximab

Results of sensitivity analyses

Table 6.6 shows the results of the univariate sensitivity analyses. Table 6.7 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 or more is unlikely to be accepted.

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.

- A patient who does not respond for psoriasis, or does not use biologic therapy, undergoes annual inpatient psoriasis treatment rather than annual UVB treatment.
- The higher cost per PASI point (including phototherapy) from the Schering-Plough[175] model 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 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.
- HAQ rebounds after withdrawal from biologic to natural history rather than to initial gain.
- Biologic treatment becomes ineffective (relative to no treatment) after 10 years.

The ICER of infliximab falls below £30,000 per QALY in any of the following univariate sensitivity analyses, assuming 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 3 vials rather than 4 vials per administration.
- The higher cost per PASI point (including phototherapy) from the Schering-Plough[175] model are used

No biologic appears cost-effective at a threshold of £30,000 per QALY if rebound of HAQ is to natural history, rather than initial gain. In the scenerio where treatment only remains effective for up to 10 years, the ICER for etanercept versus palliative care is £28,000 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 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 6.7. Cost-effectiveness of the strategies under different scenarios

#	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[174])(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 [174])(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)[43] (Base-case £103)	Ex Dom	<20k	>30k
14	Change in utility per 1 unit change in HAQ is -0.45 (Wyeth[152]) (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	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[152]	Ex Dom	<20k	>30k
22	All biologics have the same change in HAQ at 3 months for a PsARC responder	<20k	<20k	>30k
23	3 vials of infliximab (base-case: 4 vials)	Ex Dom	<20k	<20k
26	Rebound to natural history 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 of cost per PASI point without phototherapy[175]	Ex Dom	<20k	>30k
33	Schering-Plough estimates of cost per PASI point with phototherapy[175]	<20k	<20k	20k-30k
34	The effectiveness of biologic therapy lasts no longer than 10 years, compared with palliative care	Ex Dom	20k-30k	>30k

Key: <20k: Mean incremental cost-effectiveness ratio is less than £20,000 per QALY.
20-30k: Mean ICER is between £20,000- £30,000 per QALY. Ex Dom: Extended dominated. Dom: Dominated

Results of subgroup analyses

Table 6.8 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 base-line 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 £76,000 per QALY. If baseline PASI were moderate-to-severe (12.5 instead of 7.5) the ICER of adalimumab versus palliative care would be less than £15,000 per QALY, the ICER of etanercept versus adalimumab would be around £16,000 per QALY and the ICER of infliximab versus etanercept would be about £36,000 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, that is, treatment is withdrawn from patients who fail to achieve the PsARC response within 3 months of treatment. Alternative decision rules (see Box 6.2) 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 etanercept is the biologic with the highest 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 6.8 Sub-group analyses

	Description		QALY	Cost £	ICER	PCE20k	PCE30k
10	Baseline HAQ 1.8 (BSR register[184]) (Base-case 1.05)	N	2.132	46703		0.458	0.314
10		A	3.439	71044	Ex dom	0.040	0.016
10		E	3.902	76824	17023	0.482	0.548
10		I	4.209	93770	55099	0.020	0.122
11	Baseline PASI 12.5 (Base-case 7.5)	N	4.879	66871		0.374	0.256
11		A	6.320	88203	14809	0.110	0.056
11		E	6.775	95553	16154	0.432	0.410
11		I	7.135	108651	36364	0.084	0.278
7	Baseline PASI 12.5, and continue after 3 months only if respond to *both* PsARC & PASI 75 (base-case PsARC only)	N	4.879	66871		0.354	0.212
7		E	5.398	74172	Ex dom	0.050	0.078
7		A	5.855	80199	13660	0.232	0.078
7		I	6.832	102369	22703	0.364	0.632
8	Baseline PASI 12.5, and continue after 3 months if respond to *either* PsARC *or* PASI 75	N	4.879	66871		0.374	0.258
8		A	6.514	91119	14829	0.198	0.072
8		E	6.779	95619	17007	0.326	0.296
8		I	7.312	112560	31794	0.102	0.374
21	Baseline PASI 12.5, and annual inpatient	N	4.879	171901		0.190	0.084

21	treatment for uncontrolled psoriasis (Base-case UVB)	A	6.320	181009	6323	0.138	0.056
21		I	7.135	191873	13327	0.660	0.832
21		E	6.775	195112		0.012	0.028
30	Baseline PASI zero (base-case 7.5)	N	5.783	28933		0.424	0.306
30		A	7.126	54556	Ex dom	0.016	0.014
30		E	7.626	59534	16603	0.552	0.616
30		I	7.873	78368	76132	0.008	0.064

Table 6.9 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 PsA patients with mild-to-moderate skin disease. The incremental cost-effectiveness ratios depend on which drug was used as first-line therapy, and is therefore ineligible for use as second-line.

- For patients who failed adalimumab as first line for inefficacy, etanercept has an ICER of less than £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 less than £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 less than £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

Table 6.9. Costs and QALYs of biologics used as second-line therapy for patients with mild-to-moderate skin disease if first biologic fails

Scenario	Description	Trt	QALY	Cost	ICER assuming I was used 1st line	ICER assuming E was used 1st line	ICER assuming A was used 1st line
24	Second –line biologic if first failed for inefficacy	N	5.241	42205			
24		A	5.889	53349	Ex dom	17182	N/A
24		E	6.234	57418	15309	N/A	15309
24		I	6.512	69152	N/A	25363	42220
25	Second –line biologic if first failed for adverse events	N	5.241	42205			
25		A	6.334	59809	Ex dom	16103	N/A
25		E	6.699	63846	11067	N/A	11067
25		I	6.938	76842	N/A	28176	54218

NA. Therapy is not available for second-line use as failed in 1st line

6.3 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 section 6.2). A full description of the three industry models is provided in Appendix 10.7 and a critique is detailed in Appendix 10.8.

6.3.1 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 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 to DMARDs is £29,827. Etanercept is dominated by adalimumab and infliximab has an ICER of £199,596 compared to adalimumab.

Schering-Plough's base-case 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, psoriasis patients and non-psoriasis patients. The results show that palliative care is the strategy associated with the lowest QALYs in all base-case scenarios (5.79 to 6.68 depending on the group of patients). Infliximab is the most effective strategy for all PsA patients 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 to adalimumab) assuming a patient weight of 70 or 80kg. For a 60kg patient etanercept has an ICER of £12,432, compared to adalimumab, for patients without psoriasis. Infliximab dominates etanercept for psoriasis patients and all patients.

[redacted]

[redacted]Only results for all patients are presented in the base-case.

[redacted]

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 show that infliximab is the most effective treatment (QALYs = 7.43), followed by etanercept (QALYs = 7.11), then adalimumab (QALYs = 6.64). Infliximab is also the most costly treatment (£89,107), followed by etanercept (£72,172), then adalimumab (£66,408). The ICER of etanercept compared with palliative care is £15,986. Adalimumab is extendedly dominated. The ICER for infliximab compared with etanercept is £53,750 per QALY. Results are also presented for other baseline sub-groups: HAQ = 1.8, PASI = 0 and PASI = 12.5.

6.3.2 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 10.8. Table 6.10 shows the key features of each of the models. A full description of the three industry models is provided in Appendix 10.7.

Table 6.10: Comparison of the key features of each of the models

	Wyeth	**Schering-Plough**	**Abbott**	**Current York model**
Comparators	[redacted]	Palliative care	Unspecified DMARD	Palliative care
Model structure	[redacted]	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	[redacted]	Homogenous cohort Baseline HAQ = 1.14 Baseline PASI = 11 Proportion with psoriasis = 66%	Heterogeneous cohort (first order simulation) Baseline HAQ = 1.3 Baseline PASI = 6.9 Proportion with psoriasis = 40%	Homogenous cohort Baseline HAQ = 1.05 Baseline PASI = 7.5
Adjustment for placebo effect	[redacted]	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	[redacted]	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 data)	Four regressions specified: 1. Joint distribution of PsARC and ACR response (<20, ACR 20-50, etc) at12 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)	[redacted]	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

	Wyeth	**Schering-Plough**	**Abbott**	**Current York model**
Initial change in HAQ for responders and non responders	[redacted] 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, & whether on any biologic (From ADEPT 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
HAQ progression while on biologic and responder	[redacted]	Assumes a HAQ improvement for first year while on biologics, then zero	Worsening by 0.0005 per year (Bath dataset)	Zero
HAQ progression when on DMARD	[redacted]	Not applicable	0.024 per year (Leeds)	Not applicable
HAQ progression while on therapy and ACR <20	[redacted]	Not applicable	0.066 per year (Leeds)	Not applicable
HAQ progression while not on therapy	[redacted]	0.071 per year (Leeds)	0.066 per year (Leeds)	0.072 per year (NOAR)
Initial change in psoriasis on biologic	[redacted]	PASI change from baseline to 12w 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 probability density function.
Psoriasis progression on biologic	[redacted]	Zero	Zero	Zero
Psoriasis progression not on biologic	[redacted]	Zero	Zero	Zero
HAQ rebound when stopping therapy	[redacted]	To initial gain OR to natural history	To initial gain	To initial gain & using elicited values in sensitivity analysis

	Wyeth	**Schering-Plough**	**Abbott**	**Current York model**
Psoriasis rebound when stopping therapy	[redacted]	To initial gain	To initial gain	To initial gain
Withdrawal rate-biologics	[redacted]	11% per year (Geborek) per year	Average withdrawal rate across all biologics (Saad). 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	[redacted]	Not applicable	Weibull distribution used. Unclear how this was specified as only 1 data point reported (Malesci[197]).	Not applicable
Utility (HRQOL)	[redacted]	Predicted from HAQ and PASI, HAQ-squared and PASI-squared, using regression, (no interaction term) (GOREVEAL data)	Predicted from HAQ and PASI (no interaction term) (ADEPT)	Wyeth additional utility regression as the base-case and other functions as sensitivity analyses.
Mortality	[redacted]	Same rate for all treatments and no treatment (Wong)	Same rate for all treatments and no treatment (Wong)	Same rate for all treatments and no treatment (Wong)
Costs of treatments	[redacted]	Results shown assuming 3 vials of infliximab (60kg), 3.5 vials (and 4 vials (80kg)	Assumes no wastage of Infliximab (4 vials, 80kg weight)	Assumes no vial sharing (4 vials, 70-80kg weight) in base-case. 3 vials for a 60kg patients considered in sensitivity analysis
Costs of startup, admin and monitoring	[redacted]	From York model	BSR recommendations	BSR recommendations validated by clinical opinion
Cost depending on HAQ	[redacted]	RA dataset (Kobelt)	Norfolk NOAR	RA dataset (Kobelt) in base-case
Cost of psoriasis	[redacted]	Physician survey	Physician survey	For mild-moderate psoriasis: Poyner et al
Patient Subgroups	[redacted]	With psoriasis; Without psoriasis	Varying severity of HAQ and PASI at baseline	Varying severity of HAQ and PASI at baseline

Choice of comparator. The choice of comparator is crucial in determining the relative cost-effectiveness of biologics. In comparing biologics to DMARDs whilst using the effectiveness estimates of placebo from randomised trials (i.e. assume DMARD cost and placebo effectiveness), Wyeth and Schering-Plough are likely to 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 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 and [redacted] 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, 2004[198]. This approach effectively averages over the heterogeneity between patients. In contrast, the Schering-Plough 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 homogenous 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 the baseline HAQ and PASI are both low at 0.69 and 3.39 respectively. These are higher in the Abbott model at 1.3 for HAQ and 6.9 for PASI. In the Schering-Plough 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 model also includes the highest proportion of patients with psoriasis at 66%, however these are ran as a separate sub-group 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 the average observed in the RCTs (Table 5.1). The current York model also run a series of scenarios to vary base-case HAQ and PASI scores (Tables 6.6 and 6.8). For patients with a high baseline PASI (12.5) adalimumab is no longer extendedly dominated (ICER is £14,809 compared to palliative care). The ICER for etanercept is similar to the basecase at £16,154 compared to adalimumab and the ICER for infliximab falls to £36,364 compared to etanercept. These changes in ICERs are because of the differences in

PASI response rates between the different 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 £16,603 compared to palliative care. For patients with a higher baseline HAQ (1.8) the ICER for etanercept increases to £17,023 compared to 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 5.19). Schering-Plough, Abbott and the York model predict that infliximab is the most effective drug for PsARC response, then etanercept, then adalimumab. Wyeth predict etanercept is the most effective, then infliximab, then adalimumab (See Table 5.21). These differences have a substantial effect on the results of the economic analysis. The sensitivity analysis shown in Table 6.6 shows that by assuming that all treatments have the same probability of psoriasis responses (PASI 50, 75 and 90) at 3 months, the ICER for etanercept falls to £14,731, adalimumab remains extendedly dominated and the ICER for infliximab increases to over £80,000. This is because infliximab had a much higher probability of skin response in the base-case. When the same PASI response is applied to all treatments this is no longer a driver for the differences in cost-effectiveness between treatments. 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 to etanercept to over £100,000. This is because infliximab was associated with a much higher PsARC response in the base-case (see Table 6.4)

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 [redacted] 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. Another rule might be to only allow patients to continue if they respond to both PsARC and PASI 75. Table 6.6 shows that in this scenario etanercept is extendedly dominated, adalimumab has an ICER of £13,660 compared to

palliative care and infliximab has an ICER of £22,703 compared to adalimumab. If patients are assumed to continue after 3 months if they respond to *either* PsARC or PASI 75 then etanercept is less cost-effective and adalimumab is no longer extendedly dominated. Infliximab is also assocated with a lower ICER than in the base-case (£31,794 compared to etanercept).

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[89] and the results of the evidence synthesis in Section 5.2 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 assumes that PsARC and PASI responses are independent (see Appendix 10.7 for further detail). The Schering-Plough model 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 [redacted] This is a strong assumption that is difficult to vary in sensitivity analysis, and Wyeth 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 6.6). The impact on the ICER for etanercept is, however, minimal 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 estimate HAQ from PsARC response and PASI. Abbott estimate HAQ from ACR response (assumed correlated with PsARC) and other clinical and demographic variables. Schering-Plough 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 and predicts HAQ by PsARC response and treatment, and this is estimated by the evidence synthesis model. Abbott 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 other predictive variables. ACR was assumed correlated with PsARC in the Abbott evidence synthesis (See Table 5.19). 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 evidence synthesis was very complex and made use of data from biologics that are not relevant to this appraisal.

[redacted] 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 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 6.6) 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 extenedly dominated and the ICER for etanercept increases to £19,794 compared to adalimumab. Thus, adalimumab appears more cost-effective and etanercept less cost-effective if HAQ is assumed the same for all biologics, after conditioning on PsARC response. This is because, in the base-case etanercept was associated with a much higher HAQ gain for a PsARC responder (-0.623) compared to adalimumab (-0.423). When the same HAQ gain is applied to all treatments this is no longer a driver for the differences in cost-effectiveness between treatments.

To determine the initial change in PASI the current York model and the Abbott model predict the initial 12 week (and 24 week for Abbott) 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. [redacted] Schering-Plough 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 the evidence syntheses predicted that infliximab is most effective for psoriasis response, then adalimumab, then etanercept (Table 5.23). [redacted]

[redacted] The sensitivity analysis shown in Table 6.6 shows that, by assuming that all treatments have the same probability of psoriasis responses (PASI 50, 75 and 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.

HAQ 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[199] data. As detailed in Appendix 10.14, however, the Leeds dataset does have some limitations. The current York model therefore uses data from patients enrolled in the NOAR (see Appendix 10.14) dataset 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 to 0.016 in Leeds dataset) 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 dataset to estimate withdrawals. Schering-Plough employs the same rates as used in the previous York model (0.11 per year from Geborek [200]. [redacted] and Abbott [redacted] All models assumed that withdrawal rates did not vary by treatment. However, the sensitivity analysis reported in Table 6.6 shows 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 10.20), 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 10.17) 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 6.6). Only the scenario where a higher estimate of the effect of a unit change in HAQ on utility is taken from the [redacted] has a discernible impact on the results. Etanercept is more cost-effective (ICER is £10,644 compared to palliative care) and the ICER for infliximab falls to £44,881.

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 10.8) and the number of laboratory tests required for monitoring patients. The costs attached to hospital visits also differed between models. In the Abbott model, 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 10.13). 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, £4386 in the Schering-Plough model, [redacted] and £5522 in the current York model. The sensitivity analysis in Table 6.6 shows the impact of varying drug costs in the current York model. Using the costs presented in the Wyeth submission in the York model (which are higher for infliximab (see Appendix 10.8) but lower for adalimumab and etanercept than the York estimates), increases the cost-effectiveness of etanercept and increases the ICER for infliximab

(£67,587). 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 and Schering-Plough also include health-service costs according to PASI scores. The costs associated with PASI score, in particular differ quite markedly (see Appendix 10.8). Abbott and Schering-Plough 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 6.6 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 reduces the ICER for etanercept to £11,053. 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 £16146 compared to adalimumab. This reflects the beneficial effect of infliximab in terms of reducing PASI score compared to 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 are used. In this situation the ICER for infliximab is £26,578. Other sensitivity analysis on costs dependant on HAQ and PASI had little impact on the model results.

6.3.2.1 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.

6.4 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 £16,000 per QALY and the ICER of infliximab versus etanercept is about £54,000 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 0.52 at a threshold of £20,000 per QALY and 0.56 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 natural history after withdrawal.
- Results are sensitive to assumptions about the prescription cost. If 3 vials of infliximab are required rather than 4, 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.

Cost-effectiveness also varies between different sub-groups of patients;

- For patients with PsA and moderate-to-severe skin disease, the ICER of adalimumab versus palliative care is about £15,000 per QALY, the ICER of etanercept versus adalimumab is about £16,000 per QALY and the ICER for infliximab versus etanercept is about £36,000 per QALY. For patients with PsA and negligible skin involvement, the ICER of etanercept versus palliative care is about £17,000 per QALY, and the ICER of

infliximab versus etanercept is about £76,000 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 sub-group 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 health-related quality of life than DLQI[193].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 Section 6.1)[172, 175]. Changes in HAQ may be more accurately predicted by other clinical and demographic variables, such as ACR and age. The Abbott model estimated a joint distribution of ACR and PsARC, and predicted HAQ from ACR responses[174]. 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 Section 6.1).

The base-case model assumes 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, sub-group 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. Data on the natural history of PsA without biologic therapy are from an observational study of rheumatoid-factor negative, inflammatory polyarthritis patients who have failed at least 2 DMARDS. These data should be considered with caution. However, it is unlikely relevant data could be obtained from randomised trials. 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, that is, 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. It is assumed that serious adverse events will lead to withdrawal. In practice there may be longer term consequences and costs, such as for cancers and infections that are not included in the model.

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 [171] 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[190]. 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[191].

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 (2007)[172] 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, but the current York model finds that adalimumab would not be cost-effective in this sub-group.

Abbott (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 calculated the 'average' cost-effectiveness of the biologics over all PsA patients, 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. Baseline PASI was varied in subgroup analyses in the Abbott model, though it is not clear if the proportion of the cohort who was assumed not to have psoriasis was also varied in these subgroup analyses. The York model estimated cost-effectiveness for particular cohorts with varying baseline severity of psoriasis and arthritis, or minimal psoriasis. Therefore the results of the Abbott model are not easily reconciled with the results of the York model as they relate to different patient groups. The York model found that for patients with PsA and mild-to-moderate psoriasis the adalimumab is extendedly dominated and is therefore unlikely to be the most cost-effective treatment. For PsA and moderate-to-severe psoriasis,the ICER for adalimumab versus palliative care is around £15,000 per QALY. At a threshold of £20,000 per QALY, however, etanercept is likely to be considered the most cost-effective treatment for this group (ICER for etanercept is around £16,000 compared to adalimumab).

Schering-Plough (the manufacturers of infliximab) found that infliximab was cost-effective for patients of 60 kg weight if vial sharing is allowed, or patients use 3 vials per administration. If vial sharing is not allowed or patients require 4 vials per administration then Schering-Plough concluded 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 (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 found that etanercept had the highest probability of PsARC response, whereas the York evidence synthesis (and those of the other manufacturers) found inflixamab to be the most effective for PsARC

- The assumption made by Wyeth that changes in HAQ are proportional to changes in PASI. This is a strong assumption and Wyeth did not provide any clinical justification to support it.

Despite the differences in data and model structure outlined in Section 6.3, the results of the York model are broadly consistent with those of Schering-Plough, taking account of assumptions about vial sharing. The results of the York model are difficult to compare with the Abbott model because they relate to different populations. The Wyeth model appears to have over-estimated the effectiveness of etanercept, in terms of PsARC response, and makes strong and arguably unjustified assumptions about the relationship between HAQ and PASI.

7 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 PsA patients receiving biologic therapy are managed by a rheumatologist. However, PsA patients 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 diease may need dual management of both specialties, though 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 intravenous 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, though 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 employed.

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

8 Discussion

8.1 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, though 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 £16,000 per QALY, the ICER of infliximab versus etanercept is about £54,000 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 0.52 at a threshold of £20,000 per QALY and 0.56 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

8.2 Strengths and limitations of the assessment

Strengths

We conducted a rigorous systematic review which 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 [159, 161]. Efforts were also made to identify

additional studies by hand-searching company submissions, clinical trial reports and reference lists of relevant publications. Compared to the previous review [169], 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 [55]. It is important to note that all the included trials were rated as 'good' quality using the pre-specified 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. Due 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 three 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 and 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 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 Section 5.2, 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 have therefore 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.

8.3 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 PsA patients 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 (i)For patients successfully maintained on treatment, biologics reduce symptoms and prevent the progression of arthritis.(ii) 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.

9 Conclusions

9.1 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 demonstrate 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 reductions 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 employed.
- 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, though 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 PsA patients 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 £5,000.

9.2 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 whilst 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 BSR Biologics Register) 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' quality of life, 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.

10 Appendices

10.1 Literature search strategies

Full details of all databases searched and search strategies are provided below.

The search strategy was designed for searching MEDLINE through the OvidSP interface and was adapted as appropriate for all other databases searched, taking into account differences in indexing terms and search syntax for each database.

Clinical effectiveness: search for RCTS

MEDLINE: OvidSP http://ovidsp.ovid.com/

The MEDLINE search covered the date range 1950 to May Week 5 2009 for adalimumab and 01 April 2004 to May Week 5 2009, using the search field 'ed: Entry Date', for etanercept and infliximab. The search was carried out on 09 June 2009 and identified 399 records.

The strategy employs the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE, sensitivity-maximizing version (lines 1-11).[201]

1.	randomized controlled trial.pt.	272711
2.	controlled clinical trial.pt.	79394
3.	randomized.ab.	182345
4.	placebo.ab.	112659
5.	drug therapy.fs.	1317603
6.	randomly.ab.	132262
7.	trial.ab.	189408
8.	groups.ab.	909284
9.	or/1-8	2406033
10.	(animals not (humans and animals)).sh.	3290537
11.	9 not 10	2040011
12.	Arthritis, Psoriatic/	2223
13.	(psoria$ adj2 (arthrit$ or arthropath$)).ti,ab.	3596
14.	12 or 13	4138
15.	(etanercept or enbrel).ti,ab,rn.	2085
16.	(infliximab or remicade).ti,ab,rn.	4715
17.	15 or 16	5890
18.	11 and 14 and 17	450
19.	(200404$ or 200405$ or 200406$ or 200407$ or 200408$ or 200409$ or 200410$ or 200411$ or 200412$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$).ed.	3555234
20.	18 and 19	356
21.	(adalimumab or humira or D2E7 or (D2 adj E7)).ti,ab,rn.	1161
22.	11 and 14 and 21	143
23.	20 or 22	399

MEDLINE In-Process: OvidSP http://ovidsp.ovid.com/

The MEDLINE In-Process search, database dated June 8 2009, was carried out on 09 June 2009 and identified five records.

The strategy employs the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE, sensitivity-maximizing version (lines 1-11).

1.	randomized controlled trial.pt.	387
2.	controlled clinical trial.pt.	40
3.	randomized.ab.	7406
4.	placebo.ab.	3160
5.	drug therapy.fs.	20
6.	randomly.ab.	8231
7.	trial.ab.	7527
8.	groups.ab.	42954
9.	or/1-8	56348
10.	(animals not (humans and animals)).sh.	8
11.	9 not 10	56346
12.	Arthritis, Psoriatic/	1
13.	(psoria$ adj2 (arthrit$ or arthropath$)).ti,ab.	125
14.	12 or 13	125
15.	(etanercept or enbrel).ti,ab,rn.	164
16.	(infliximab or remicade).ti,ab,rn.	287
17.	(adalimumab or humira or D2E7 or (D2 adj E7)).ti,ab,rn.	110
18.	or/15-17	438
19.	11 and 14 and 18	5

EMBASE: OvidSP http://ovidsp.ovid.com/

The EMBASE search covered the date range 1980 to 2009 Week 23 for adalimumab and 01 January 2004 to 2009 Week 23, using the search field 'em: Entry Week', for etanercept and infliximab. The search was carried out on 09 June 2009 and identified 369 records.

The strategy employs the Hedges Team best sensitivity strategy for detecting clinically sound treatment studies in EMBASE (lines 17-20).[202]

Note: A pragmatic approach was taken to reduce the number of irrelevant records retrieved and to negate the over indexing of records in EMBASE; EMTREE drug terms were focussed in this strategy.

1.	Psoriatic Arthritis/ 4225	
2.	(psoria$ adj2 (arthrit$ or arthropath$)).ti,ab.	3339
3.	1 or 2	5024
4.	*Etanercept/	1973
5.	(etanercept or enbrel).ti,ab.	2192
6.	*Infliximab/	3482
7.	(infliximab or remicade).ti,ab.	3991
8.	or/4-7	6134
9.	(2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$).em.	3193493
10.	8 and 9	4694
11.	*Adalimumab/	881
12.	(adalimumab or humira or D2E7 or (D2 adj E7)).ti,ab.	958
13.	11 or 12	1236
14.	3 and 10	500
15.	3 and 13	219
16.	14 or 15	561

17.	random$.tw.	399406
18.	clinical trial$.mp.	608378
19.	exp Health Care Quality/	802714
20.	or/17-19	1446048
21.	16 and 20	369

Cochrane Central Register of Controlled Trials (CENTRAL): The Cochrane Library http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME

Issue 2, 2009 of The Cochrane Library was searched to identify trials on CENTRAL. The etanercept and infliximab search covered the date range 2004 to 2009. The search for adalimumab had no date limits. The search was carried out on 09 June 2009 and identified 37 records.

#1	MeSH descriptor Arthritis, Psoriatic, this term only	99
#2	(psoria* NEAR/2 arthrit*) in Clinical Trials	132
#3	(psoria* NEAR/2 arthropath*) in Clinical Trials	6
#4	(#1 OR #2 OR #3)	199
#5	(etanercept or enbrel):ti,ab,kw, from 2004 to 2009 in Clinical Trials	184
#6	(infliximab or remicade):ti,ab,kw, from 2004 to 2009 in Clinical Trials	224
#7	(adalimumab or humira or D2E7 or (D2 adj E7)):ti,ab,kw in Clinical Trials 91	
#8	(#5 OR #6 OR #7)	579
#9	(#4 AND #8)	37

Science Citation Index: ISI Web of Knowledge http://wok.mimas.ac.uk

The Science Citation Index search covered the date range 1900 to 2009 for adalimumab and 2004 to 2009 for etanercept and infliximab. The search was carried out on 09 June 2009 and identified 302 records.

The strategy employs the terms used in the 2006 HTA report[74] to identify RCTs in the Science Citation Index (lines #1-7).

# 13	302	#10 or #12
Databases=SCI-EXPANDED Timespan=All Years		
# 12	108	#7 and #8 and #11
Databases=SCI-EXPANDED Timespan=All Years		
# 11	1,676	TS=(adalimumab or humira or D2E7 or "D2 E7")
Databases=SCI-EXPANDED Timespan=All Years		
# 10	275	#7 and #8 and #9
Databases=SCI-EXPANDED Timespan=2004-2009		
# 9	9,327	TS=(etanercept or enbrel or infliximab or remicade)
Databases=SCI-EXPANDED Timespan=All Years		
# 8	4,706	TS=((psoria* same arthrit*) or (psoria* same arthropath*))
Databases=SCI-EXPANDED Timespan=All Years		
# 7	>100,000	#5 not #6
Databases=SCI-EXPANDED Timespan= All Years		
# 6	>100,000	TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*)
Databases=SCI-EXPANDED Timespan=All Years		
# 5	>100,000	#1 or #2 or #3 or #4

Databases=SCI-EXPANDED Timespan=All Years
# 4 >100,000 TS=(placebo* or random* or control* or prospectiv* or volunteer*)
Databases=SCI-EXPANDED Timespan=All Years
# 3 >100,000 TS=(clinic* same trial*)
Databases=SCI-EXPANDED Timespan=All Years
# 2 >100,000 TS=((singl* or doubl* or trebl* or tripl*) SAME (blind* or mask*))
Databases=SCI-EXPANDED Timespan=All Years
# 1 >100,000 TS=((study or studies) SAME design*)
Databases=SCI-EXPANDED Timespan=All Years

Conference Proceedings Citation Index - Science (CPCI-S): ISI Web of Knowledge http://wok.mimas.ac.uk

The CPCI-S search covered the date range 1990 to 2009 for adalimumab and 2004 to 2009 for etanercept and infliximab. The search was carried out on 09 June 2009 and identified 37 records.

The strategy employs the terms used in the 2006 HTA report to identify RCTs in the CPCI-S (previously ISI Science and Technology Proceedings) (lines #1-7).

# 13 37 #10 or #12
Databases=CPCI-S Timespan=1990-2009
# 12 12 #7 and #8 and #11
Databases=CPCI-S Timespan=1990-2009
# 11 635 TS=(adalimumab or humira or D2E7 or "D2 E7")
Databases=CPCI-S Timespan=1990-2009
# 10 29 #7 and #8 and #9
Databases=CPCI-S Timespan=2004-2009
# 9 2,588 TS=(etanercept or enbrel or infliximab or remicade)
Databases=CPCI-S Timespan=1990-2009
# 8 797 TS=((psoria* same arthrit*) or (psoria* same arthropath*))
Databases=CPCI-S Timespan=1990-2009
# 7 >100,000 #5 not #6
Databases=CPCI-S Timespan=1990-2009
# 6 >100,000 TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats
or bovine or sheep or guinea*)
Databases=CPCI-S Timespan=1990-2009
# 5 >100,000 #1 or #2 or #3 or #4
Databases=CPCI-S Timespan=1990-2009
# 4 >100,000 TS=(placebo* or random* or control* or prospectiv* or volunteer*)
Databases=CPCI-S Timespan=1990-2009
# 3 22,210 TS=(clinic* same trial*)
Databases=CPCI-S Timespan=1990-2009
# 2 15,096 TS=((singl* or doubl* or trebl* or tripl*) SAME (blind* or mask*))
Databases=CPCI-S Timespan=1990-2009
# 1 >100,000 TS=((study or studies) SAME design*)
Databases=CPCI-S Timespan=1990-2009

ClinicalTrials.gov http://clinicaltrials.gov/

The ClinicalTrials.gov registry was searched for ongoing trials information. The search was carried out on 09 June 2009 and identified 27 studies.

Basic Search: *((psoriatic arthritis OR psoriatic arthropathy) AND (etanercept OR enbrel OR infliximab OR remicade OR adalimumab or humira or D2E7 or "D2 E7"))*

metaRegister of Controlled Trials (mRCT): Current Controlled Trials
http://controlled-trials.com/mrct

The mRCT was searched for ongoing trials information. The search was carried out on 10 June 2009 and identified 41 studies.

SEARCH FOR [all registers]: *((“psoriatic arthritis” OR “psoriatic arthropathy”) AND (etanercept OR enbrel OR infliximab OR remicade OR adalimumab or humira or D2E7 or "D2 E7"))*

Cost-effectiveness search

MEDLINE: OvidSP http://ovidsp.ovid.com/

The MEDLINE search covered the date range 1950 to June Week 1 2009 for adalimumab and 01 April 2004 to June Week 1 2009, using the search field ‘ed: Entry Date’, for etanercept and infliximab. The search was carried out on 11 June 2009 and identified 24 records.

The strategy employs the Centre for Reviews and Dissemination NHS EED strategy for identifying economic evaluations in MEDLINE (lines 13-39).[203]

1.	Arthritis, Psoriatic/	2225
2.	(psoria$ adj2 (arthrit$ or arthropath$)).ti,ab.	3601
3.	1 or 2	4143
4.	(etanercept or enbrel).ti,ab,rn.	2086
5.	(infliximab or remicade).ti,ab,rn.	4731
6.	4 or 5	5906
7.	3 and 6	488
8.	(200404$ or 200405$ or 200406$ or 200407$ or 200408$ or 200409$ or 200410$ or 200411$ or 200412$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$).ed.	3568700
9.	7 and 8	387
10.	(adalimumab or humira or D2E7 or (D2 adj E7)).ti,ab,rn.	1164
11.	3 and 10	152
12.	9 or 11	432
13.	economics/	25433
14.	exp "Costs and Cost Analysis"/	143147
15.	VALUE OF LIFE/	5039
16.	economics, dental/	1776
17.	exp economics, hospital/	15981
18.	economics, medical/	7044
19.	economics, nursing/	3784
20.	economics, pharmaceutical/	2048
21.	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom$).ti,ab.	300152
22.	(expenditure$ not energy).ti,ab.	12542
23.	(value adj1 money).ti,ab.	12
24.	budget$.ti,ab.	12911
25.	or/13-24	407009

26.	((energy or oxygen) adj cost).ti,ab.	2082
27.	(metabolic adj cost).ti,ab.	512
28.	((energy or oxygen) adj expenditure).ti,ab.	11540
29.	or/26-28	13584
30.	25 not 29	403828
31.	letter.pt.	654164
32.	editorial.pt.	239274
33.	historical article.pt.	272822
34.	or/31-33	1155003
35.	30 not 34	381317
36.	Animals/	4399394
37.	Humans/	10777302
38.	36 not (36 and 37)	3292558
39.	35 not 38	361076
40.	12 and 39	24

MEDLINE In-Process: OvidSP http://ovidsp.ovid.com/

The MEDLINE In-Process search, database dated June 11 2009, was carried out on 12 June 2009 and identified one record.

The strategy employs the Centre for Reviews and Dissemination NHS EED strategy for identifying economic evaluations in MEDLINE (lines 9-35).

1.	Arthritis, Psoriatic/	1
2.	(psoria$ adj2 (arthrit$ or arthropath$)).ti,ab.	130
3.	1 or 2	130
4.	(etanercept or enbrel).ti,ab,rn.	174
5.	(infliximab or remicade).ti,ab,rn.	298
6.	(adalimumab or humira or D2E7 or (D2 adj E7)).ti,ab,rn.	113
7.	or/4-6	457
8.	3 and 7	21
9.	economics/	1
10.	exp "Costs and Cost Analysis"/	7
11.	VALUE OF LIFE/	0
12.	economics, dental/	0
13.	exp economics, hospital/	11
14.	economics, medical/	0
15.	economics, nursing/	0
16.	economics, pharmaceutical/	0
17.	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom$).ti,ab.	15266
18.	(expenditure$ not energy).ti,ab.	422
19.	(value adj1 money).ti,ab.	2
20.	budget$.ti,ab.	620
21.	or/9-20	15898
22.	((energy or oxygen) adj cost).ti,ab.	103
23.	(metabolic adj cost).ti,ab.	14
24.	((energy or oxygen) adj expenditure).ti,ab.	435
25.	or/22-24	536
26.	21 not 25	15762
27.	letter.pt.	14507
28.	editorial.pt.	8936
29.	historical article.pt.	2

30.	or/27-29	23445
31.	26 not 30	15515
32.	Animals/	12
33.	Humans/	105
34.	32 not (32 and 33)	8
35.	31 not 34	15515
36.	8 and 35	1

EMBASE: OvidSP http://ovidsp.ovid.com/

The EMBASE search covered the date range 1980 to 2009 Week 23 for adalimumab and 01 January 2004 to 2009 Week 23, using the search field 'em: Entry Week', for etanercept and infliximab. The search was carried out on 12 June 2009 and identified 80 records.

The strategy employs the Centre for Reviews and Dissemination NHS EED strategy for identifying economic evaluations in EMBASE (lines 17-43).

Note: A pragmatic approach was taken to reduce the number of irrelevant records retrieved and to negate the over indexing of records in EMBASE; EMTREE drug terms were focussed in this strategy.

1.	Psoriatic Arthritis/ 4225	
2.	(psoria$ adj2 (arthrit$ or arthropath$)).ti,ab.	3339
3.	1 or 2	5024
4.	*Etanercept/	1973
5.	(etanercept or enbrel).ti,ab.	2192
6.	*Infliximab/	3482
7.	(infliximab or remicade).ti,ab.	3991
8.	or/4-7	6134
9.	(2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$).em.	3193493
10.	8 and 9	4694
11.	*Adalimumab/	881
12.	(adalimumab or humira or D2E7 or (D2 adj E7)).ti,ab.	958
13.	11 or 12	1236
14.	3 and 10	500
15.	3 and 13	219
16.	14 or 15	561
17.	Health Economics/	10611
18.	exp Economic Evaluation/	104472
19.	exp "Health Care Cost"/	107017
20.	exp PHARMACOECONOMICS/	56975
21.	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).tw.	234263
22.	(expenditure$ not energy).ti,ab.	9859
23.	(value adj2 money).ti,ab.	462
24.	budget$.ti,ab.	8863
25.	or/17-24	347643
26.	(metabolic adj cost).ti,ab.	388
27.	((energy or oxygen) adj cost).ti,ab.	1707
28.	((energy or oxygen) adj expenditure).ti,ab.	10088
29.	or/26-28	11689
30.	25 not 29	345077
31.	(letter or note or editorial).pt.	925192

32.	30 not 31	298277
33.	exp Animal/	18276
34.	exp Animal Experiment/	1298147
35.	Nonhuman/	3232877
36.	(rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab.	1737766
37.	or/33-36	3643672
38.	exp human/	6568828
39.	exp Human Experiment/	257542
40.	38 or 39	6569696
41.	37 not (37 and 40)	2983952
42.	32 not 41	274297
43.	16 and 42	80

Cochrane Central Register of Controlled Trials (CENTRAL): The Cochrane Library
http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME

A search of CENTRAL was not repeated for cost-effectiveness evidence. The search carried out on 09 June 2009 (shown above in the clinical effectiveness section) was not limited by study design and would also have identified economic evaluations.

Science Citation Index: ISI Web of Knowledge http://wok.mimas.ac.uk

The Science Citation Index search covered the date range 1900 to 2009 for adalimumab and 2004 to 2009 for etanercept and infliximab. The search was carried out on 12 June 2009 and identified 31 records.

The strategy employs the terms used in the 2006 HTA report to identify economic evaluations in the Science Citation Index (lines #7-10).

# 10 31 #8 not #9
Databases=SCI-EXPANDED Timespan=1900-2009
# 9 >100,000 TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*)
Databases=SCI-EXPANDED Timespan=1900-2009
# 8 33 #6 and #7
Databases=SCI-EXPANDED Timespan=1900-2009
# 7 >100,000 TS=(econom* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom* or budget*)
Databases=SCI-EXPANDED Timespan=1900-2009
# 6 666 #3 or #5
Databases=SCI-EXPANDED Timespan=1900-2009
# 5 211 #1 and #4
Databases=SCI-EXPANDED Timespan=1900-2009
# 4 1,699 TS=(adalimumab or humira or D2E7 or "D2 E7")
Databases=SCI-EXPANDED Timespan=1900-2009
# 3 570 #1 and #2
Databases=SCI-EXPANDED Timespan=1900-2009
# 2 7,383 TS=(etanercept or enbrel or infliximab or remicade)
Databases=SCI-EXPANDED Timespan=2004-2009
# 1 4,736 TS=((psoria* same arthrit*) or (psoria* same arthropath*))
Databases=SCI-EXPANDED Timespan=1900-2009

Conference Proceedings Citation Index - Science (CPCI-S): ISI Web of Knowledge http://wok.mimas.ac.uk

The CPCI-S search covered the date range 1990 to 2009 for adalimumab and 2004 to 2009 for etanercept and infliximab. The search was carried out on 12 June 2009 and identified three records.

The strategy employs the terms used in the 2006 HTA report to identify economic evaluations in the CPCI-S (previously ISI Science and Technology Proceedings) (lines #7-10).

# 10 3 #8 not #9
Databases=CPCI-S Timespan=1990-2009
# 9 >100,000 TS=(animal or animals or dog or dogs or hamster* or mice or mouse or rat or rats or bovine or sheep or guinea*)
Databases=CPCI-S Timespan=1990-2009
# 8 3 #6 and #7
Databases=CPCI-S Timespan=1990-2009
# 7 >100,000 TS=(econom* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconom* or budget*)
Databases=CPCI-S Timespan=1990-2009
# 6 196 #3 or #5
Databases=CPCI-S Timespan=1990-2009
# 5 62 #1 and #4
Databases=CPCI-S Timespan=1990-2009
# 4 651 TS=(adalimumab or humira or D2E7 or "D2 E7")
Databases=CPCI-S Timespan=1990-2009
# 3 140 #1 and #2
Databases=CPCI-S Timespan=1990-2009
# 2 2,192 TS=(etanercept or enbrel or infliximab or remicade)
Databases=CPCI-S Timespan=2004-2009
# 1 814 TS=((psoria* same arthrit*) or (psoria* same arthropath*))
Databases=CPCI-S Timespan=1990-2009

NHS Economic Evaluation Database (NHS EED) http://www.crd.york.ac.uk/CRDWeb/

The NHS EED was searched for economic evaluations. As no records were identified in the 2006 HTA review, no date limits were set. The search was carried out on 12 June 2009 and identified seven records.

Note: The strategy was run across the entire Centre for Reviews and Dissemination databases and the final results shown here, 20 records, relate to the total number of records found.

# 1	MeSH Arthritis, Psoriatic	22
# 2	(psoria* NEAR arthrit*)	43
# 3	(psoria* NEAR arthropath*)	1
# 4	#1 or #2 or #3	44
# 5	etanercept OR enbrel OR infliximab OR remicade	165
# 6	adalimumab OR humira OR D2E7 OR “D2 AND E7”	48
# 7	#5 or #6	182
# 8	#4 and #7	20

Health Economic Evaluations Database (HEED) http://heed.wiley.com/ohe/

The HEED was searched for economic evaluations. As no records were identified in the 2006 HTA review, no date limits were set. The search was carried out on 12 June 2009 and identified eight records.

Compound Search
All Data: ((psoria* AND arthrit*) OR (psoria* AND arthropath*))
AND
All Data: etanercept OR enbrel OR infliximab OR remicade OR adalimumab OR humira OR D2E7 OR 'D2 E7'

EconLit: OvidSP http://ovidsp.ovid.com/

The EconLit database was searched for economic evaluations. The search carried out on 12 June 2009, covered the date range 1969 to May 2009, identified no records.

1.	(psoria$ adj2 (arthrit$ or arthropath$)).ti,ab.	0
2.	(etanercept or enbrel or infliximab or remicade or adalimumab or humira or D2E7 or "D2 E7").ti,ab.	3
3.	#1 and #2	0

Additional Searches

Side-effects/adverse effects search

The following resources were search for information on side-effects:

Center for Drug Evaluation and Research. *Drugs@FDA*. Silver Spring, MD: U.S. Food and Drug Administration. [cited 2009 Jun 08]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

EPARs for authorised medicinal products for human use. London: European Medicines Agency. [cited 2009 Jun 08]. Available from: http://www.emea.europa.eu/htms/human/epar/a.htm

Additional information on side-effects was gathered by supplementary searches. The following searches were designed to capture the major side-effects that had been identified as arising from the use of etanercept, infliximab or adalimumab: urinary tract infections, lower respiratory tract infections, skin infections, bone infections, joint infections, malignancy, and the reactivation of latent tuberculosis.

A pragmatic approach to searching was adopted for the supplementary side-effects search. This can be seen in the reliance of indexed terms to search for the side-effects and the use of subheadings linked to specific side-effects, such as the MeSH subheading 'Chemically Induced' and the EMTREE subheading 'Side Effect'. This search approach enhances the precision of a search but has an unknown effect on its sensitivity.

MEDLINE: OvidSP http://ovidsp.ovid.com/

The MEDLINE search covered the date range 1950 to June Week 1 2009. The search was carried out on 16 June 2009 and identified 60 records.

1.	(etanercept or enbrel).ti,ab.	2086
2.	(infliximab or remicade).ti,ab.	3743
3.	(adalimumab or humira or D2E7 or (D2 adj E7)).ti,ab.	878
4.	or/1-3	5297
5.	Safety/	26929
6.	(safe or safety).ti,ab.	271847
7.	(side effect or side effects).ti,ab.	130142
8.	treatment emergent.ti,ab.	867
9.	undesirable effect$.ti,ab.	1448
10.	tolerability.ti,ab.	19551
11.	Drug Toxicity/	2820
12.	toxicity.ti,ab.	173622
13.	Adverse Drug Reaction Reporting Systems/	3900
14.	adrs.ti,ab.	975
15.	(adverse adj3 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.	147732
16.	(undesir$ adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.	4632
17.	Drug Hypersensitivity/	17725
18.	(hypersensit$ or hyper sensit$).ti,ab.	45094
19.	harm$.ti,ab.	54739
20.	or/5-19	750762
21.	4 and 20	1654
22.	exp Infection/ci [Chemically Induced]	2859
23.	exp Urinary Tract Infections/ci [Chemically Induced]	61
24.	exp Respiratory Tract Infections/ci [Chemically Induced]	3678
25.	exp Skin Diseases, Infectious/ci [Chemically Induced]	451
26.	exp Bone Diseases, Infectious/	27676
27.	exp Arthritis, Infectious/ci [Chemically Induced]	55
28.	exp Neoplasms/ci [Chemically Induced]	50219
29.	exp Tuberculosis/ci [Chemically Induced]	315
30.	or/22-29	84100
31.	21 and 30	60
32.	(animals not (humans and animals)).sh.	3292558
33.	31 not 32	60

EMBASE: OvidSP http://ovidsp.ovid.com/

The EMBASE search covered the date range 1980 to 2009 Week 24. The search was carried out on 17 June 2009 and identified 648 records.

Note: A pragmatic approach was taken to reduce the number of irrelevant records retrieved and to negate the over indexing of records in EMBASE; EMTREE drug terms were focussed in this strategy.

1.	(etanercept or enbrel).ti,ab.	2202
2.	(infliximab or remicade).ti,ab.	3999
3.	(adalimumab or humira or D2E7 or (D2 adj E7)).ti,ab.	960
4.	or/1-3	5648
5.	*Etanercept/	1979
6.	*Infliximab/	3486

7.	*Adalimumab/	882
8.	or/5-7	5086
9.	4 or 8	6595
10.	(safe or safety).ti,ab.	246785
11.	side effect$.ti,ab.	123415
12.	treatment emergent.ti,ab.	963
13.	undesirable effect$.ti,ab.	1421
14.	tolerability.ti,ab.	22410
15.	toxicity.ti,ab.	164169
16.	adrs.ti,ab.	1214
17.	(adverse adj3 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.	144000
18.	Safety/ or Drug Safety/	183510
19.	Side Effect/	94185
20.	Adverse Drug Reaction/	95592
21.	Drug Tolerability/	54359
22.	Toxicity/ or Drug Toxicity/	47998
23.	Drug Surveillance Program/	7235
24.	Adverse Outcome/	1414
25.	hypersensit$.ti,ab.	35011
26.	harm$.ti,ab.	46014
27.	Drug Hypersensitivity/	25074
28.	or/10-27	892235
29.	9 and 28	2822
30.	*Etanercept/ae, to [Adverse Drug Reaction, Drug Toxicity]	917
31.	*Infliximab/ae, to [Adverse Drug Reaction, Drug Toxicity]	1636
32.	*Adalimumab/ae, to [Adverse Drug Reaction, Drug Toxicity]	442
33.	or/30-32	2470
34.	29 or 33	3651
35.	Urinary Tract Infection/si [Side Effect]	2059
36.	Lower Respiratory Tract Infection/si [Side Effect]	144
37.	Skin Infection/si [Side Effect]	488
38.	Bone Infection/si [Side Effect]	26
39.	Infectious Arthritis/si [Side Effect]	55
40.	Neoplasm/si [Side Effect]	452
41.	Tuberculosis/si [Side Effect]	1297
42.	or/35-41	4150
43.	34 and 42	648

10.2 Quality assessment tool

All of the criteria listed below should be scored with one of the following responses:
Yes (Y);
No (N);
Partial (P);
Not stated (NS);
Not applicable (NA);
Unclear (U).

Study:

1	Were the eligibility criteria for the study adequately specified? *Adequate: study population clearly defined*	
2	Was an a priori power calculation for adequate sample size performed?	
3	Was the sample size adequate for the analysis of the primary outcome variable?	
4	Was the number of participants who were randomised stated?	
5	Was the method used to assign participants to treatment groups truly random? *Adequate: computer generated random numbers, random number tables* *Inadequate: alternation, case record numbers, birth dates, days of the week*	
6	Was the trial described as double-blind?	
7	Was allocation of treatment concealed? *Adequate: centralised or pharmacy controlled assignment, serially numbered containers, serially numbered opaque envelopes, on-site computer-based systems where assignment is unreadable until after allocation, other robust measures to prevent revelation of a participant's treatment* *Inadequate: alternation, case record numbers, days of the week, open random number lists*	
8	Were the individuals administering the treatment blinded to the treatment allocation?	
9	Were the outcome assessors blinded to the treatment allocation?	
10	Were the participants blinded to the treatment allocation?	
11	Was the blinding procedure successful?	
12	Were adequate details of the treatment groups at baseline presented? Adequate: information on age, nature and severity of psoriasis, previous treatments	
13	Were the treatment groups comparable at baseline? *Answer 'Yes' if no important differences or if appropriate adjustments had been made for any differences in the baseline characteristics of the treatment groups*	
14	Were the treatment groups similar in terms of co-interventions that could influence the results?	
15	Was participant compliance with the assigned treatment adequate?	
16	Were all participants who were randomised accounted for at the end of the trial?	
17	Was a valid ITT analysis performed? *Adequate: all participants randomised included in efficacy analysis, all randomised participants who took at least one dose of trial medication included in efficacy analysis*	
18	Were at least 80% of those randomised included in the follow-up assessment? *Answer 'Yes' if at least 80% of those randomised provided complete data with regard to the primary outcome(s)*	

Quality rating =
Excellent: The answer is 'Yes' to all of the criteria.
Good: The answer is 'Yes' to all of the following criteria: 1, 3, 4, 6, 10, 12-14, 16-18.
Satisfactory: The answer is 'Yes' to all of the following criteria: 1, 3, 6, 13, 17.
Poor: The answer is NOT 'Yes' to one or more of the criteria listed for 'Satisfactory'.

10.3 Data extraction tables

10.3.1 Clinical efficacy - etanercept

Study details and design	Participant details	Intervention/outcome/analyses details	Results
Mease, 2000, USA[79] **Type of publication** Full publication **Funding** Immunex Corporation **Study design** Stage 1: Double-blind RCT, parallel group monotherapy Stage 2; Open-label follow-up **Setting** Outpatient **Duration of follow-up** Stage 1:12 weeks Stage 2: 24 wks **Frequency of follow-up** Stage 1: Baseline, 4, 8 and 12 wks Stage 2: 16 and 36 wks Extracted by: HY	**Inclusion/exclusion criteria** Adults between 18 to 70 years of age with active psoriatic arthritis (defined as ≥3 swollen joints and ≥3 tender or painful joints) and an inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs), and were thought candidates for immunomodulatory therapy. Patients taking a stable dose of MTX (≤25 mg/wk) were permitted to continue with that dose. Other disease-modifying anti-rheumatic drugs (DMARDs) were discontinued at least 2 wks prior to the trial. Corticosteroids were allowed during the study at a dose of ≤ 10mg/day of prednisone if it was stable for at least 2 wks prior to the trial and maintained during the trial. For patients with skin involvement psoriasis, therapies had to be discontinued (phototherapy 4 weeks before and topical therapies and oral retinoids 2 wks before). **Number randomised** 60 **Age**	**Intervention etanercept** Dose regimen: 25 mg etanercept twice a wk Length of treatment: 12 wks No. randomised: 30 No. completed: 30 **Comparator placebo** Dose regimen: placebo twice a wk Length of treatment: 12 wks No. randomised: 30 No. completed: 26 **Primary Outcome** The proportion of patients meeting the PsARC at 12 wks **Sample size calculation** Assuming that a response rate of 30% on placebo and 75% on etanercept, the sample size of 30 patients per group gives 80% power to detect a significant difference between treatments in the primary outcome, with α =0.05 (two-sided). **Statistical analyses** Proportions of patients' responding were compared using the Mantel-Haenszel χ^2 test adjusted for the MTX use. Continuous variables were ranked and analysed by a general linear model with factors of treatment, MTX use and their interaction. The Breslow-Day test was used to test for heterogeneity of relative response between MTX use strata. The last observation carried forward (LOCF) approach was used for imputing missing data **ITT analysis** All randomised patients included in the analysis.	EFFICACY OUTCOMES (STAGE 1, RANDOMISED) **ACR 20** Etanercept 25 mg 12 wks = 22/30 (73%); Placebo 12 wks = 4/30 (13%); p<0.0001 **ACR 50** Etanercept 25 mg 12 wks = 15/30 (50%); Placebo 12 wks = 1/30 (3%); p=0.0001 **ACR 70** Etanercept 25 mg 12 wks = 4/30 (13%); Placebo 12 wks = 0/30 (0%); p=0.0403 **PsARC** Etanercept 25 mg 4 wks = 23/30 (77%); Placebo 4 wks = 4/30 (14%); p<0.0001 Etanercept 25 mg 8 wks = 25/30 (83%); Placebo 4 wks = 8/30 (27%); p<0.0001 Etanercept 25 mg 12 wks = 26/30 (87%); Placebo 12 wks = 7/30 (23%); p<0.0001 **HAQ** *median (25th and 75th percentiles)* Etanercept 25mg baseline 1.3 [redacted] 12 wks 0.1 [redacted] Placebo baseline 1.2 [redacted] 12 wks 1.1 [redacted] p<0.001(at 12 wks) **mean (SD)** Etanercept 25mg baseline 1.2 [redacted] 12 wks 0.5 [redacted] Placebo baseline 1.2 [redacted] 12 wks 1.1 [redacted] % improvement at 12 wks (mean (SD): Etanercept 25 mg (n=29) 64.2 [redacted] placebo (n=30) 9.9 [redacted] **Median (range) PASI at baseline** Etanercept 25 mg = 10.1 (2.3-30.0); Placebo = 6.0 (1.5-17.7) **PASI 50** Etanercept 25 mg 12 wks = 8/19 (42%); Placebo 12 wks = 4/19 (21%); Treatment difference p=0.295

Checked by: MR	*Median age (range)* Etanercept: 46.0 yrs (30.0-70.0 yrs) Placebo: 43.5 yrs (24.0-63.0) **Gender** Etanercept: Male, 16/30 (53%) Placebo: Male, 18/30 (60%) **Psoriatic arthritis history** Duration of psoriatic arthritis median (range) Etanercept: 9.0 yrs (1.0-31.0 yrs) Placebo: 9.5 yrs (1.0-30.0 yrs) Psoriasis history *Duration of psoriasis median (range)* Etanercept: 19.0 yrs (4.0-53.0 yrs) Placebo: 17.5 yrs (2.0-43.0 yrs) **Psoriasis Evaluation** Patients with ≥ 3% body surface area affected with psoriasis: Etanercept: 19/30 (63%) Placebo: 19/30 (63%) **Concurrent therapies** Patients taking a stable dose of MTX (≤25 mg/wk) were permitted to continue with that dose if it had been stable for 4 wks prior to study entry and remained constant during the study. Corticosteroids were allowed during the study at a dose of ≤ 10 mg/day prednisolone and if the dose had been stable at study entry and if it was maintained during the trial		**PASI 75** Etanercept 25 mg 12 wks = 5/19 (26%); Placebo 12 wks = 0/19 (0%); p=0.0154 **100% improvement in physician global assessment** Etanercept 25mg 12 wks = 6/30 (20%); placebo 12 wks = 0/30 (0%). **100% improvement in patient global assessment** Etanercept 25mg 12 wks = 5/30 (17%); placebo 12 wks = 0/30 (0%). ADVERSE EVENTS (STAGE 1, RANDOMISED) **Infectious adverse events** (no. patients (%)) Placebo (n=30) Etanercept (n=30) Respiratory tract infection 4 (13%) 8 (27%) Pharyngitis 3 (10%) 5 (17%) Rhinitis 4 (13%) 6 (20%) Sinusitis 2 (7%) 3(10%) Influenza syndrome 6 (20%) 0 **Infections that required hospitalisation or intravenous antibiotics** Etanercept: 0 Placebo: 0 **Cancer** Not reported **Reactivation of latent tuberculosis** Not reported **Deaths** None **Withdrawals due to adverse events** None *EFFICACY OUTCOMES (STAGE 2, OPEN-LABEL)* **PsARC** Etanercept 25 mg 16 wks = 26/30 (87%); Placebo/Etanercept 16 wks = 19/28 (68%). Etanercept 25 mg 36 wks = 26/30 (87%); Placebo/Etanercept 36 wks = 21/28 (75%). **ACR 20** Etanercept 25 mg 16 wks = 22/30 (73%); Placebo/Etanercept 16 wks = 12/28 (43%). Etanercept 25 mg 36 wks = 26/30 (87%); Placebo/Etanercept 36 wks = 17/28 (61%). **ACR 50**

	Concomitant therapy during trial Corticosteroids: etanercept group 6/30 (20%); placebo group 12/30 (40%) NSAIDS: etanercept group 20/30 (67%); placebo group 23/30 (77%) MTX: etanercept group 14/30 (47%); placebo group 14/30 (47%)		Etanercept 25 mg 16 wks = 13/30 (43%); Placebo/Etanercept 16 wks = 8/28 (29%). Etanercept 25 mg 36 wks = 19/30 (63%); Placebo/Etanercept 36 wks = 13/28 (46%). **ACR 70** Etanercept 25 mg 16 wks = 7/30 (23%); Placebo/Etanercept 16 wks = 0/28. Etanercept 25 mg 36 wks = 10/30 (33%); Placebo/Etanercept 36 wks = 7/28 (25%). [redacted] [redacted] **PASI** (patients evaluable for psoriasis only) *PASI 50:* Etanercept 25 mg 36 wks = 11/19 (58%); Placebo/Etanercept 36 wks = 10/18 (56%) *PASI 75:* Etanercept 25 mg 36 wks = 7/19 (37%); Placebo/Etanercept 36 wks = 5/18 (28%). *ADVERSE EVENT OUTCOMES (STAGE 2, OPEN-LABEL, 24 WKS)* Placebo/ n=28 — Etanercept n=30 **Infectious adverse events including any serious infections** occurring in >5% of patients by treatment: Respiratory tract infection: 9 (32%) — 7 (23%) Pharyngitis: 2 (7%) — 1 (3%) Influenza syndrome: 4 (14%) — 3 (10%) Urinary tract infection: 2 (7%) — 0 Infection (not specified): 0 — 2 (7%) **Cancer** None [redacted] [redacted] [redacted]

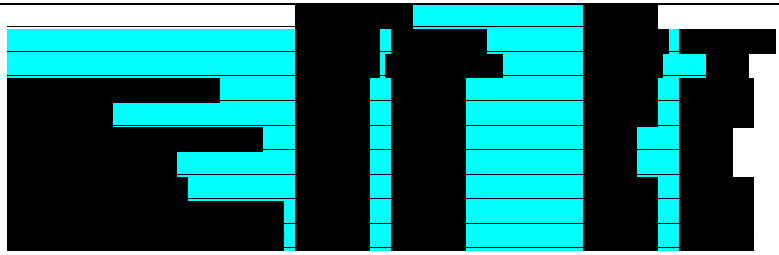
			Comments All efficacy data in Stage 2 relates to non-randomised patients. All patients in Stage 2 had received etanercept

Mease, 2004,USA[53, 98, 100, 106, 108, 111] **Type of publication** Full publication **Funding** Immunex Corporation **Study design** Stage 1: Double-blind placebo controlled RCT Stage 2: Maintenance period Stage 3: Open label follow-up **Duration of follow-up** Stage 1: 24 wks Stage 2: < 24 wks Stage 3: 48 wks **Frequency of follow-up** Stage 1: Baseline, 4, 12 and 24 wks Stage 2: 12 wk intervals thereafter Stage 3: 48 wks Extracted by: HY Checked by: MR	**Inclusion criteria** Patients between 18 and 70 years of age with active psoriatic arthritis and stable plaque psoriasis (target lesion > 2cm diameter) with >3 swollen joints and >3 tender joints. Patients had at least one of the following subtypes of psoriatic arthritis: distal interphalangeal joint involvement, polyarticular arthritis, arthritis mutilans, asymmetric peripheral arthritis, or ankylosing spondylitis-like arthritis. Patients taking a stable dose of MTX (≤25 mg/wk) for 2 months were permitted to continue with that dose. Other DMARDs were discontinued at least 4 wks prior to the trial. Corticosteroids were allowed during the study at a dose of ≤ 10mg/day of prednisone if it was stable for at least 4 wks prior to the trial. For patients with skin involvement psoriasis, phototherapy therapies had to be discontinued prior to the trial. Oral retinoids, tropical vitamin A or D analog preparations, and anthralin were not allowed. Tropical therapies were only permitted on the scalp, axillae, and groin. **Number randomised and treated** Stage 1: 205 [redacted] Stage 3: 168	**Intervention Etanercept** Stage 1: Dose regimen: 25mg SC twice a wk Duration/frequency of treatment: 24 wks No. of participants: 101 Stage 2: After completing stage 1, patients could chose to continue on their blinded study treatment in this maintenance period until all patients had completed 24 wks of study treatment and the database was locked Dose regimen: 25mg SC twice a wk Duration/frequency of treatment: < 24wks [redacted] Stage 3: After the database was locked all patients [redacted] were eligible to enter a 48-week open label extension. [redacted] Duration/frequency of treatment: 48 wks No. of participants: 168 (87 previously on etanercept; 81 stage 1 previously on placebo) [redacted] **Comparator Placebo** Stage 1: Placebo (n=104): Equivalent	STAGE 1: EFFICACY OUTCOMES **PsARC** Etanercept 25 mg 4 wks = 57 (56%); Placebo 4 wks = 25 (24%); (p<0.001) Etanercept 25 mg 12 wks = 73 (72%); Placebo 12 wks = 32 (31%); (p<0.001) Etanercept 25 mg 24 wks = 71 (70%); Placebo 24 wks = 24 (23%); (p<0.001) Subgroup analysis (with and without MTX) Etanercept +MTX 12 wks = 32/42 (76%); Placebo 12 wks = 14/43 (33%) Etanercept -MTX 12 wks = 41/59 (69%); Placebo 12 wks = 18/61 (30%) Etanercept +MTX 24 wks = 31/42 (74%); Placebo 24 wks = 11/43 (26%) Etanercept -MTX 24 wks = 40/59 (68%); Placebo 24 wks = 13/61 (21%) **ACR 20** Etanercept 25 mg 4 wks = 38 (38%); Placebo 4 wks = 11 (11%); (p<0.001). Etanercept 25 mg 12 wks = 60 (59%); Placebo 12 wks = 16 (15%); (p<0.001). Etanercept 25 mg 24 wks = 50 (50%); Placebo 24 wks = 14 (13%); (p<0.001). Subgroup analysis (with and without MTX) Etanercept +MTX 12 wks = 26/42 (62%); Placebo 12 wks = 8/43 (19%) Etanercept -MTX 12 wks = 34/59 (58%); Placebo 12 wks = 8/61 (13%) Etanercept +MTX 24 wks = 23/42 (55%); Placebo 24 wks = 8/43(19%) Etanercept -MTX 24 wks = 27/59 (46%); Placebo 24 wks = 6/61 (10%) **ACR 50** Etanercept 25 mg 4 wks = 11 (11%); Placebo 4 wks = 2 (2%); (p=0.009) Etanercept 25 mg 12 wks = 38 (38%); Placebo 12 wks = 4 (4%); (p<0.001) Etanercept 25 mg 24 wks = 37 (37%); Placebo 24 wks = 4 (4%); (p<0.001) Subgroup analysis (with and without MTX) Etanercept +MTX 12 wks = 17/42 (40%); Placebo 12 wks = 1/43 (2%) Etanercept -MTX 12 wks = 21/59 (36%); Placebo 12 wks = 3/61 (5%) Etanercept +MTX 24 wks = 16/42 (38%); Placebo 24 wks = 3/43 (7%) Etanercept -MTX 24 wks = 21/59 (36%); Placebo 24 wks = 1/61 (2%) **ACR 70** Etanercept 25 mg 4 wks = 1 (1%); Placebo 4 wks = 0; (p=0.493) Etanercept 25 mg 12 wks = 11 (11%); Placebo 12 wks = 0; (p<0.001) Etanercept 25 mg 24 wks = 9 (9%); Placebo 24 wks = 1 (1%); (p=0.009) Subgroup analysis (with and without MTX) Etanercept +MTX 12 wks = 4/42 (10%); Placebo 12 wks = 0/43 (0%)

	Age (mean) Etanercept: 47.6 yrs Placebo: 47.3 yrs *Gender* Etanercept: male 58/101(57%) Placebo: male 47/104 (45%) **Psoriatic arthritis history** Duration of psoriatic arthritis (mean) Etanercept: 9.0 yrs Placebo: 9.2 yrs **Psoriasis history** Duration of psoriasis (mean) Etanercept: 18.3 yrs Placebo: 19.7 yrs **Psoriasis Evaluation** Patients with ≥ 3% body surface area affected with psoriasis: Etanercept: 66/101 (65%) Placebo: 62/104 (60%) **Concurrent therapies** Concomitant therapy at baseline MTX: etanercept 42/101 (42%); placebo 43/104 (41%) Corticosteroids: etanercept 19/101 (19%); placebo 16/104 (15%) NSAIDS: etanercept 89/101(88%); placebo 86/104(83%).	Stage 2: Placebo (n=59): Equivalent **Primary Outcome** The proportion of patients meeting the ACR 20 at 24 wks **Sample size calculation** Assuming that an ACR 20 rate of 60% on etanercept and 30% on placebo, a sample size of 100 patients per group gives a power of 90% power to detect a significant difference between treatments in the primary outcome, with α =0.05 (two-sided). **Statistical analyses** Binary response rates were compared using the Cochran-Mantel-Haenszel test or Fisher's exact test. Continuous variables were analysed by Wilcoxon's rank sum test, using LOCF for missing data or early termination. **ITT analysis** All randomised patients who received at least one dose of blinded study drug were included in the analysis. **Comments** Patients receiving MTX were randomised separately.	Etanercept -MTX 12 wks = 7/59 (12%); Placebo 12 wks = 0/61 (0%) Etanercept +MTX 24 wks = 2/42 (5%); Placebo 24 wks = 0/43 (0%) Etanercept -MTX 24 wks = 7/59 (12%); Placebo 24 wks = 0/61 (0%) **HAQ** Mean (SD) absolute values Etanercept 25mg baseline (n=101) 1.1 [redacted] placebo baseline (n=104) 1.1 [redacted] Etanercept 25mg 4 wks (n=101) 0.7 [redacted] placebo 4wks (n=104) 1.0 [redacted] Etanercept 25mg 12 wks (n=101) 0.6 [redacted] placebo 12 wks (n=104) 1.0 [redacted] Etanercept 25mg 24 wks (n=101) 0.5 [redacted] placebo 24 wks (n=104) 1.0 [redacted] Mean (SD) % changes from baseline Etanercept 25mg 4 wks (n=96) 35.1 [redacted] placebo 4 wks (n=99) 8.0 [redacted] p<0.001 Etanercept 25mg 12 wks (n=96) 53.5 [redacted] placebo 12 wks (n=99) 6.3 [redacted] p<0.001 Etanercept 25mg 24 wks (n=96) 53.6 [redacted] placebo 24 wks (n=99) 6.4 [redacted] p<0.001 **Total Sharp Score (TSS)** Mean (SD) annualised rate of progression at 6 months Etanercept (n=101) –0.03 (0.73); Placebo (n=104) 0.53 (1.39); p=0.0006 Subgroup analysis (with and without MTX) *Mean (SD)* Etanercept +MTX (n=42) [redacted] Placebo (n=43) [redacted] Etanercept -MTX (n=59) [redacted] Placebo (n=61) [redacted] **Mean PASI score at baseline** [redacted] **PASI 50** No. (%) improvement in PASI 50 Etanercept 25 mg 24 wks (n=66): 31 (47%); Placebo 24 wks (n=62): 11 (18%); p<0.001 **PASI 75** *No. (%) improvement in PASI 75* Etanercept 25 mg 24 wks (n=66): 15 (23%); Placebo 24 wks (n=62): 2 (3%); p=0.001 **PASI 90** *No. (%) improvement in PASI 90* Etanercept 25 mg 24 wks (n=66): 4 (6%); Placebo 24 wks (n=62): 2 (3%); p=0.681 **Target lesion score** No. (%) with 50% improvement from baseline Etanercept 25 mg 24 wks (n=101): 43 (43%); Placebo 24 wks (n=104): 18 (17%); p<0.001

			No. (%) with 75% improvement from baseline Etanercept 25 mg 24 wks (n=101): 22 (22%); Placebo 24 wks (n=104): 10 (10%); p=0.017 **Physician global assessment** Mean (median) % improvement from baseline Etanercept 25mg 4 wks 36.0 (50.0); placebo 4 wks 2.9 (0); p<0.001 Etanercept 25mg 12 wks 44.9 (50); placebo 12 wks 0.3 (0); p<0.001 Etanercept 25mg 24 wks 47.2 (50); placebo 24 wks 2.3 (0); p<0.001 **Patient global assessment** Mean (median) % improvement from baseline Etanercept 25mg 4 wks 21.6 (25.0); placebo 4 wks 1.3 (0); p<0.001 Etanercept 25mg 12 wks 36.1 (33.3); placebo 12 wks -0.3 (0); p<0.001 Etanercept 25mg 24 wks 40.4 (50.0); placebo 24 wks –3.9 (0); p<0.001 **SF-36 – mental component score** Mean (median) % changes from baseline Etanercept 25mg 4 wks 2.3 (0.9); placebo 4 wks 1.7 (0.9); p=0.748 Etanercept 25mg 12 wks 2.3 (1.0); placebo 12 wks 0.8 (0.3); p=0.392 Etanercept 25mg 24 wks 2.7 (1.1); placebo 24 wks –0.1 (-0.1); p=0.062 **SF-36 – physical component score** Mean (median) % changes from baseline Etanercept 25mg 4 wks 5.8 (5.1); placebo 4 wks 0.5 (0.7); p<0.001 Etanercept 25mg 12 wks 8.9 (6.8); placebo 12 wks 1.2 (1.6); p<0.001 Etanercept 25mg 24 wks 9.3 (7.7); placebo 24 wks 0.7 (0.5); p<0.001 STAGE 1: ADVERSE EVENTS **Infectious adverse events** (no. of patients (%) after 24 weeks) Etanercept (n=101) Placebo (n=104) Any infection 40 (40%) 45 (43%) Upper respiratory infection 21 (21%) 24 (23%) Sinusitis 6 (6%) 8 (8%) Urinary tract infection 6 (6%) 6 (6%) **Infections that required hospitalisation or use of intravenous antibiotics** Etanercept: 0/101 Placebo: 1/104 (1 Gastroenteritis) **Cancer** None

			Reactivation of latent tuberculosis Not reported **Deaths** (no. of patients) Etanercept: 0 Placebo: 1 (Surgery complications for perforated bowel) **Withdrawals due to adverse events** (no. of patients) Etanercept: 1 (Elevated liver enzymes) Placebo: 1(Increased psoriasis) *STAGE 2: EFFICACY OUTCOMES* Not reported *STAGE 3: EFFICACY OUTCOMES* ACR 20/50/70 responses were maintained or improved over the open follow-up stage of the trial in those patients who had taken etanercept from baseline. Data reported in graphical form only (not extractable). Radiographic results ***Total Sharp Score (TSS)*** Mean (SD) annualised rate of progression at 12 months Etanercept (n=101) –0.03 [redacted] Placebo (n=104) 1.00 [redacted] p=0.0001 Subgroup analysis (with and without MTX) *Mean (SD)* [redacted] ***Total Sharp Score (TSS) excluding DIP joints*** Mean (SE) annualised rate of progression at 12 months [redacted] *Erosion score Mean rate of change (units/year)* Etanercept (n=101) –0.08; Placebo (n=104) 0.69; p=0.0001 ***Joint space narrowing*** *Mean rate of change (units/year)* Etanercept (n=101) 0.06; Placebo (n=104) 0.35; p=0.04 PsA-specific radiographic features No. (%) patients

			 *STAGE 2: ADVERSE EVENTS* [redacted] *STAGE 3: ADVERSE EVENTS* [redacted] Serious infection n=1 (pneumonia) [redacted]

			STAGE 2 AND STAGE 3 COMBINED: ADVERSE EVENTS 

10.3.2 Efficacy data extraction –infliximab

Study details and design	Participant details	Intervention/outcome/analyses details	Results
IMPACT, 2005, USA[80-82, 90, 97, 110, 112, 114-116, 118, 119] **Type of publication** Full publication **Funding** Centocor and Schering-Plough **Study design** Double-blind RCT with open uncontrolled extension **Setting** Outpatient Multicentre **Duration of follow-up** Stage I: 16 wks Stage II: >34 wks **Frequency of follow-up** *Stage I: Baseline, 2, 6, 14, 16 wks* Stage II: 18, 22, 30, 46 and 50 wks Extracted by: HY Checked by: MR	**Inclusion/exclusion criteria** Adults aged 18 years or above diagnosed with psoriatic arthritis for at least 6 months, with negative results of the serum tests for rheumatoid factor. Patients must have active peripheral polyarticular arthritis (defined as ≥5 swollen and tender joints), with at least one of the following criteria: erythrocyte sedimentation rate (ESR) ≥28 mm/hour, C-reactive protein (CRP) level ≥ 15 mg/litre, and/or morning stiffness lasting 45 minutes or longer. Patients must have failed to the treatment of at least one DMARD. **Number randomised** 104 **Mean Age (SD)** Infliximab: 45.7 yrs (11.1) Placebo: 45.2 yrs (9.7) **Gender (% male)** Infliximab: 30/52 (57.7%) Placebo: 30/52 (57.7%). **Psoriatic arthritis history** *Mean (SD) duration* Infliximab: 11.7 yrs (9.8) Placebo: 11.0 yrs (6.6) Psoriasis History *Mean (SD) duration* Infliximab: 16.9 yrs (10.9) Placebo: 19.4 yrs (11.6) **Psoriasis Evaluation**	**Intervention Infliximab** Dose regimen: 5mg/kg at wks 0, 2, 6, 14 Length of treatment: 16 wks No. randomised: 52 No. completed: 49 **Comparator Placebo** Dose regimen: Equivalent Length of treatment: 16 wks No. randomised: 52 No. completed: 50 Patients in the placebo group in Stage I received 5mg/kg infliximab at wks 16, 18, 22, 30, 38, and 46. Patients that were in the infliximab group in Stage I received placebo at weeks 16 and 18, and 5mg/kg infliximab at weeks 22, 30, 38, and 46. **Primary Outcome** ACR 20 at wk 16 **Sample size calculation** Assuming that an ACR 20 rate of 50% on infliximab and 20% on placebo, a sample size of 45 patients per group gave 80% power to detect a significant difference between treatments on the primary outcome, with α =0.05 (two-sided). **Statistical analyses** Categorical outcomes (including ACR 20) were compared using the Chi-square test. The Mantel-haenszel test was conducted to estimate the odds ratios of the two	*STAGE I: EFFICACY OUTCOMES* **ACR 20** Infliximab: 14 wks: 67.3% (35/52); Placebo: 14 wks: 11.5% (6/52); p<0.01. Infliximab 16 wks= 65.4% (34/52); Placebo 16 wks =9.6% (5/52); p<0.001. **ACR 50** Infliximab: 14 wks: 36.5% (19/52); Placebo: 14 wks: 1.9% (1/52); p<0.01 Infliximab 16 wks = 46.2% (24/52); Placebo 16 wks = 0% (0/52); p<0.001. **ACR 70** Infliximab: 14 wks: 21.2% (11/52); Placebo: 14 wks: 0% (0/52); p<0.01 Infliximab 16 wks = 28.8% (15/52); Placebo 16 wks = 0% (0/52); p<0.001. **PsARC** **Infliximab: 14 wks: 76.9% (40/52); Placebo: 14 wks: 13.5% (7/52); p<0.01.** Infliximab 16 wks = 75% (39/52); Placebo 16 wks = 21% (11/52); p<0.001. **HAQ mean (SD)** Infliximab baseline = 1.2 (0.7); Placebo baseline= 1.2 (0.7); [redacted] *HAQ mean (SE) % change from baseline* Infliximab: 16 wks: (n=48) –49.8 (8.2); Placebo: 16 wks: (n=47) 1.6 (8.3) **Mean (SD) PASI at baseline for all patients measured** Infliximab (n=52) = 5.1 (5.9); Placebo (n=52) = 4.2 (5.8) [redacted] [redacted] **PASI 50** Infliximab 16 wks = 100% (22/22) ; Placebo 16 wks = 0% (0/16) **PASI 75** Infliximab 16 wks = 68.2% (15/22) ; Placebo 16 wks = 0% (0/16)

	Patients with baseline PASI≥2.5 Infliximab: 22/52 Placebo: 17/52 **Concurrent therapies** Patients receiving one on the following DMARDs were eligible; methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, intramuscular gold, penicillamine, and azathioprine. Patients receiving a DMARD must have received a stable dosage for at least 4 wks prior to the trial and throughout the investigation. Dosages of corticosteroids and NSAIDs were permitted to remain stable throughout the study if the dosages had been stable for at least 2 weeks prior to screening. Stable dose of topical treatment for psoriatic lesions (e.g. topical steroids) were also permitted. Therapy with PUVA was not permitted. Patients could not receive any investigational drug within 3 months of screening or any previous treatment with a monoclonal antibody or fusion protein. *Concomitant therapy at baseline* Concomitant DMARD at baseline: Placebo 41/52 (79%) Infliximab 33/52 (63%) The most commonly used DMARD was MTX.	treatment groups. Continuous outcomes were analysed using one-way ANOVA. **ITT analysis** The analyses were performed on an intention-to-treat basis	**PASI 90** Infliximab 16 wks = 36.4% (8/22) ; Placebo 16 wks = 0% (0/16) **Patient global assessment of disease mean (SE)** Infliximab 16 wks = -47.5 (7.4) ; Placebo 16 wks = 13.9 (7.5), P<0.001. **Physician global assessment of disease mean (SE)** Infliximab 16 wks = -58.4 (6.0) ; Placebo 16 wks = 4.7 (6.0), P<0.001. *STAGE I: ADVERSE EVENTS* **Infectious adverse events including any serious infections** Bronchitis: Placebo 4/51 (7.8%); Infliximab 3/52 (5.8%) Rhinitis: Placebo 2/51 (3.9%)); Infliximab 3/52 (5.7%) Upper respiratory tract infection: Placebo 5/51 (9.8%); Infliximab 1/52 (1.9%) **Infections that required hospitalisation or use of intravenous antibiotics** Not reported. **Non-infectious adverse events** Infliximab: 1 synovitis (culture negative) Placebo: 1 rectal bleeding due to diverticulitis **Cancer** None **Reactivation of latent tuberculosis** None. **Deaths** Not reported **Withdrawals due to adverse events (no. of patients)** Not reported

			STAGE II: EFFICACY OUTCOMES **ACR 20 response** Infliximab: 18 wks: 77.6% (38/49); Placebo/infliximab: 18 wks: 52.0% (26/50). Infliximab: 22 wks: 71.4% (35/49); Placebo/infliximab: 22 wks: 62.0% (31/50). Infliximab: 30 wks: 65.3% (32/49); Placebo/infliximab: 30 wks: 66.0% (33/50). Infliximab: 38 wks: 57.1% (28/49); Placebo/infliximab: 38 wks: 62.0% (31/50). Infliximab: 46 wks: 57.1% (28/49); Placebo/infliximab: 46 wks: 66.0% (33/50). Infliximab: 50 wks: 69.4% (34/49); Placebo/infliximab: 50 wks: 68.0% (34/50). ***Subgroup results (baseline MTX or no baseline MTX) at 50 weeks*** [redacted] **ACR 50 response** Infliximab: 18 wks: 49.0% (24/49); Placebo/infliximab: 18 wks: 26.0% (13/50). Infliximab: 22 wks: 38.8% (19/49); Placebo/infliximab: 22 wks: 36.0% (18/50). Infliximab: 30 wks: 42.9% (21/49); Placebo/infliximab: 30 wks: 44.0% (22/50). Infliximab: 38 wks: 40.8% (20/49); Placebo/infliximab: 38 wks: 48.0% (24/50). Infliximab: 46 wks: 49.0% (24/49); Placebo/infliximab: 46 wks: 46.0% (23/50). Infliximab: 50 wks: 53.1% (26/49); Placebo/infliximab: 50 wks: 42.0% (21/50). **ACR 70 response** Infliximab: 18 wks: 28.6% (14/49); Placebo/infliximab: 18 wks: 8.0% (4/50). Infliximab: 22 wks: 22.4% (11/49); Placebo/infliximab: 22 wks: 20.0% (10/50). Infliximab: 30 wks: 26.5% (13/49); Placebo/infliximab: 30 wks: 22.0% (11/50). Infliximab: 38 wks: 26.5% (13/49); Placebo/infliximab: 38 wks: 28.0% (14/50). Infliximab: 46 wks: 32.7% (16/49); Placebo/infliximab: 46 wks: 24.0% (12/50). Infliximab: 50 wks: 38.8% (19/49); Placebo/infliximab: 50 wks: 34.0% (17/50). **Mean (SD) % ACR improvement** [redacted] **PsARC** Infliximab: 18 wks: 81.6% (40/49); Placebo/infliximab: 18 wks: 70.0% (35/50). Infliximab: 22 wks: 77.6% (38/49); Placebo/infliximab: 22 wks: 74.0% (37/50). Infliximab: 30 wks: 73.5% (36/49); Placebo/infliximab: 30 wks: 78.0% (39/50). Infliximab: 38 wks: 71.4% (35/49); Placebo/infliximab: 38 wks: 82.0% (41/50). Infliximab: 46 wks: 69.4% (34/49); Placebo/infliximab: 46 wks: 74.0% (37/50). Infliximab: 50 wks: 73.5% (36/49); Placebo/infliximab: 50 wks: 76.0% (38/50). **HAQ (0 to3)** [redacted]

			[redacted] [redacted] Infliximab: 50 wks: (n=45) –42.5 (8.8); [redacted] **Change in PASI mean (SE) change from baseline** Infliximab: 50 wks: (n=35) -4.8 (1.0); Placebo/infliximab: 50 wks: (n=37) -2.7 (1.0) **PASI 50** Infliximab 86.3% (19/22) ; Placebo/infliximab 68.8% (11/16) **PASI 75** Infliximab 59.1% (13/22) ; Placebo/infliximab 50% (8/16) **PASI 90** Infliximab 40.9% (9/22) ; Placebo/infliximab 37.5% (6/16) **Mean (SD) total modified van der Heijde-Sharp (vdH-S) score** *Baseline* Infliximab (n=37) 69.2 (94.9) ; Placebo/infliximab (n=35) 32.3 (39.7) *Week 50 change from baseline* Infliximab (n=37) -1.52 (NR) ; Placebo/infliximab (n=33) -1.95 (NR); combined (n=70) -1.72 (5.82) ***STAGE II: ADVERSE EVENTS*** [redacted] *Serious infection* – 1 patient on infliximab/placebo: *Salmonella* infection [redacted]

			[redacted]
IMPACT 2, 2005, USA[83, 91, 92, 96, 99, 107, 113, 117] **Type of publication** Full publication **Funding** Centocor & Schering-Plough **Study design** Double-blind RCT and open-label extension **Setting** Outpatient Multi-centre	**Inclusion/exclusion criteria** Adult patients diagnosed with active psoriatic arthritis at least 6 months before the first infusion of infliximab, with ≥5 swollen and tender joints and either CRP of ≥15mg/l and/or morning stiffness lasting 45 minutes or longer. Patient must have had an inadequate response to current or previous DMARDs or NSAIDs. Patient had a negative rheumatoid factor and active plaque psoriasis with at least one qualifying target lesion (≥2cm diameter). **Number randomised** 200	**Intervention Infliximab** Dose regimen: 5mg/kg at wks 0, 2, 6, 14, and 22 Length of treatment: 24 wks No. randomised: 100 No. completed: 93 **Comparator Placebo** Dose regimen: Equivalent Length of treatment: 24 wks No. randomised: 100 No. completed: 92 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	*STAGE I: EFFICACY OUTCOMES* **ACR 20** Infliximab 14 wks= 58% (58/100); Placebo 14 wks = 11% (11/100); p<0.001. Infliximab 24 wks = 54% (54/100); Placebo 24 wks =16% (16/100); p<0.001. **ACR 50** Infliximab 14 wks = 36% (36/100); Placebo 14 wks =3% (3/100); p<0.001. Infliximab 24 wks = 41% (41/100); Placebo: 24 wks = 4% (4/100); p<0.001. **ACR 70** Infliximab 14 wks = 15% (15/100); Placebo 14 wks =1% (1/100); p<0.001. Infliximab 24 wks = 27% (27/100); Placebo 24 wks = 2% (2/100); p<0.001. **PsARC** Infliximab 14 wks = 77% (77/100); Placebo 14 wks = 27% (27/100); p<0.001. Infliximab: 24 wks= 70% (70/100); Placebo 24 wks = 32% (32/100); p<0.001.

Duration of follow-up Stage I: 24 wks RCT Stage II: Open label follow-up to 54 wks **Frequency of follow-up** Baseline, 2, 6, 14, 24, 54 wks Extracted by: HY Checked by:	**Mean Age (SD)** Infliximab: 47.1 yrs (12.8) Placebo: 46.5 yrs (11.3) **Gender (% male)** Infliximab: 71% Placebo: 51% **Psoriatic arthritis history** Mean (SD) duration: Infliximab: 8.4 yrs (7.2) Placebo: 7.5 yrs (7.8) **Psoriasis History** Mean (SD) duration: Infliximab: 16.8 yrs (12.0) Placebo: 16.2 yrs (11.0) **Psoriasis Evaluation** Patients with ≥ 3% body surface area affected with psoriasis: Infliximab: 83/100 (83%) Placebo: 87/100 (87%) **Concurrent therapies** Concomitant MTX (up to 25 mg/wk) was permitted at least 3 months prior to the first infusion and was maintained at a stable dose for at least 4 weeks prior to first infusion. A stable dose (≤10mg) of oral prednisone was permitted. DMARDs or intra-articular corticosteroids were prohibited within 4 wks before the first infusion. DMARDs other than MTX were not permitted during the trial. Systematic or topical treatment for psoriasis was not permitted (except for low potency topical corticosteroids on face or groin).	placebo either at weeks 16 or 24) with further follow-up at week 54. **Primary Outcome** ACR 20 at wk 14 **Sample size calculation** Assuming that an ACR 20 rate of 42% on infliximab and 20% on placebo, a sample size of 100 patients per group gives 90% power to detect a significant difference between treatments on the primary outcome, with α =0.05 (two-sided). **Statistical analyses** Cochran-Mantel-Haenszel Chi-square test stratified by baseline MTX use was used to analyse categorical outcomes. A two-sided F test using ANOVA with baseline MTX as a factor was used to analyse continuous data. The LOCF approach was used for imputing missing data **ITT analysis** The analyses were performed on an intention-to-treat basis	**Mean (SD) HAQ at baseline:** Infliximab = 1.1 (0.6); Placebo = 1.1 (0.6) **HAQ % change from baseline (SD)** Infliximab 14 wks = 48.6 (43.3); Placebo 14 wks = -18.4 (90.5); p<0.001. Infliximab 24 wks = 46.0 (42.5); Placebo 24 wks = -19.4 (102.8); p<0.001 **HAQ improvement (≥0.3 decrease)** Infliximab 14 wks = 59%; Placebo 14 wks = 19%; p<0.001. Infliximab 24 wks = 52%; Placebo 24 wks = 20%; p<0.001. **PASI 50 (in patients with ≥3% BSA psoriasis)** Infliximab 14 wks = 82% (68/83); Placebo 14 wks = 9% (8/87); p<0.001. Infliximab 24 wks =75% (62/83); Placebo 24 wks = 8% (7/87); p<0.001. **PASI 75 (in patients with ≥3% BSA psoriasis)** Infliximab 14 wks = 64% (53/83); Placebo 14 wks = 2% (2/87); p<0.001. Infliximab 24 wks = 60% (50/83); Placebo 24 wks = 1% (1/87); p<0.001. **PASI 90 (in patients with ≥3% BSA psoriasis)** Infliximab 14 wks = 41% (34/83); Placebo 14 wks = 0% (0 /87); p<0.001. Infliximab 24 wks = 39% (32 /83); Placebo 24 wks = 0% (0 /87); p<0.001.  **Mean (SD) SF-36 at baseline** Physical component Infliximab = 33.0 (9.4); Placebo = 31.0 (9.0) Mental component Infliximab = 45.5 (11.9); Placebo = 47.0 (11.9)

			SF-36 mean change from baseline (SD) Physical component Infliximab 14 wks = 9.1 (9.3); Placebo 14 wks =1.1 (8.4); p<0.001. Infliximab 24 wks = 7.7 (9.8); Placebo 24 wks = 1.3 (8.2) ; p=0.001 Mental component Infliximab 14 wks = 3.8 (11.1); Placebo 14 wks = -1.2 (9.3); p<0.001. Infliximab 24 wks = 3.9 (11.9) ; Placebo 24 wks = 0.4 (11.6); p=0.05 *STAGE I: ADVERSE EVENTS* **Infectious adverse events including any serious infections (up to wk 24)** Placebo (n=97) Infliximab (all patients who received an infliximab dose, n=150) Upper respiratory tract infection 14 (14%) 15 (10%) Pharyngitis 4 (4%) 8 (5%) Sinusitis 4 (4%) 8 (5%) **Infections that required hospitalisation or use of intravenous antibiotics** Not reported. . Malignancy Placebo: 1 (basal cell carcinoma of skin) Infliximab: 0 **Reactivation of latent tuberculosis** None **Deaths** None **Total serious adverse events** Placebo: 6 (6%) Infliximab: 13 (9%) **Withdrawals due to adverse events (no. of patients)** Infliximab: 6 Placebo: 1 ***STAGE II: EFFICACY OUTCOMES*** **PsARC** Infliximab 54 wks = 74.4% (67/90); Placebo/infliximab 54 wks = 81.9% (68/83)

			PASI 50 (in patients with ≥3% BSA psoriasis) Infliximab 54 wks = 69.5% (57/82); Placebo/infliximab 54 wks = 80% (64/80) **PASI 75 (in patients with ≥3% BSA psoriasis)** Infliximab 54 wks = 48.8% (40/82); Placebo/infliximab 54 wks = 58.8% (47/80) **PASI 90 (in patients with ≥3% BSA psoriasis)** Infliximab 54 wks = 39% (32/82); Placebo/infliximab 54 wks = 81.9% (68/80) **Mean (SD) total modified van der Heijde-Sharp (vdH-S) score** *Baseline* Infliximab 30.3 (61.4) ; Placebo/infliximab 39.1 (82.8) *Week 54 change from baseline* Infliximab -0.94 (3.4); Placebo/infliximab 0.53 (2.6) *STAGE II: ADVERSE EVENTS* **Infectious adverse events including any serious infections** (through week 54) Combined infliximab/placebo (all who received an infliximab dose, n≥173)  **Infections that required hospitalisation or use of intravenous antibiotics** Not reported. Malignancy 2 (1 basal cell carcinoma, 1 Hodgin's lymphoma) **Reactivation of latent tuberculosis** None **Deaths** None **Total serious adverse events** 22 (11.5%) **Withdrawals due to adverse events (no. of patients)** 16 (8.4%)

10.3.3 Efficacy data extraction - adalimumab

Study details and design	Participant details	Intervention/outcome/analyses details	Results
ADEPT 2005, USA[52, 89, 93, 94, 101-105] **Type of publication** Full publication **Funding** Abbott Laboratories **Study design** Stage I: Double-blind RCT Stage II: Open-label extension **Setting** Outpatient **Duration of follow-up** Stage I: 24 wks	**Inclusion/exclusion criteria** Adults aged 18 years or above diagnosed with moderately or severely PsA (defined as ≥3 swollen and tender or painful joints). Patients must have either active psoriatic skin lesions or a documented history of psoriasis, with an adequate response or intolerance to NSAIDs. Patients were excluded if they had the following treatment: 1) within 4 wks of the baseline visit with cyclosporine, tacrolimus, DMARDs other than MTX, or oral retinoids; 2) topical therapy for psoriasis within 2 wks of baseline, other than medicated shampoos or low-potency topical steroids; 3) concurrent therapy with MTX at dosage >30mg/wk and/or corticosteroids in a prednisone-equivalent dosage of >10mg/day; and	**Intervention Adalimumab** Dose regimen: 40mg every other week. Length of treatment: 24 wks No. randomised: 153 No. completed: 140 **Comparator Placebo** Dose regimen: Equivalent Length of treatment: 24 wks No. randomised: 162 No. completed: 149 **Primary Outcome** *ACR 20 at wk 12 and the change in TSS of structural damage on radiographs of the hands and feet at wk 24.* **Sample size calculation** Assuming that the effect size of anticipated change in the modified total	*STAGE I: EFFICACY OUTCOMES* **ACR 20** Adalimumab 12wks= 58% (88 /151); Placebo 12 wks = 14% (23/162); p<0.001. Adalimumab 24wks =57% (86 /151); Placebo 24 wks = 15% (24 /162); p<0.001. Adalimumab+MTX 12 wks = 55% (42/77); Adalimumab alone 12 wks = 61% (45/74); p=0.511 Adalimumab+MTX 24 wks = 55% (42/77); Adalimumab alone 24 wks = 59% (44/74), p=0.622 **ACR 50** Adalimumab 12wks= 36% (54 /151); Placebo 12 wks = 4% (6/162); p<0.001. Adalimumab 24wks =39% (59 /151); Placebo 24 wks = 6% (10/162); p<0.001. Adalimumab+MTX 12 wks = 36% (28/77); Adalimumab alone 12 wks = 36% (27/74), p>0.999 Adalimumab+MTX 24 wks = 36% (28/77); Adalimumab alone 24 wks = 42% (31/74), p=0.509 **ACR 70** Adalimumab 12wks= 20% (30 /151); Placebo 12 wks = 1% (1/162); p<0.001. Adalimumab 24wks = 23% (35 /151); Placebo 24 wks = 1% (1 /162); p<0.001. Adalimumab+MTX 12 wks = 17% (13/77); Adalimumab alone 12 wks = 23% (17/74); p=0.416 Adalimumab+MTX 24 wks = 22% (17/77); Adalimumab alone 24 wks = 23% (17/74); p>0.999

Stage II: 24-144 wks **Frequency of follow-up** Baseline, 2, 4, 8, 12, 16, 20, and 24 wks Extracted by: HY Checked by: MR	4) anti-TNF therapy at any time. Number randomised 315 **Mean Age (SD)** Adalimumab: 48.6yrs (12.5); Placebo: 49.2yrs (11.1) **Gender (% male)** Adalimumab: 85/151(56.3%); Placebo: 89/162 (54.9%) **Psoriatic arthritis history** ***Mean (SD) duration*** Adalimumab: 9.8yrs (8.3); Placebo: 9.2yrs (8.7) **Psoriasis History** *Mean (SD) duration* Adalimumab: 17.2 yrs (12); Placebo: 17.1yrs (12.6) **Psoriasis Evaluation** Patients with >3% body surface area affected with psoriasis: Adalimumab: 70/151 (46.4%) Placebo: 70/162 (43.2%) **Concurrent therapies** MTX use was permitted if it had been taken for ≥3 months previously, with a stable dose for ≥ 4 wks prior to the trial. *Concomitant therapy at baseline* Concomitant MTX at baseline: Adalimumab 77/151 (51%) Placebo 81/162 (50%)	Sharp score is 0.325, the sample size of 150 per treatment group gave 80% power to detect a significant difference between treatments on this primary outcome, with α =0.05 (two-sided). **Statistical analyses** Proportions of patients' responding were compared using the Cochran-Mantel-Haenszel mean score test adjusted for the MTX use. Continuous data were analysed by ANOVA with factors of treatment, baseline, MTX use and extent of psoriasis. Nonresponder imputation was used, in which participants who discontinued or had missing data were counted as nonresponders. Patients who received rescue therapy were considered to be nonresponders at the time that rescue therapy was initiated. **ITT analysis** The analyses were performed on an intention-to-treat basis	**PsARC** Adalimumab 12wks= 62% (94 /151); Placebo 12 wks = 26% (42/162). Adalimumab 24wks = 60% (91 /151); Placebo 24 wks = 23% (37/162). **Mean HAQ at baseline (SD)** Adalimumab= 1.0 (0.6); Placebo= 1.0 (0.7) **HAQ mean change from baseline (SD)** Adalimumab 12wks= -0.4(0.5); Placebo 12 wks = -0.1(0.5); p<0.001. Adalimumab 24wks = -0.4(0.5); Placebo 24 wks = -0.1(0.4); p<0.001. Adalimumab+MTX 12 wks = -0.3 (0.4); Adalimumab alone 12 wks = -0.4 (0.5); p=0.188 Adalimumab+MTX 24 wks = -0.4 (0.5); Adalimumab alone 24 wks = -0.4 (0.5); p=0.690 **12 week HAQ mean change conditional on PsARC response at 12 weeks** PsARC responders: Adalimumab (n=93) = -0.5 (0.4); Placebo (n=42) = -0.3 (0.5) PsARC non-responders: Adalimumab (n=58) = -0.1 (0.4); Placebo (n=120) = -0.0 (0.4) **24 week HAQ mean change conditional on PsARC response at 12 weeks** PsARC responders: Adalimumab (n=90) = -0.5 (0.49); Placebo (n=37) = -0.3 (0.49) PsARC non-responders: Adalimumab (n=61) = -0.1 (0.39); Placebo (n=125) = -0.1 (0.39) **Mean PASI at baseline (SD)** Adalimumab= 7.4 (6.0); Placebo= 8.3 (7.2) **PASI 50** Adalimumab 12wks= 72% (50/69); Placebo 12 wks = 15% (10/69); p<0.001. Adalimumab 24wks = 75% (52/69); Placebo 24 wks = 12% (8/69); p<0.001. Adalimumab+MTX 12 wks = 76% (17/29); Adalimumab alone 12 wks = 70% (28/40); p=0.785 Adalimumab+MTX 24 wks = 86% (25/29); Adalimumab alone 24 wks = 68% (27/40); p=0.094 **PASI 75** Adalimumab 12wks= 49% (34/69); Placebo 12 wks = 4% (3/69); p<0.001. Adalimumab 24wks = 59% (41/69); Placebo 24 wks = 1% (1/69); p<0.001. Adalimumab+MTX 12 wks = 59% (17/29); Adalimumab alone 12 wks = 43% (17/40); p=0.227 Adalimumab+MTX 24 wks = 72% (21/29); Adalimumab alone 24 wks = 50% (20/40); p=0.083 **PASI 90** Adalimumab 12wks= 30% (21/69); Placebo 12 wks = 0% (0/69); p<0.001. Adalimumab 24wks = 42% (29/69); Placebo 24 wks = 0% (0/69); p<0.001.

			Adalimumab+MTX 12 wks = 38% (11/29); Adalimumab alone 12 wks = 25% (10/40); p=0.295 Adalimumab+MTX 24 wks = 52% (/1529); Adalimumab alone 24 wks = 35% (14/40); p=0. **Concurrent joint and skin response (PsARC and PASI 75)** Adalimumab 12wks= 42% (29/69); Placebo 12 wks = 1% (1/69); p<0.001 Adalimumab 24wks = 42% (29/69); Placebo 24 wks = 0% (0/69); p<0.001 **Total Sharp Score (TSS) change from baseline** Adalimumab 24wks = -0.2 (n=144); Placebo 24 wks = 0.1 (n=152); p<0.001 **SF-36 mean change from baseline (SD)** Physical component summary Adalimumab baseline= 33.2 (9.9); Placebo baseline = 33.3 (9.8); p<0.001. Change, adalimumab 12wks= 9.3 (10.0); Placebo 12 wks = 1.4 (8.7); p<0.001. Change, adalimumab 24wks = 9.3 (10.1); Placebo 24 wks =1.4 (9.6); p<0.001. Mental component summary Adalimumab baseline= 48.1 (10.2); Placebo baseline = 46.6 (12.2); p<0.001. Change, adalimumab 12wks= 1.6 (10.1); Placebo 12 wks = 1.2 (10.2); p=0.71 Change, adalimumab 24wks = 1.8 (9.3); Placebo 24 wks = 0.6 (10.4); p=0.29. *STAGE I: ADVERSE EVENTS* **Infectious adverse events including any serious infections** Placebo — Adalimumab Upper respiratory tract infection: 24/162 (14.8%) — 19/151 (12.6%) Nasopharyngitis: 15/162 (9.3%) — 15/151 (9.9%) Diarrhoea: 9/162 (5.6%) — 3/151 (2.0%) **Infections that required hospitalisation or use of intravenous antibiotics** Adalimumab: 1/ 151 (1 viral meningitis) Placebo: 2/162 (1 pericarditis; 1 cellulitis) **Malignancy** None **Reactivation of latent tuberculosis** Not reported. **Deaths** None

			Withdrawals due to adverse events (no. of patients) Adalimumab: 3 Placebo: 1 *STAGE 2: EFFICACY OUTCOMES (24-144 WEEKS)* **ACR 20** Adalimumab 48wks= 58.7% (165 /281) Adalimumab 104wks=57.3% (161/281) **ACR 50** Adalimumab 48wks= 42.7% (120 /281) Adalimumab 104wks=45.2 % (127/281) **ACR 70** Adalimumab 48wks= 27.8% (78/281) Adalimumab 104wks=29.9 % (84/281). **HAQ mean change from baseline (SD)** Adalimumab (n=298) 48wks= -0.3 (0.5) Adalimumab (n=271) 104wks= -0.3 (0.5) **HAQ percentage change from baseline (SD)** Adalimumab 48wks= -41.9% (114 /271) Adalimumab 104wks= -42.7% (116 /271) **Mean changes in modified Total Sharp Score** Adalimumab (n=115) 48wks=0.1(1.95); Adalimumab/Placebo (n=128) 48wks = 0.8(4.23) Adalimumab (n=115) 144wks= 0.5(4.20); Adalimumab/Placebo (n=128) 144 wks = 0.9(6.36) **Percentage changes (increase) in modified Total Sharp Score** Adalimumab 48wks= 26.6% (34/115); Adalimumab/Placebo 48wks =11.3 % (13/128) Adalimumab 144wks=20.9% (24 /115); Adalimumab/Placebo 144 wks = 31.3% (40/128) **PASI 50** Adalimumab 48wks= 67% (46/69); Adalimumab/placebo 48 wks =61% (42/69) **PASI 75** Adalimumab 48wks= 58% (40/69); Adalimumab/placebo 48 wks =53% (37/69) **PASI 90** Adalimumab 48wks= 46% (32/69) ; Adalimumab/placebo 48 wks =44 % (30/69)

			STAGE II: Adverse events (24-144 weeks) **Any serious adverse events** Adalimumab exposure: 16.8% (50/298) **Infections that required hospitalisation or use of intravenous antibiotics** Adalimumab exposure: 5% (15/298) **Cancer** Any malignancies: 1.3% (4/298) Lymphoma: 0.3% (1/298) Non-melanoma skin cancers: 0.7% (2/298) Other malignancies: 0.3% (1/298) **Reactivation of latent tuberculosis** Adalimumab exposure: 0.3% (1/298) **Deaths** Adalimumab exposure: 1.0% (3/298) **Withdrawals due to adverse events (no. of patients)** Adalimumab exposure: 6.7% (20/298) *STAGE I: EFFICACY OUTCOMES* **ACR 20** Adalimumab 12 wks= 39% (20/51); Placebo 12 wks = 16% (8/49); p<0.05. **ACR 50** Adalimumab 12 wks= 25% (13 /51); Placebo 12 wks =2 % (1/49); p<0.001. **ACR 70** Adalimumab 12 wks= 14% (7/51); Placebo 12 wks = 0% (0/49); p<0.05. **PsARC** Adalimumab 12 wks= 51% (26/51); Placebo 12 wks = 24% (12/49); p=0.007 **Mean HAQ at baseline (SD)** Adalimumab= 0.9(0.5); Placebo= 1.0(0.7) **HAQ mean change from baseline (SD)** Adalimumab 12 wks= -0.3(0.5); Placebo 12 wks = -0.1(0.3); p<0.01. **12 week HAQ mean change conditional on PsARC response at 12 weeks**

Genovese, 2007 USA[84] Type of publication Full publication Funding Abbott Laboratories Study design Stage I: Double-blind RCT Stage II: Open-label extension Setting Outpatient Duration of follow-up **Stage I: 0-12 wks** Stage II: 12-24 wks Frequency of follow-up Baseline, 2, 4, 8, 12 , 14, 18, 24 wks Extracted by: HY Checked by: MR	**Inclusion/exclusion criteria** Adults aged 18 years or above had generally good health based on medical history, physical examination, laboratory profile, chest radiograph, and 12-lead electrocardiogram. Patient must have ≥3 swollen and tender or painful joints, and either an active cutaneous lesion of chronic plaque psoriasis or a documented history of chronic plague psoriasis. All patients received concomitant DMARD therapy or had a history of DMARD therapy with an inadequate response. Patients were excluded if they had the following treatment: 1) previous [redacted] therapy; 2) IV infusion or intra-articular injections of corticosteroids within 4 wks of baseline; 3) topical psoriasis therapies within 2 wks of baseline; 4) UVA phototherapy or use of tanning booth within 2 wks of baseline; 5) oral retinoids within 4 wks of the baseline	**Intervention Adalimumab** Dose regimen: 40mg every other week. Length of treatment: 12 wks No. randomised: 51 No. completed: 50 **Comparator Placebo** Dose regimen: Equivalent Length of treatment: 12 wks No. randomised: 51 No. completed: 46 **Primary Outcome** *American College of Rheumatology 20% criteria for improvement in rheumatoid arthritis (ACR 20) at wk 12* **Sample size calculation** Assuming that a response rate of 25% on placebo and 60% on adalimumab, the sample size of 50 patients per groups gave 90% power to detect a significant difference between treatments on the primary outcome, with α =0.05 (two-	PsARC responders: Adalimumab (n=26) = -0.4 (0.4); Placebo (n=12) = -0.2 (0.3) PsARC non-responders: Adalimumab (n=26) = -0.1 (0.4); Placebo (n=12) = -0.1 (0.3) **Patient global assessment of disease activity (improvement from baseline)** Adalimumab 12 wks= -14.8 (24.5); Placebo 12 wks = -0.4 (24.9); p<0.004. **Physician global assessment of disease activity (improvement from baseline)** Adalimumab 12 wks= -21.4 (22.4); Placebo 12 wks =-9.7 (18.2); p<0.005. **Physician global assessment for psoriasis ("Clear" or "Minimal")** Adalimumab 12 wks= 40.6 % (13/32); Placebo 12 wks = 6.7% (2/30); p<0.002. **Target lesion score mean change from baseline (SD)** Adalimumab 12 wks= -3.7 (3.3); Placebo 12 wks = -0.3 (3.1); p<0.001. **Mean (SD) SF-36 at baseline** Physical component summary Adalimumab = 34.9 (9.2); Placebo = 32.7 (11.3) Mental component summary Adalimumab = 48.1 (10.2); Placebo = 46.6 (10.2) **SF-36 mean change from baseline (SD)** Physical component summary Adalimumab 12 wks= 5.7(8.5); Placebo 12 wks = 2.8(7.1); p=0.08. Mental component summary Adalimumab 12 wks= 1.1(7.4); Placebo 12 wks = -0.6 (7.8); p=0.24 **DLQI mean change from baseline (SD)** Adalimumab 12 wks= -3.4 (4.5); Placebo 12 wks = -1.7 (5.3); p=0.171 *STAGE I: ADVERSE EVENTS* **Infectious adverse events including any serious infections** Placebo Adalimumab Any infectious AE 16/49 (32.7%) 9/51 (17.6%) Upper respiratory tract infection 4/49(8.2%) 7/51(13.7%)

	visit, alefacept or siplizumab within 12 wks, or any other biologic or investigational therapy within 6 wks of the baseline visit; 6) antiretroviral therapy at any time. **Number randomised** 102 **Mean Age (SD)** Adalimumab: 50.4yrs (11.0); Placebo: 47.7 yrs (11.3) **Gender** Adalimumab: Male 29/51 (56.9%); Placebo: Male 25/49 (51%) **Psoriatic arthritis history** Mean (SD) duration: Adalimumab: 7.5 yrs (7.0) Placebo: 7.2yrs (7.0) **Psoriasis History** Mean (SD) duration: Adalimumab: 18.0 yrs (13.2) Placebo: 13.8yrs (10.7) **Psoriasis Evaluation** Patients with [redacted] **Concurrent therapies** All patients were permitted to use concomitant DMARD therapy or had a history of DMARD therapy with an inadequate response. Oral corticosteroids were permitted to use if the dosage did not exceed the equivalent of prednisone 10mg/day and had been stable during the 4 wks prior to the trial. Concomitant treatments with MTX or other	sided). **Statistical analyses** Proportions of patients' responding were compared using the Cochran-Mantel-Haenszel test, with baseline DMARD use as the stratification factor. ACR 20 at response rates at time points except for wk 12 and ACR 50 and ACR 70 rates at all timepoints were analysed using Fisher's exact test, combining baseline DMARD use categories. Continuous data were analysed using ANOVA with factors of baseline DMARD use and treatment. Nonresponder imputation for missing data was used for analyses of ACR and PsARC responses, and last observation carried forward was used for all other efficacy measures. **ITT analysis** The analyses were performed on an intention-to-treat basis	Diarrhoea 3 /49 (6.1%) 1/51 (2.0%) **Infections that required hospitalisation or use of intravenous antibiotics** Adalimumab: 1/51 Placebo: 1/49 **Non-infectious serious adverse events** Adalimumab: 1/51 (diverticulitis) Placebo: 2/49 (1 sublingual abscess, 1 benign perigangloma neoplasm) **Cancer** None **Reactivation of latent tuberculosis** None **Deaths** None **Withdrawals due to adverse events (no. of patients)** Adalimumab: 1 Placebo: 2 ***STAGE II: EFFICACY OUTCOMES*** **ACR 20** Adalimumab 24 wks= 65% (33/51); Adalimumab/placebo 24 wks = 57% (26/46) **ACR 50** Adalimumab 24 wks= 43% (22/51); Adalimumab/placebo 24 wks = 37% (17/46) **ACR 70** Adalimumab 24 wks= 27% (13/51); Adalimumab/placebo 24 wks = 22% (10/46) **PsARC** Adalimumab 24 wks= 75% (38/51); Adalimumab/placebo 24 wks = 70% (32/46) **HAQ mean change from baseline (SD)** Adalimumab 24 wks= -0.3(0.5); Adalimumab/placebo 24 wks = -0.4(0.4) **Physician global assessment for psoriasis ("Clear" or "Minimal")** Adalimumab 24 wks= 56.3% (18/32); Adalimumab/placebo 24 wks = 50% (13/26) **SF-36 mean change from baseline (SD)** Physical component summary Adalimumab 24 wks= 8.6(7.4); Adalimumab/placebo 24 wks = 11.7(9.1)

	DMARD, with the exception of cyclosporine and tacrolimus received within 4 wks of the baseline visit, were permitted if the patient had received a minimum of 3 months of therapy and the dosage was stable during the 4 wks prior to the trial. The maximum allowable MTX dosage was 30mg/wk. *Concomitant therapy at baseline* Concomitant MTX at baseline: Adalimumab 24/51 (47.1%) Placebo 23/49 (46.9%)		Mental component summary Adalimumab 24 wks= 1.9(8.2); Adalimumab/placebo 24 wks = 0.3 (9.7) **DLQI mean change from baseline (SD)** Adalimumab 24 wks= -3.5 (5.1); Adalimumab/placebo 24 wks = -3.9 (6.4) *STAGE II: ADVERSE EVENTS (WKS 12-24)* **Infectious adverse events including any serious infections** Adalimumab/placebo Any infectious AE 29/97 (29.9%) Upper respiratory tract infection 6/97 (6.2%) Diarrhoea 2/97 (2.1%) **Infections that required hospitalisation or use of intravenous antibiotics** Adalimumab/placebo = 0% (0/97) **Malignancy** 3 cases (1 non-Hodgkin's lymphoma, 1 squamous cell carcinoma of the skin, 1 adenocarcinoma of the prostate) **Reactivation of latent tuberculosis** None **Deaths** None **Withdrawals due to adverse events (no. of patients)** Not reported

10.3.4 Adverse events data extraction

Study details and design	Intervention and duration of follow-up	Number of patients receiving anti-TNFs	Number of patients with any infection	Infections that required hospitalisation or use of intravenous antibiotics (No. of patients)	Malignancy (No. of patients)	Tuberculosis (No. of patients)	Deaths (No. of patients)	Withdrawals due to adverse events (No. of patients)
Multiple biologics								
Brassard 2006, Case control study[136]	Etanercept & Inflixmab; 373.9 days(mean)	Etanercept: 2349 RA patients Infliximab: 1074 RA patients	NR	NR	NR	Etanercept: 32 (1.4%) Infliximab: 19 (1.8%)	NR	NR
Carmona 2005, Multicenter surveillance study[142]	Etanercept, Infliximab & Adalimumab 5 years	Total: 4092 patients of RA, AS, PsA, juvenile idiopathic arthritis and other chronic inflammatory rheumatic conditions. It includes 2833 (69%) RA patients: Etanercept: 2227 Infliximab: 739 Adalimumab: 154	NR	NR	NR	Infliximab: 34 (4.6%; of whom 28 had RA). Etanercept: None (0%) Adalimumab: None (0%)	1 TB patient died of liver failure.	NR
Curtis 2007, Retrospective cohort study[135]	Etanercept, Infliximab & Adalimumab; 20 months (mean)	Etanercept: 1201 Infliximab: 792 Adalimumab: 118 More than one anti-TNFs: 282 Total: 2393 RA patients	NR	65 (2.7%)	NR	NR	NR	NR
Dixon 2006, Prospective cohort study[137]	Etanercept, Infliximab & Adalimumab;	Etanercept: 3596 Infliximab: 2878 Adalimumab: 1190 Total: 7664 RA	NR	Etanercept: 209 (5.8%) Infliximab: 255 (8.9%) Adalimumab: 61 (5.1%)	NR	Etanercept: 2 (0.06%) Infliximab: 7 (0.2%) Adalimumab: 1	NR	NR

	1.26 years (median)	patients				(0.08%)		
Dixon 2007, Prospective cohort study[148]	Etanercept, Infliximab & Adalimumab; 24 months	Etanercept: 3844 Infliximab: 2944 Adalimumab: 1871 Total: 8659 RA patients	NR	Etanercept: 432 (11.2%) Infliximab: 405 (13.8%) Adalimumab: 138 (7.3%)	NR	NR	NR	NR
Dreyer 2009 Prospective cohort study[149]	Etanercept, Infliximab & Adalimumab; 6092 patient-years	Total :3688	NR	NR	NR	30 cancers in 28 patients (0.76%)	NR	NR
Favalli 2009, Cohort study[130]	Etanercept, Infliximab & Adalimumab; 24.21 months	Etanercept: 242 Infliximab: 519 Adalimumab: 303 Total: 1064 RA patients	NR	Etanercept: 11 (4.5%) Infliximab: 42 (8.1%) Adalimumab: 20 (6.6%)	NR	Etanercept: 1 (0.4%) Infliximab: 3 (0.6%) Adalimumab: 1 (0.3%)	Total (all serious infection): 4 (0.4%)	NR
Gomez-Reino 2003, Multicenter surveillance study[147]	Etanercept Infliximab 1.1 years (mean)	1540 patients of RA, PsA and AS.	118 (7.6%)	10 sepsis (0.65%)	NR	Etanercept: 0 (0%) Infliximab: 17 (1.1%)	Serious infection: 2 (0.1%)	NR
Gomez-Reino 2007, Multicenter surveillance study[133]	Etanercept, Infliximab & Adalimumab; NR	Etanercept: 1336 Infliximab: 1137 Adalimumab: 615 Total: 3088 patients of rheumatic diseases	NR	NR	NR	Etanercept: 2 (0.1%) Infliximab: 5 (0.4%) Adalimumab: 1 (0.2%)	NR	NR
Listing 2005, prospective cohort study[123]	Etanercept & Infliximab; 12 months	Etanercept: 512 RA patients Infliximab: 346 RA patients	Etanercept: 109 (21.3%) Infliximab: 92 (26.6%)	Etanercept: 31 (6.1%) Inflixmab: 20 (5.8%)	NR	Etanercept: 0 (0%) Infliximab: 1 (0.3%)	Serious infection: 4 (0.5%)	NR
Etanercept								

Fleischmann 2006, Integrated data of trials[100]	Etanercept NR	Etanercept: 3132 patients of RA, PsA and AS Control: 1190 patients receiving placebo or MTX	Etanercept: 1704 (54.4%) Control (placebo or MTX): 493 (41.4%)	Etanercept: 155 (4.9%) Control (placebo or MTX): 25 (2.1%)	NR	None	Etanercept and control: 41 (0.9%)	Etanercept: 204 (6.5%) Control (placebo or MTX): 57 (4.8%)
Horneff 2009, Open, non-randomised study[126]	Etanercept 12 months	604 patients of juvenile idiopathic arthritis	58 (9.6%)	26 (4.3%)	NR	NR	None (0%)	NR
Klareskog 2006, Open label extension[121]	Etanercept 5 years	549 RA patients	146 (26.5%)	89 (16.2%)	Total: 7 (1.3%) Lung cancer: 2 (0.4%) Breast cancer: 3 (0.5%) Lymphoma: 1 (0.2%) Basocellular skin cancer: 2 (0.4%)	None	Total: 10 (1.8%) Serious infection: 7 (1.3%)	25 (4.6%)
Mease 2006, Open label extension[98]	Etanercept 48 weeks	169 PsA patients	3 (1.8%)	1 (0.6%)	NR	NR	None (0%)	None (0%)
Moreland 2006, Data from RCTs or open label extension[122]	Etanercept 7 years	714 RA patients	NR	94 (13.2%)	Total: 41 (5.7%) Squamous cell carcinoma of larynx: 1 Lymphoma: 7 Lung cancer: 5 Ovarian cancer: 4 Breast cancer: 3 Leukemia: 2 Prostate cancer: 2 Malignant melanoma: 2 Squamous cell skin carcinomas: 4 Basal cell skin carcinomas: 11	None	Total: 22 (3.1%) Serious infection: 2 Malignancy: 3	97 (13.6%; due to adverse events and deaths):

Feltelius 2005, Nationwide postmarketing cohort study[143]	Etanercept 24 months	1073 RA patients	120 (11%)	Total: 28 (2.6%) Sepsis: 8 Pneumonia: 8 Osteitis: 3 Infectious arthritis: 2 Soft tissue abscess: 2 Gastroenteritis: 2 Recurrent fever: 1 Skin inflammation: 1 Encephalitis: 1	Total: 11 (1%) Lymphoma: 3 Benign respiratory tract neoplasm: 2 Unspecified liver cancer: 1 Primary liver cancer: 1 Benign gastrointestinal neoplasm: 1 Ovarian cancer: 1 Cervical cancer: 1 Rectal cancer: 1	NR	Total: 3 (0.3%) Serious infection: 1 Malignancy: 1	59 (5.5%)
Infliximab								
Antoni 2008, Open label extension[90]	Infliximab 98 weeks	78 PsA patients	Upper respiratory tract infection: 30 (38.5%) Diarrhoea: 7 (9.0%) Pharyngitis: 7 (9.0%) Sinusitis: 4 (5.1%) Urinary tract infection: 4 (5.1%)	2 (2.6%; 1 knee wound, 1 bowel)	Total: 4 neoplasms (5.1%) Benign abdominal mucinous systoma: 1 Nonresectable pancreatic ductal adenocarcinoma: 1 Mild hemangioma: 1 Leukocythemia: 1	None (0%)	NR	5 (6.4%)
Caspersen 2008, Cohort study[129]	Infliximab 6 years	651 patients with Crohn's disease	NR	Total: 66 (10.1%) Abscesses: 34 Pneumonia: 16 Sepsis: 8 Pleuritis: 2 Aspergillus Pneumonia: 2 Keratoconjunctivitis: 2 Bone infection in Jaw: 1 Exacerbation of osteomyelitis: 1	Total: 4 (0.6%) Relapse of breast cancer: 1	2 (0.3%)	Total: 13 (2.0%) Serious infection: 4 Malignancy: 1	NR
Colombel 2004, Retrospective cohort study[125]	Infliximab 17 months (median)	500 patients with Crohn's disease	48 (9.6%)	Total: 15 (3.0%) Sepsis: 2 Pneumonia: 8 Histoplasmosis: 1 Viral infections: 1	Total: 9 (1.8%) Cancer: 7 (2 lung cancer; 1 abdominal carcinomatosis, 2 squamous cell	NR	Total: 10 (2%) Serious infection: 4 Malignancy:2	NR

				Abscesses: 2 Cutaneous infections: 1	carcinoma, 2 basal cell carcinoma) Non-Hodgkin's lymphoma: 1 Hodgkin's lymphoma: 1			
Fidder 2009, Retrospective cohort study[120]	Infliximab 58 months (median)	734 patients with IBD	NR	48 (6.5%)	21 (2.9%)	1 (0.1%)	Total: 12 (1.6%) Serious infection: 1 Malignancy: 3	NR
Oka 2006, Post-marketing surveillance data[138]	Infliximab 22 weeks	5000 RA patients	NR	Lung infections: 155 (3.1%)	NR	14 (0.3%)	Total: 3 (0.06%) Serious infection: 3	NR
Schnitzler 2009 Retrospective cohort study [128]	Infliximab 55 months (median)	614 Crohn's disease patients	NR	5 serious infections (0.8%): 1 fatal Aspergillus, 1 abdominal tuberculosis	1 pancreatic carcinoma (0.16%)	NR	Total: 10 (1.6%) 1 fatal *Aspergillus* infection	70 (12.8%)
St. Clair 2004 [144] RCT	Infliximab + MTX ~54 weeks	749 early RA patients	URTI: 200 (26.7%) Sinusitis: 73 (9.7%) Pharyngitis: 103 (13.8%)	At least 1 serious infection: 40 (5.3%) Pneumonia: 15 (2.0%) Tuberculosis: 4 (0.5%) Sepsis: 3 (0.4%) Bronchitis: 2 (0.27%) Septic bursitis: 2 (0.27%)	Total: 4 (0.5%) 1 endometrial cancer 1 pancreatic cancer 1 colon adenocarcinoma 1 acute myeloid leukaemia	4 (0.5%)	Total: 2 (0.27%) 1 pancreatic cancer	69/722 (9.6%)
Takeuchi 2008 [131] Prospective cohort study	Infliximab 6 months	5000 RA patients	Total: 433 (8.7%)	Bacterial pneumonia: 108 (2.2%) (Suspected *P jirovecii* pneumonia: 22 (0.4%) Interstitial pneumonitis: 25 (0.5%)	All neoplasms: 8 (0.16%)	14 (0.3%)	NR	NR
Westhovens 2006 [140]	Infliximab + MTX 22 weeks	721 RA patients at 22 weeks 1001 RA patients at	*0-22 weeks* URTI: 78 (10.8%) Pharyngitis: 34 (4.7%) Sinusitis: 30 (4.2%)	*0-22 weeks* Pneumonia: 6 (0.8%) Tuberculosis: 3 (0.4%) Cellulitis: 2 (0.3%)	Total: 26 (2.6%) Details reported	*0-22 weeks:* 3 (0.4%) *22-54 weeks*: 4 (0.4%)	Total: 4 (0.4%) 1 tuberculosis	*0-22 weeks* 38/721 (5.3%) *22-54 weeks*

RCT 54 weeks		54 weeks.	Pneumonia: 6 (0.8%) Tuberculosis: 3 (0.4%) Cellulitis: 2 (0.3%) UTI: 2 (0.3%) *22-54 weeks* Total: 354 (35.4%)	UTI: 2 (0.3%) *22-54 weeks* Total: 31 (3.1%) Pneumonia: 12 (1.2%) Tuberculosis: 4 (0.4%) Abscess: 6 (0.6 %) Pyelonephritis: 3 (0.3%)				87/1084 (8.0%)
Wolfe 2004 [145] Prospective cohort study	Infliximab 2.5 years	6,460 RA patients	NR	NR	NR	4 (0.06%)	NR	NR
Adalimumab								
Breedveld 2006 [141] RCT	Adalimumab +/- MTX 2 years	542 RA patients	Total: 9.12% (estimated)	Total: 12 (2.2%) Pulmonary infection: 4 (0.74%) Sinus infection: 1 (0.18%) Wound infection: 1 (0.18%) Septic arthritis: 2 (0.37%) Infected hygroma: 1 (0.18%) Cellulitis: 2 (0.37%) UTI: 1 (0.18%)	Total: 6 (1.1%)	1 (0.18%)	Total: 5 (0.9%) Cancer: 3 (0.55%)	58/542 (10.7%)
Burmester 2007 [132] Uncontrolled open-label study	Adalimumab +/- DMARD Median 211 days	6610 RA patients	NR	202 (3.1%)	43 (0.7%)	21 (0.3%)	Total: 35 (0.5%) Tuberculosis: 1	682/6610 (10.3%)
Colombel 2007 [134] RCT	Adalimumab 56 weeks	CD patients 0-4 weeks, n=854 4-56 weeks, n=517	*0-4weeks* 130 (15.2%) *4-56 weeks* 234 (45.3%)	*0-4weeks* 10 (1.2%) *4-56 weeks* 14 (2.7%)	*4-56 weeks* 1 breast cancer (0.2%)	*4-56 weeks* 2 (0.4%)	*4-56 weeks* 1 (0.2%)	*0-4weeks* 54/854 (6.3%) *4-56 weeks* 30/517 (5.8%)
Rudwaleit 2009 [127] Uncontrolled open-label study	Adalimumab Median: 12 weeks	969 AS patients with advanced spinal fusion	NR	4 (0.4%)	NR	NR	NR	NR

Schiff 2006 [139] Analysis of clinical trial safety database	Adalimumab NR	10,050 RA patients	NR	638 (6.3%)	15 lymphomas (0.1%)	34 (0.3%)	NR	NR

10.4 Table of excluded studies with rationale

10.4.1 Studies excluded from efficacy search

Study	Reason for exclusion[a]
Anandarajah AP, Ritchlin CT. Etanercept in psoriatic arthritis. *Expert Opinion on Biological Therapy* 2003;3(1):169-177.	2
Antoni CE. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT) (errata). *Arthritis and Rheumatism* 2005;52(9):2951.	2
Bathon J, Fleischmann R, Peloso P, Chon Y, Hooper M, Lin SL. Rates of cardiovascular events in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis treated with etanercept or placebo in clinical trials [abstract 344]. *Arthritis and Rheumatism* 2006;54(9 Suppl):S188.	2
Bongiorno MR, Pistone G, Doukaki S, Arico M. Adalimumab for treatment of moderate to severe psoriasis and psoriatic arthritis. *Dermatologic Therapy* 2008;21 Suppl 2:S15-S20.	2
Brodszky V, Pentek M, Gulacsi L. Efficacy of adalimumab, etanercept, and infliximab in psoriatic arthritis based on ACR 50 response after 24 weeks of treatment. *Scandinavian Journal of Rheumatology* 2008;37(5):399-400.	2
Colombel JF. Efficacy and safety of adalimumab for the treatment of Crohn's disease in adults. *Expert Review of Gastroenterology and Hepatology* 2008;2(2):163-176.	2
Cruyssen BV, De Keyser F, Kruithof E, Mielants H, Van den Bosch F. Comparison of different outcome measures for psoriatic arthritis in patients treated with infliximab or placebo [abstract SAT0315]. *Annals of the Rheumatic Diseases* 2006;65 Suppl 2:546-547.	2
Frankel EH, Strober BE, Crowley JJ, Fivenson DP, Woolley JM, Yu EB, et al. Etanercept improves psoriatic arthritis patient-reported outcomes: results from EDUCATE. *Cutis* 2007;79(4):322-326.	2
Gottlieb AB, Kircik L, Eisen D, Jackson JM, Boh EE, Strober BE, et al. Use of etanercept for psoriatic arthritis in the dermatology clinic: the Experience Diagnosing, Understanding Care, and Treatment with Etanercept (EDUCATE) study. *Journal of Dermatological Treatment* 2006;17(6):343-352.	2
Hamza S, Chon Y, Hooper M, MacPeek D, Lin S. Rates of serious infectious events and opportunistic infections in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis treated with etanercept or placebo in clinical trials [abstract THU0153]. *Annals of the Rheumatic Diseases* 2007;66 Suppl 2:171-172.	2
Kimball AB, Jackson JM, Sobell JM, Boh EE, Grekin S, Pharmd EBY, et al. Reductions in healthcare resource utilization in psoriatic arthritis patients receiving etanercept therapy: results from the educate trial. *Journal of Drugs in Dermatology: JDD* 2007;6(3):299-306.	2
Kristensen LE, Gulfe A, Saxne T, Geborek P. Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register. *Annals of the Rheumatic Diseases* 2008;67(3):364-369.	2
Kvien TK, Heiberg MS, Lie E, Kaufmann C, Mikkelsen K, Nordvag	2

BY, et al. A Norwegian DMARD register: prescriptions of DMARDs and biological agents to patients with inflammatory rheumatic diseases. *Clinical and Experimental Rheumatology* 2005;23 Suppl 39:S188-S194.

McHugh N, van den Bosch F, Manger B, Goupille P, Cooper R, Kron M, et al. Adalimumab treatment is effective in patients with psoriatic arthritis (PSA) in day-to-day clinical practice - results from the stereo trial [abstract 259]. *Rheumatology* 2008;47 Suppl 2:ii76. 2

Mease P. Infliximab (Remicade) in the treatment of psoriatic arthritis. *Therapeutics and Clinical Risk Management* 2006;2(4):389-400. 2

Mease PJ, Choy EHS, Atkins CJ, Sasso EH. Effectiveness of adalimumab in psoriatic arthritis patients with oligoarticular arthritis: subanalysis of ADEPT [abstract P-022]. *4th European Academy of Dermatology and Venereology (EADV) Spring Symposium Saariselka, Lapland, Finland . February 9-12th, 2006* 2006:P-022. 5

Ravindran V, Scott DL, Choy EH. A systematic review and meta-analysis of efficacy and toxicity of disease modifying anti-rheumatic drugs and biological agents for psoriatic arthritis. *Annals of the Rheumatic Diseases* 2008;67(6):855-859. 2

Revicki D, Willian MK, Saurat JH, Papp KA, Ortonne JP, Sexton C, et al. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. *British Journal of Dermatology* 2008;158(3):549-557. 3

Rinaldi F, Provenzano G, Termini A, Spinello M, La Seta F. Long term infliximab treatment for severe psoriatic arthritis: evidence of sustained clinical and radiographic response. *Annals of the Rheumatic Diseases* 2005;64(9):1375-1376. 2

Ritchlin C. Efficacy and safety of infliximab for the treatment of psoriatic arthritis. *Nature Clinical Practice Rheumatology* 2006;2(6):300-301. 2

Romero-Mate A, Garcia-Donoso C, Cordoba-Guijarro S. Efficacy and safety of etanercept in psoriasis/psoriatic arthritis: an updated review. *American Journal of Clinical Dermatology* 2007;8(3):143-155. 2

Saad AA, Symmons DPM, Noyce PR, Ashcroft DM. Risks and benefits of tumor necrosis factor-alpha inhibitors in the management of psoriatic arthritis: systematic review and metaanalysis of randomized controlled trials. *Journal of Rheumatology* 2008;35(5):883-890. 2

Scheinfeld N. Adalimumab: a review of side effects. *Expert Opinion on Drug Safety* 2005;4(4):637-641. 2

Simpson D, Scott LJ. Adalimumab: in psoriatic arthritis. *Drugs* 2006;66(11):1487-1496. 2

Spadaro A, Ceccarelli F, Scrivo R, Valesini G. Life-table analysis of etanercept with or without methotrexate in patients with psoriatic arthritis. *Annals of the Rheumatic Diseases* 2008;67(11):1650-1651. 2

Strober B, Teller C, Yamauchi P, Miller JL, Hooper M, Yang YC, et al. Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. *British Journal of Dermatology* 2008;159(2):322-330. 4

Toussirot E, Streit G, Wendling D. Infectious complications with anti-TNFalpha therapy in rheumatic diseases: a review. *Recent Patents on Inflammation and Allergy Drug Discovery* 2007;1(1):39-47. 2

Van den Bosch F, Manger B, Goupille P, Kron M, Kary S, Kupper H. Clinical remission and good clinical responses in patients with psoriatic arthritis (PsA) treated with adalimumab (HUMIRA (R)): results of the STEREO trial [abstract 1100]. *Arthritis and Rheumatism* 2008;58(9 Suppl):S576. 2

van den Bosch F, Manger B, Goupille P, McHugh N, Roedevand E, Holck P, et al. Adalimumab (Humira (R)) is effective in treating patients with psoriatic arthritis (PSA) in real-life clinical practice: results of the STEREO trial [abstract OP0147]. *Annals of the Rheumatic Diseases* 2007;66 Suppl 2:98.	2
Van den Bosch F, Reece R, Manger B, Goupille P, Roedevand E, Holck P, et al. Adalimumab (HUMIRA (R)) is effective and safe in treating psoriatic arthritis (PsA) in real-life clinical practice: preliminary results of the STEREO trial [abstract 1810]. *Arthritis and Rheumatism* 2006;54(9 Suppl):S719-S720.	2
Van Kuijk AWR, Gerlag DM, Vos K, Wolbink G, Zwinderman AH, Dijkmans BAC, et al. A randomized, placebo-controlled study to identify biomarkers associated with active treatment in psoriatic arthritis: effects of adalimumab treatment on synovial biomarkers [abstract 674]. *Arthritis and Rheumatism* 2008;58(9 Suppl):S415.	4
Vandenbosch F, McHugh NJ, Reece R, Cooper R, Manger B, Goupille P, et al. Treatment with adalimumab (Humira (R)) is safe and effective in psoriatic arthritis (PsA) patients in real-life clinical practice: preliminary results of the stereo trial [abstract 87]. *Rheumatology* 2007;46 Suppl 1:i52-i53.	2
Winterfield LS, Menter A. Infliximab. *Dermatologic Therapy* 2004;17(5):409-426.	2
Winthrop KL, Siegel JN, Jereb J, Taylor Z, Iademarco MF. Tuberculosis associated with therapy against tumor necrosis factor alpha. *Arthritis and Rheumatism* 2005;52(10):2968-2974.	2

[a] Reasons for exclusion: 1 - Not relevant drug; 2– not RCT or extension; 3 – not PsA. 4 – no eligible outcomes. 5 – unable to order

10.4.2 Studies excluded from adverse event searches

Study	Reason for exclusion[a]
Anandarajah AP, Ritchlin CT. Etanercept in psoriatic arthritis. *Expert Opinion on Biological Therapy* 2003;3(1):169-177.	2
Author not found. [Active tuberculosis after use of infliximab (Remicade)]. *Geneesmiddelenbulletin* 2001;35(3):33.	2
Author not found. Infection risk with infliximab. *Pharmaceutical Journal* 2001;266(7129):7.	2
Baldin B, Dozol A, Spreux A, Chichmanian RM. [Tuberculosis and infliximab treatment: national surveillance from January 1, 2000, through June 30, 2003]. *Presse Medicale* 2005;34(5):353-357.	2
Boehncke WH, Prinz J, Gottlieb AB. Biologic therapies for psoriasis. A systematic review. *Journal of Rheumatology* 2006;33(7):1447-1451.	4
Brimhall AK, King LN, Licciardone JC, Jacobe H, Menter A. Safety and efficacy of alefacept, efalizumab, etanercept and infliximab in treating moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. *British Journal of Dermatology* 2008;159(2):274-285.	4
Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. *Arthritis and Rheumatism* 2002;46(12):3151-3158.	2
Caviglia R, Boskoski I, Cicala M. Long-term treatment with infliximab in inflammatory bowel disease: safety and tolerability issues. *Expert Opinion on Drug Safety* 2008;7(5):617-632.	4
Colombel JF. The CHARM trial of adalimumab in Crohn's disease. *Gastroenterology & Hepatology* 2006;2(7):486-488.	4
Colombel JF. Efficacy and safety of adalimumab for the treatment of Crohn's disease in adults. *Expert Review of Gastroenterology and Hepatology* 2008;2(2):163-176.	4
Drosou A, Kirsner RS, Welsh E, Sullivan TP, Kerdel FA. Use of infliximab, an anti-tumor necrosis alpha antibody, for inflammatory dermatoses. *Journal of Cutaneous Medicine and Surgery* 2003;7(5):382-386.	2
Dunlop H. Infliximab (Remicade) and etanercept (Enbrel): serious infections and tuberculosis. *Canadian Medical Association Journal* 2004;171(8):992-993.	1
Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 2008;372(9636):375-382.	1
European Medicines Agency. Scientific discussion [Internet]: London: EMEA, 2004.	1
European Medicines Agency. Scientific discussion [Internet]: London: EMEA, 2004.	1
European Medicines Agency. Humira EMEA/H/C/481/II/06: scientific discussion [Internet]: London: EMEA, 2004.	1
European Medicines Agency. Scientific discussion [Internet]: London: EMEA, 2005.	1
European Medicines Agency. Humira EMEA/H/C/481/II/22: scientific discussion [Internet]: London: EMEA, 2005.	1

European Medicines Agency. Humira EMEA/H/C/481/II/21: scientific discussion [Internet]: London: EMEA, 2005. 1
European Medicines Agency. Remicade EMEA/H/C/240/II/73: scientific discussion [Internet]: London: EMEA, 2006. 1
European Medicines Agency. Remicade EMEA/H/C/240/II/65: scientific discussion [Internet]: London: EMEA, 2006. 1
European Medicines Agency. Assessment report for Remicade [Internet]: London: EMEA, 2007. 1
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Food and Drug Administration. Review of BLA submission 99-O 128. Infliximab (REMICADE) for signs and symptoms of rheumatoid arthritis [Internet]. : Rockville, MD: U.S. Food and Drug Administration, Center for Biologic Evaluation and Research, 1999. 1
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Food and Drug Administration. Approval package for: application number: 103795/S-5097 [Internet]: Rockville, MD: U.S. Food and Drug Administration, Center for Drug Evaluation and Research, 2003. 1
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Food and Drug Administration. Statitsical review. Application number: sBLA 125057/110 [Internet]: Rockville, MD: U.S. Food and Drug 1

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Food and Drug Administration. Risk assessment and risk mitigation review(s). Application number: sBLA 125057/110 [Internet]: Rockville, MD: U.S. Food and Drug Administration, Center for Drug Evaluation and Research, 2008. 1
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Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, Allaart CF, Van Zeben D, Kerstens PJSM, Hazes JMW, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Annals of Internal Medicine* 2007;146(6):406-415. 1
Gordon KB, Gottlieb AB, Leonardi CL, Elewski BE, Wang A, Jahreis A, et al. Clinical response in psoriasis patients discontinued from and then reinitiated on etanercept therapy. *Journal of Dermatological Treatment* 2006;17(1):9-17. 1
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Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis and Rheumatism* 2004;50(5):1400-1411. 1
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Langley RG, Gupta AK, Cherman AM, Inniss KA. Biologic therapeutics in the treatment of psoriasis. Part 1: review. *Journal of Cutaneous Medicine and Surgery* 2007;11(3):99-122. 4
McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, et al. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. *Health Technology Assessment* 2007;11(28). 4
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Montilla Salas J, Munoz Gomariz E, Collantes E. [Meta-analysis of efficacy of anti-TNF alpha therapy in ankylosing spondylitis patients]. *Reumatologia Clinica* 2007;3(5):204-212. 4
Moss AC, Farrell RJ. Infliximab for induction and maintenance therapy 4

for ulcerative colitis. *Gastroenterology* 2006;131(5):1649-1651.
Neven N, Vis M, Voskuyl AE, Wolbink GJ, Nurmohamed MT, Dijkmans BAC, et al. Adverse events in patients with rheumatoid arthritis treated with infliximab in daily clinical practice. *Annals of the Rheumatic Diseases* 2005;64(4):645-646. 2
Orlando A, Mocciaro F, Civitavecchia G, Scimeca D, Cottone M. Minimizing infliximab toxicity in the treatment of inflammatory bowel disease. *Digestive and Liver Disease* 2008;40 Suppl 2:S236-S246. 4
Panes J, Gomollon F, Taxonera C, Hinojosa J, Clofent J, Nos P. Crohn's disease: a review of current treatment with a focus on biologics. *Drugs* 2007;67(17):2511-2537. 4
Papoutsaki M, Costanzo A, Mazzotta A, Gramiccia T, Soda R, Chimenti S. Etanercept for the treatment of severe childhood psoriasis. *British Journal of Dermatology* 2006;154(1):181-183. 2
Papp KA. The long-term efficacy and safety of new biological therapies for psoriasis. *Archives of Dermatological Research* 2006;298(1):7-15. 4
Pariente A, Gregoire F, Fourrier-Reglat A, Haramburu F, Moore N. Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. *Drug Safety* 2007;30(10):891-898. 2
Romero-Mate A, Garcia-Donoso C, Cordoba-Guijarro S. Efficacy and safety of etanercept in psoriasis/psoriatic arthritis: an updated review. *American Journal of Clinical Dermatology* 2007;8(3):143-155. 4
Scheinfeld N. Adalimumab: a review of side effects. *Expert Opinion on Drug Safety* 2005;4(4):637-641. 4
Subramanian V, Pollok RCG, Kang JY, Kumar D. Systematic review of postoperative complications in patients with inflammatory bowel disease treated with immunomodulators. *British Journal of Surgery* 2006;93(7):793-799. 1
Tyring S, Gordon KB, Poulin Y, Langley RG, Gottlieb AB, Dunn M, et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Archives of Dermatology* 2007;143(6):719-726. 3
Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet* 2006;367(9504):29-35. 1
Van Der Heijde D, Klareskog L, Landewe R, Bruyn GAW, Cantagrel A, Durez P, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis and Rheumatism* 2007;56(12):3928-3939. 1
Van Der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis and Rheumatism* 2006;54(4):1063-1074. 1
Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clinical Infectious Diseases* 2004;38(9):1261-1265. 1
Weisman MH, Paulus HE, Burch FX, Kivitz AJ, Fierer J, Dunn M, et al. A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. *Rheumatology* 2007;46(7):1122-1125. 1
Winterfield LS, Menter A. Infliximab. *Dermatologic Therapy* 2004;17(5):409-426. 2

Winthrop KL, Siegel JN, Jereb J, Taylor Z, Iademarco MF. Tuberculosis associated with therapy against tumor necrosis factor alpha. *Arthritis and Rheumatism* 2005;52(10):2968-2974.	4
Wong A, Fonseca MCM, Sandron CA. [Descriptive analyses of safety data for anti-TNF therapies using related outcomes from Uppsala Monitoring Centre (UMC) of World Health Organization (WHO)]. *Revista Brasileira de Medicina* 2007;64(7):323-333.	1

[a] Reasons for exclusion: 1- not relevant drug or no denominator; 2 – <500 patients receiving biologic; 3 – does not report adverse events; 4 – an overview/systematic review of adverse events.

10.5 Evidence Synthesis Overview

Background

A Bayesian mixed treatment comparison (MTC) (indirect comparison) is an extension of a meta-analysis, but where a meta-analysis includes only *direct* evidence an MTC analysis draws on both *direct* and *indirect* evidence.[204] As in a meta-analysis, it is the summary treatment effect from each study that is utilised in the MTC analysis; hence the benefit of randomisation in each study is retained.

A standard meta-analysis combines the results from two or more studies that have comparable populations, interventions, comparators and outcomes. Study quality and other study characteristics are also assumed to be similar. Similarly, to make indirect comparisons, it is assumed that the study characteristics are comparable. This is known as *exchangeability* which can be investigated through the consistency of the direct and indirect evidence.[205]

These types of evidence syntheses require a 'network of evidence' between all the treatments of interest. In the context of the present review this would mean that the network is required to comprise trials of adalimumab, etanercept , infliximab and placebo, where each treatment has been compared either directly or indirectly with every other. For example, although adalimumab and etanercept may not have been directly compared within a single trial, they can be compared *indirectly* if both have been assessed against a common comparator, placebo. The common comparator need not be placebo and, within a MTC, there can be more than one common comparator. Within a MTC *all* the available trials' data on a treatment for the specified indication should be included.

In the present analysis all six trials compared one of the three biologics to placebo. Several outcomes were deemed clinically relevant to determining the effectiveness of the biologics and a Bayesian indirect comparison was conducted for each of these outcomes. All included trials were assessed as part of the clinical review and it was determined that the population, intervention protocols, outcomes and other study characteristics were sufficiently exchangable for synthesis to be conducted. The analysis was undertaken using WinBUGS version 1.4.2.[206] WinBUGS is a Bayesian analysis software that, through the use of Monte Carlo Markov Chains (MCMC), calculates posterior distributions for the parameters of interest given likelihood functions derived from data and prior probabilities. The MCMC simulation begins the simulation with an approximate distribution and, if the model is a good fit to the data, the distribution converges to the true distribution. For all models used in the present analysis the first 10000 iterations were considered to be 'burn in' and excluded, and a

further 100,000 iterations were performed in order to calculate the results. The WinBUGS codes for the different analyses are presented in Section 10.5.7 of this appendix. All data used in the evidence synthesis is presented in Tables 10.5.1 to 10.5.4.

An evidence synthesis was conducted for each of the four main outcomes. The primary outcome of this analysis is the probability of response to treatment in terms of PsARC (PsARC response) at 12 weeks following the British Society of Rheumatology guidelines. The changes in HAQ score conditional on a PsARC response to treatment, the probability of achieving the PASI 50, 75 and 90 response, and the probability of achieving the ACR 20, 50, 70 response were also calculated. Three different models were produced to allow the separate outcomes to be synthesised. An overview of each model, along with the formal model is presented in the following section.

10.5.1 PsARC Response

The probability of initial response to each treatment, as determined by the PsARC outcome at 12 weeks, was modelled using a common-effects meta-analysis. Outcomes at 14 weeks were included in the analysis and assumed equivalent to outcomes at 12 weeks. Data were available from all six trials (two for each active treatment) for this outcome measure (Table 10.5.1). Each trial reported the number of events in the control group ($r^{C}{}_{i}$) and the number of events under active treatment ($r^{T}{}_{i}$), where i represents a trial *(i= Mease 2000, Mease 2004, IMPACT, IMPACT 2, ADEPT, Genovese* 2007). It was assumed that both $r^{C}{}_{i}$ and $r^{T}{}_{i}$ are binomially distributed.

The common baseline for each treatment effect was the probability of response to placebo. In order to achieve this, a meta-analysis on the placebo arms of the six RCTs was conducted. Each of the individual studies estimate the same true treatment effect δ_i (i.e., the underlying effect), and that differences between studies are solely due to chance. The observed effect of each study equals a fixed effect common to all studies plus sampling error;[207] In the Bayesian evidence synthesis, δ_i was assigned a non-informative normal prior distribution. Formally:

$$r^{C}{}_{i} \sim Binomial(p^{C}{}_{i}, n^{C}{}_{i})$$
$$r^{T}{}_{i} \sim Binomial(p^{T}{}_{i}, n^{T}{}_{i})$$

$$Logit(p^{C}{}_{i}) = \mu_i$$
$$Logit(p^{T}{}_{i}) = \mu_i + \delta_i$$

Treatment effects on probability of response were additive to the placebo probability of response on the log-odds scale. The probability of response to the intervention is given by:

$P(\text{Re}\,sponse_k) = \frac{\exp(T_k)}{1+\exp(T_k)}$, with $T_k = \mu + \delta_k$ being the treatment effect on the intervention *k (k=Placebo, Etanercept, Infliximab, Adalimumab)* and δ_k being the true treatment effect of the intervention *k* (on a log-odds scale).

The common effects model was compared with a random-effects model for both fit, as measured by the DIC, convergence and correlation. The data for these models are presented in Table10.5.1. The DIC statistic combines model deviance and the effective number of parameters. The DIC statistics were very similar 128.288 for the common effect model versus 128.274 for the random effects model. Convergence and autocorrelation were assessed using graphical tools available within WinBUGS. The common-effect model was a good fit, converged well and did not display any issues with autocorrelation. The random-effect model did not converge well and displayed issues with autocorrelation. For these reasons the common-effect model was used.

Table 10.5.1: PsARC model data inputs

Study	treatment	response	n
Mease 2000	Placebo	7	30
	Etanercept	26	30
Mease 2004	Placebo	32	104
	Etanercept	73	101
IMPACT	Placebo	7	52
	Infliximab	40	52
IMPACT 2	Placebo	27	100
	Infliximab	77	100
ADEPT	Placebo	42	162
	Adalimumab	94	151
Genovese	Placebo	12	49
	Adalimumab	26	51

10.5.2 Changes in HAQ

Trials that reported the absolute changes in HAQ from baseline conditional on whether the patient responds to therapy at 12 weeks were modelled using a random-effects meta-analysis. Data were available from five of the six trials for this outcome measure: etanercept data were not available from the Mease 2000 trial [208].

Let TR be the treatment responders, TNR be the treatment non- responders, PR be the placebo responders and PNR be the placebo non-responders. Also, let *i* represent the trial and *j* the

alternative treatments. We have assumed changes in HAQ given placebo non-responders as common baseline (μ_{PNR}) – a non-informative normal distribution was assign to this parameter. The effects of treatment response ($\delta.diff_{TRij}$) and non-response ($\delta.diff_{TNRij}$) on HAQ change are assumed to be treatment specific and additive to the placebo probability of non-response on the log-odds scale as illustrated below:

$$\mu_{PNR\,i} = baseline$$
$$\mu_{PR\,i} = \mu_{PNR\,i} + \delta.diff_{PRi}$$
$$\mu_{TNR\,i} = \mu_{PNR\,i} + \delta.diff_{TNRij}$$
$$\mu_{TR\,i} = \mu_{PNR\,i} + \delta.diff_{TRij}$$

For each of the different trials the true effect may be study specific and vary across studies although remain common across biologics. These true effects are described by a normal distribution. Hence, the variation in observed individual study results is caused not only by sampling error (as with the common-effect approach) but also by the variation in the true (underlying) effects of each study;[209]

When estimating HAQ separately for those who responded to PsARC we investigated a number of alternative modelling scenarios including:

- a fixed effects model, assuming all biologics have the same effectiveness after conditioning on PsARC response;
- a random effects assuming all biologics have the same effectiveness after conditioning on PsARC response, assuming that heterogeneity in effects is the same for responders and non-responders;
- a random effects with all biologics having different (non related) effectiveness after conditioning on PsARC response, assuming heterogeneity in effects is the same for responders and non-responders;
- a random effects assuming all biologics have the same effectiveness after conditioning on PsARC response, including a response effect as a fixed effect and an interaction term to allow treatment/response interaction.

Due to the volume of data informing the synthesis, and the need to derive clinically relevant estimates for the economic model, the decision was made to limit the choice to a fixed/common effects model, assuming all biologics have the same effectiveness (after

conditioning on PsARC response) and a random effects with all biologics having different (non related) effectiveness (after conditioning on PsARC response), whilst assuming heterogeneity in effects is the same for responders and non-responders. Finally, two alternative modelling scenarios were tested in an attempt to identifying the most appropriate model. The data for these two alternatives are presented in Table 10.5.2. The DIC statistic, convergence and autocorrelation were all assessed and informed model selection. The DIC statistics were -42.925 for the random effect model and -55.095 for the fixed/common effect model. As there was no issues with convergence or autocorrelation the random effect model was selected for use in the base-case of the economic decision model and the common treatment effect evidence synthesis estimate was used in a sensitivity analysis of the economic decision model. The results of the common effect model have been presented in Table 10.5.5 at the end of this appendix, not in the main clinical chapter.

Table 10.5.2: HAQ|PsARC model inputs

HAQ given PsARC response		standard error	HAQ given NO PsARC response		standard error
Placebo	-0.258	0.006	Placebo	-0.002	0.042
Etanercept	-0.635	0.062	Etanercept	-0.196	0.072
Placebo	-0.27	0.14	Placebo	0.02	0.05
Infliximab	-0.65	0.09	Infliximab	-0.2	0.09
Placebo	-0.16	0.096	Placebo	0.07	0.042
Infliximab	-0.58	0.057	Infliximab	-0.11	0.06
Placebo	-0.3	0.077	Placebo	0	0.037
Adalimumab	-0.5	0.041	Adalimumab	-0.1	0.053
Placebo	-0.2	0.0429	Placebo	0.1	0.0429
Adalimumab	-0.4	0.056	Adalimumab	-0.1	0.056

10.5.3 PASI 50, 75 and 90

Data were available from five of the six trials for this outcome measure: adalimumab data were not available form the Genovese trial (#17) trial. Furthermore, the IMPACT 2 trial only reported the results at 24 weeks so a coefficient was included in the linear predictor to estimate whether the difference in follow-up time was significant. The probability of response in terms of the PASI 50, PASI 75 and PASI 90 scores was modelled using an ordered multinomial logit model. In the ordered logit model the probability of an outcome is calculated by estimating a latent variable as a linear function of the independent variable plus a set of thresholds/cut-off points. In this analysis these thresholds represent the different outcomes of PASI 50, 75 and 90. The probability of observing the latent variable equals the probability that the estimated linear function is within the cut points estimated for the outcome. This type of model allows the ordered nature of the outcomes to be maintained.

Outcomes estimated are the probability of achieving each of the three PASI levels. A number of assumptions were made to facilitate modelling:

- A common effect model was used to estimate baseline; this was estimated using data from placebo non-responders (i.e those receiving placebo and not achieving PASI 50);
- Common effects were assumed for each treatment class (etanercept, infliximab, adalimiumab);
- Thresholds were assumed fixed across trials;
- The baseline latent variable was assumed fixed.

The response of a patient to treatment for psoriasis is measured using the PASI scoring system. The RCTs typically measure the change in psoriasis in each participant by comparing the percentage change in PASI with the score at baseline, and report the number of patients who achieved the following responses, in trial *i* and treatment *j*, where *j*= 0 is placebo, and *j*= 1,2,3 are the three biologic therapies:

$PASI\ 50_{ij}$ – at least a 50% change
$PASI\ 75_{ij}$ – at least a 75% change
$PASI\ 90_{ij}$ - at least a 90% change

The statistical analysis used a multi-categorical response model to analyse these data. The multivariate response variable r_{ij} is a vector of the number of participants in arm *j* of study *i* reporting one of the four possible values

$R_{ij1} = N_{ij} - PASI\ 50_{ij}$, or the number not achieving PASI 50
$R_{ij2} = PASI\ 50_{ij} - PASI\ 75_{ij}$, the number achieving PASI 50 but not PASI 75
$R_{ij3} = PASI\ 75_{ij} - PASI\ 90_{ij}$, the number achieving PASI 75 but not PASI 90
$R_{ij4} = PASI\ 90_{ij}$, the number achieving PASI 90

In a trial arm of size N_{ij}, r_{ij} is multinomially distributed
$r_{ij} \sim M(N_{ij}, p_{ij})$
where
$r_{ij} = (R_{ij1},\ldots R_{ij4})$, $p_{ij} = (P_{ij1}, \ldots P_{ij4})$ and
$p_{ijr} = Pr(R_{ijr} = r\ |x_{ij})$

We estimate the probability that patients have a PASI 50, 75 or 90 response by a cumulative threshold or ordered logit model. We define Z_{ij} to be a latent variable representing the mean improvement in psoriasis in arm *j* of trial *i*. The latent variable is determined by the explanatory variables in a linear form:

$$Z_{ij} = (a_i + b_1T_{i1}+b_2T_{i2}+b_3T_{i3})+ e_{ij}$$

Where a_i represents the mean improvement in the placebo arm of trial *i* and coefficient *bj* represents the mean improvement that can be attributed to treatment *j*, for *j*=1,2,3, and T_{ij} is a dummy variable for the biologic that was trialled in RCT *i*. Coefficient a_i is a fixed-effect for trial *i* and coefficient b_j is assumed to be common across all trials for treatment *j*. As this is an ordered logit model, coefficient b_j can be interpreted as the log-treatment effect of drug *j* relative to placebo.

R and Z are connected by:

$r_{ij} = r \leftrightarrow \theta_r < Z_{ij} < \theta_{r+1}$, for *r*=2,3,4

where $-\infty = \theta_1 < \theta_2 < \theta_3 < \theta_4 < \theta_5 = \infty$

The parameters θ_r represent thresholds for observing a particular psoriasis response, rather than a less strong response. The error term eij was assumed to take a logistic distribution function *F(e) = 1/(1+exp(-e))*

.

We define variable Y_{ijr} to be the cumulative probability of achieving a response r or greater, so that Y_{ij1} is the probability of a patient achieving a PASI 50 response in trial *i* and treatment *j*, Y_{ij2} is the probability of achieving a PASI 75 response, and Y_{ij3} the probability of achieving a PASI 90 response.

Therefore,

$$Y_{ijr} = 1 - \Pr(r_{ij} \le r | x_{ij})$$

$$= \Pr(Z_{ij} > \theta_{r+1}) = \Pr(a_i + b_j x_{ij} + e_{ij} > \theta_{r+1})$$

$$= \Pr(e_{ij} > \theta_{r+1} - (a_i + b_j x_{ij})) = F(-e_{ij})$$

$= F(-(\theta_{r+1} - (a_i + b_j x_{ij})))$, for *r*=2,3,4

Parameter θ_2 is not estimated as it is co-linear with the intercept term.

It follows that:

$$logit(Y_{ij1}) = -(a_i + b_j x_{ij})$$

$$logit(Y_{ij2}) = \theta_3 - (a_i + b_j x_{ij})$$

$$logit(Y_{ij3}) = \theta_4 - (a_i + b_j x_{ij})$$

To avoid problems with estimation that may occur if the thresholds are very similar, the thresholds θ_3 and θ_4 were reparameterised by
$\theta_3 = exp\,(\omega_3)$ and $\theta_4 = exp\,(\omega_3) + exp\,(\omega_4)$

In the Bayesian evidence synthesis, all parameters of the model (a_i, b_j,and ω_r) were assigned non-informative normal prior distributions.

One of the aims of the model was to provide predictions of PASI 50, 75 and 90 response rates for each treatment. This requires an estimate of parameter *a*, the intercept of the linear latent variable function. This was made by assuming it is equivalent to the pooled (mean) log-odds of a PASI 50 response across all the placebo arms of the RCTs.

As with the other evidence synthesis models, different modelling scenarios were assessed using criteria such as the DIC statistic, convergence and autocorrelation graphs. These models included an ordered probit model and random- effect versions of both the ordered logit and probit. The model selected was the best fit and presented good convergence and no sign of autocorrelation. The data for these models are presented in Table 10.5.3. The ordered logit models both had lower DIC statists than the ordered probit models, 146.301 for the common effects versus 147.421 for the random effects. As with other models issues with convergence and autocorrelation made the common effects a better choice. The ordered probit models, whilst behaving quite well in terms of convergence did show signs of autocorrelation. Additionally, both the common and random effect models produced DIC statistics in excess of 1800.

Table 10.5.3: PASI model data inputs

Trial	Treatment	Outcome (% change in PASI)	n
Mease 2000	Placebo	<50	15
	Placebo	50-75	4
	Placebo	75	0
	Placebo	*>90*	*no data*
	Etanercept	<50	11
	Etanercept	50-75	3
	Etanercept	75	5
	Etanercept	*>90*	*no data*
Mease 2004*	Placebo	<50	51
	Placebo	50-75	9
	Placebo	75-90	0
	Placebo	>90	2
	Etanercept	<50	35
	Etanercept	50-75	16
	Etanercept	75-90	11
	Etanercept	>90	4
IMPACT	Placebo	<50	16
	Placebo	50-75	0
	Placebo	75-90	0
	Placebo	>90	0
	Infliximab	<50	0
	Infliximab	50-75	7
	Infliximab	75-90	7
	Infliximab	>90	8
IMPACT 2	Placebo	<50	79
	Placebo	50-75	6
	Placebo	75-90	2
	Placebo	>90	0
	Infliximab	<50	15
	Infliximab	50-75	15
	Infliximab	75-90	19
	Infliximab	>90	34
ADEPT	Placebo	<50	59
	Placebo	50-75	7
	Placebo	75-90	3
	Placebo	>90	0
	Adalimumab	<50	19
	Adalimumab	50-75	16
	Adalimumab	75-90	13
	Adalimumab	>90	21

10.5.4 ACR 20, 50 and 70

Data were available from all of the six trials for this outcome across all three thresholds. As with the PASI data the ACR data were modelled using an ordered multinomial logit model.

The same set of modelling assumptions which were applied to the PASI model was used for the ACR model. As stated previously, different modelling scenarios were assessed using criteria such as the DIC statistic, convergence and autocorrelation graphs. These models included an ordered probit model and random- effect versions of both the ordered logit and probit. The model selected was the best fit and presented good convergence and no sign of autocorrelation. The data for these models are presented in Table 10.5.4. Like the PASI models, the ACR ordered probit models behaving well in terms of convergence although they

also showed signs of autocorrelation. They again produced DIC statistics in excess of 1800. Both the ordered logit models both had lower DIC statistics, 200.88 for the common effect and 202.069 for the random effect. Again, the random effect model having some issues with autocorrelation, hence making the common effects model a better choice.

The formal model for the ACR data is extremely similar to the PASI model outlined above.

Table 10.5.4: ACR model data inputs

Trial	Treatment	Outcome (% change in ACR	n
Mease 2000	Placebo	<20	26
	Placebo	20-50	3
	Placebo	50-75	1
	Placebo	>75	0
	Etanercept	<20	8
	Etanercept	20-50	7
	Etanercept	50-75	11
	Etanercept	>75	4
Mease 2004	Placebo	<20	88
	Placebo	20-50	12
	Placebo	50-75	4
	Placebo	>75	0
	Etanercept	<20	41
	Etanercept	20-50	22
	Etanercept	50-75	27
	Etanercept	>75	11
IMPACT	Placebo	<20	46
	Placebo	20-50	5
	Placebo	50-75	1
	Placebo	>75	0
	Infliximab	<20	17
	Infliximab	20-50	16
	Infliximab	50-75	8
	Infliximab	>75	11
IMACT 2	Placebo	<20	89
	Placebo	20-50	8
	Placebo	50-75	2
	Placebo	>75	1
	Infliximab	<20	42
	Infliximab	20-50	22
	Infliximab	50-75	21
	Infliximab	>75	15
ADEPT	Placebo	<20	139
	Placebo	20-50	17
	Placebo	50-75	5
	Placebo	>75	1
	Adalimumab	<20	63
	Adalimumab	20-50	34
	Adalimumab	50-75	24
	Adalimumab	>75	30
Genovese	Placebo	<20	41
	Placebo	20-50	7
	Placebo	50-75	1
	Placebo	>75	0
	Adalimumab	<20	31
	Adalimumab	20-50	7
	Adalimumab	50-75	6
	Adalimumab	>75	7

10.5.5 Results for HAQ|PsARC common effect

Table 10.5.5 shows the results for the evidence synthesis of HAQ conditional on PsARC response assuming that all three biologics have the same underlying treatment effect. The results are presented here as they were used in a sensitivity analysis scenario in the economic decision model.

Table 10.5.5: HAQ|PsARC common treatment effect

HAQ | Response. Common treatment effects (common baseline)			
		Credible inteval	
	mean	**2.50%**	**97.50%**
Treatment Changes in HAQ | Response	-0.5688	-0.6305	-0.5073
Treatment Changes in HAQ | No-Response	-0.1697	-0.2362	-0.1038
Placebo Changes in HAQ | Response	-0.2606	-0.3149	-0.2062

10.5.6 WinBUGS code

Evidence Synthesis Models WinBUGS Code

Model one: probability of PsARC response to each treatment (and placebo).

```
model
{
for (i in 1:N) #Calculate Odds Ratios

{
r[i]~dbin(p[i], n[i])        # Likelihood

logit(p[i])<-mu[s[i]]+delta[i]*(1-equals(t[i],b[i]))# Model

delta[i] ~ dnorm(m[i], prec)        # Distribution of specif LORs

m[i]<-d[t[i]]-d[b[i]]        # Mean of study-specific LORs

}

for (j in 1:NS)
{
mu[j]~dnorm(0,1.0E-6) # Vague priors for trial baselines
}
d[1]<-0
for (k in 1:4)
{
```

```
d[k]~dnorm(0,1.0E-6)            # Vague priors for basic parameters

OR[k]<-exp(d[k])
}
# Meta-analysis on the placebo arms to get a baseline treatment effect (and probability of
response) of placebo
for (j in 1:NS)
{
        rplac[j]~dbin(pplac[j],nplac[j])  # control response

        logit(pplac[j])<-mp[j]

                mp[j]~dnorm(Mean,Tau)

}
        Tau<-1/(sigma*sigma)
        sigma~dunif(0,10)
        Mean~dnorm(0,0.000001)
Prob.response.plac <- exp(Mean)/(1+exp(Mean))
#Calculate treatment effects, T[k], on natural scale

for (k in 1:4)
{
T[k] <- Mean + d[k]
prob[k]<-exp(T[k])/(1+exp(T[k])) #Probability of response
}
}
#end model
```

Model Two: HAQ conditional on PsARC response

```
model {
for (i in 1:5)      {

### Converting standard errors into precisions
prec.HAQ.TR[i] <- 1/ (se.HAQ.TR[i] *se.HAQ.TR[i])

prec.HAQ.PR[i] <- 1/ (se.HAQ.PR[i]*se.HAQ.PR[i])

prec.HAQ.TNR[i] <- 1/ (se.HAQ.TNR[i] * se.HAQ.TNR[i])

prec.HAQ.PNR[i] <- 1/ (se.HAQ.PNR[i] * se.HAQ.PNR[i])

### Likelihood for data
HAQ.TR[i] ~ dnorm(response.trt[i], prec.HAQ.TR[i])
HAQ.PR[i] ~ dnorm(response.plac[i], prec.HAQ.PR[i])



HAQ.TNR[i] ~ dnorm(no.response.trt[i], prec.HAQ.TNR[i])
HAQ.PNR[i] ~ dnorm(no.response.plac[i], prec.HAQ.PNR[i])

### Simple meta-analysis model
baseline.HAQ[i]~dnorm(0, 0.0000001)

no.response.plac[i]<-baseline.HAQ[i]

response.plac[i]<-baseline.HAQ[i]+delta.plac.diff.response[i]

no.response.trt[i] <-baseline.HAQ[i]+delta.trt.diff.no.response[trial.tnf[i],i]

response.trt[i] <-baseline.HAQ[i]+delta.trt.diff.response[trial.tnf[i],i]



### Vague prior distributions
delta.trt.diff.response[trial.tnf[i],i] ~ dnorm(trt.diff.response[trial.tnf[i]], inv.tau.sq)
```

```
delta.trt.diff.no.response[trial.tnf[i],i] ~ dnorm(trt.diff.no.response[trial.tnf[i]], inv.tau.sq)

delta.plac.diff.response[i] ~ dnorm(plac.diff.response, inv.tau.sq)

        }

for (j in 1:3)      {
trt.diff.response[j]~ dnorm(0,1.0E-6)
 trt.diff.no.response[j]~ dnorm(0,1.0E-6)

        }

plac.diff.response ~ dnorm(0,1.0E-6)

inv.tau.sq<-1/(sigma*sigma)
sigma~dunif(0,10)


for (i in 1:5){

HAQ.PNR[i]~dnorm(mu,inv.tau.sq.b)}   #Likelihood

mu~dnorm(0,0.000001) #Prior for mu

inv.tau.sq.b<-1/(sigma.b*sigma.b)

sigma.b~dunif(0,10)


        }

#end model
```

Model three: Probability of achieving PASI response

```
#ordered multinomial logit

model #Fixed treatment effects
{
for(i in 1:8){                          #4 trials x 2 arms

R[i,1:4]~dmulti(p[i,],N[i])  #multinomial likelihood


#Y[i,] is the cumulative density function of the error term of a continuous latent variable
representing PASI change from the start of the trial in trial i


z[i,1]<-aa[Trial[i]]+ b[1]*E[i]+b[2]*A[i]+b[3]*I[i]+

w24*offset[i] #linear predictor of latent variable


#assume logistic distribution for error term

logit(Y[i,1])<- -z[i,1]
#first threshold (PASI >50) differing across trials with a[trial[i]]
logit(Y[i,2])<- -(z[i,1] +exp(theta[1]))
#second threshold PASI >75
logit(Y[i,3])<-  -(z[i,1] +exp(theta[1])+exp(theta[2]))
# third threshold PASI>90

#exp(theta 1 ) and exp (theta 2) ensures that the gaps between thresholds are strictly positive
p[i,1]<-1-Y[i,1]            #PASI CHANGE LESS THAN 50
p[i,2]<-Y[i,1]-Y[i,2]       #PASI CHANGE 50 TO 74
p[i,3]<-Y[i,2]-Y[i,3]       #PASI CHANGE 75 TO 89
p[i,4]<-Y[i,3]                      #PASI CHANGE >90

}
w24~dnorm(0,1.0E-6)
```

```
for (t in 1:3){
b[t]<-m[t]                    #fixed effects for each treatment
m[t]~dnorm(0,1.0E-6)

}

for (c in 1:2){               # thresholds
theta[c]~dnorm(0,0.00001)
}

#other data: trial 1 reports number with PASI change 50 & 75 but not other PASI thresholds

r.pasi50[1]~dbin(Y[9,1], n[1])
r.pasi50[2]~dbin(Y[10,1], n[2])
r.pasi75[1]~dbin(Y[9,2], n[1])
r.pasi75[2]~dbin(Y[10,2], n[2])


z[9,1]<-  aa[1]               #Baseline of trial number 1: placebo arm
z[10,1]<- aa[1]+b[1]      #Treatment effect of trial 1
logit(Y[9,1]) <-   -z[9,1]
#prediction of what PASI >50 would have been in placebo arm of trial
logit(Y[10,1]) <- -z[10,1]
#prediction of what PASI >50 would have been in trt arm of trial
logit(Y[9,2]) <-   -(z[9,1] +exp(theta[1]))
#PASI>75 in this trial in placebo arm
logit(Y[10,2]) <- -(z[10,1]+ exp(theta[1]))
#PASI>75 in trt arm
logit(Y[9,3]) <-   -(z[9,1] +exp(theta[1])+exp(theta[2])) #prediction of PASI>90 in plac arm
of trial
logit(Y[10,3]) <- -(z[10,1]+ exp(theta[1])+exp(theta[2]))
#prediction of PASI>90 in trt arm of trial


for (i in 1:5){
#latent baseline
```

```
aa[i]~dnorm(0,1.0E-6)
}

#baseline
for (j in 1:5)  # trials
{
rplac[j]~dbin(pplac[j],nplac[j])  # control response
logit(pplac[j])<-a
}
a~dnorm(0,0.000001)

Prob.response.plac <- exp(a)/(1+exp(a))

#predictions for treatment + placebo group
z.mn[1]<-a
z.mn[2]<-(a+m[1])#etanercept
z.mn[3]<-(a+m[2])#adalimumab
z.mn[4]<-(a+m[3])#infliximab
for (t in 1:4){
logit(Pr[t,1])<- -z.mn[t]
#first threshold (PASI >50)
logit(Pr[t,2])<- -(z.mn[t] +exp(theta[1]))
#second threshold PASI >75
logit(Pr[t,3])<-  -(z.mn[t] +exp(theta[1])+exp(theta[2]))
# third threshold PASI>90
}

}

#end model
```

Model Four: Probability of achieving ACR response

ordered multinomial logit

```
model {                                 #Fixed treatment effects
for(i in 1:12){                         #6 trials x 2 arms

R[i,1:4]~dmulti(p[i,],N[i])         #multinomial likelihood

#Y[i,] is the cumulative density function of the error term of a continuous latent variable
representing ACR change from the start of the trial in trial i

z[i,1]<-aa[Trial[i]]+ b[1]*E[i]+b[2]*A[i]+b[3]*I[i]
#linear predictor of latent variable


#assume logistic distribution for error term
logit(Y[i,1])<- -z[i,1]
#first threshold (ACR >20) differing across trials with a[trial[i]]
logit(Y[i,2])<- -(z[i,1] +exp(theta[1]))
#second threshold ACR >50
logit(Y[i,3])<-  -(z[i,1] +exp(theta[1])+exp(theta[2]))
# third threshold ACR>70

#exp(theta 1 ) and exp (theta 2) ensures that the gaps between thresholds are strictly positive

p[i,1]<-1-Y[i,1]#ACR CHANGE LESS THAN 20
p[i,2]<-Y[i,1]-Y[i,2]#ACR CHANGE 20 TO 49
p[i,3]<-Y[i,2]-Y[i,3]#ACR CHANGE 50 TO 69
p[i,4]<-Y[i,3] #ACR CHANGE >70

}


for (t in 1:3){                         #fixed effects for each  treatment
b[t]<-m[t]
m[t]~dnorm(0,1.0E-6)
}
```

```
for (c in 1:2){# thresholds
theta[c]~dnorm(0,0.00001)
}

for (i in 1:6){                          #latent baseline

aa[i]~dnorm(0,1.0E-6)
}

#baseline
for (j in 1:6)  # trials
{
rplac[j]~dbin(pplac[j],nplac[j])  # control response
logit(pplac[j])<-a
}
a~dnorm(0,0.000001)

Prob.response.plac <- exp(a)/(1+exp(a))
#predictions for treatment + placebo group
z.mn[1]<-a
z.mn[2]<-(a+m[1])#etanercept
z.mn[3]<-(a+m[2])#adalimumab
z.mn[4]<-(a+m[3])#infliximab
for (t in 1:4){
logit(Pr[t,1])<- -z.mn[t]
#first threshold (ACR >20)
logit(Pr[t,2])<- -(z.mn[t] +exp(theta[1]))
#second threshold ACR >50
logit(Pr[t,3])<-  -(z.mn[t] +exp(theta[1])+exp(theta[2]))
# third threshold ACR>70
}
}

#end model
```

10.6 Clarifications from manufacturers

Wyeth

1. Decision to withdraw depending on initial response

The model requires patients to withdraw from biologic therapy if no response is achieved at either 12 or 24 weeks. How are responses at 12 and 24 weeks correlated? Is there a regression model to link response at 12 weeks with response at 24 weeks?

No, it was not possible to include any correlation between the response rates at 12 weeks and 24 weeks given the evidence available (MTC - STA). Data from a previous published MTC (STA – ADL) was used to model the response rate at either 12 and 24 weeks independently. It is believed that data presented in the MTC for the response rate at 24 weeks is independent to the response at 12 weeks when looking at the sample size of patients included in the MTC. For instance, all patients randomised in the etanercept arm in the Mease trial (2004) or in the infliximab arm in the IMPACT 2 trial were included at 24 weeks in the MTC, whether or not they responded at 12 weeks. Consequently, this suggests that response rates reported in the MTC at 12 and 24 weeks were not conditional of each other. The response rates at 12 and 24 weeks were therefore sampled independently of each other. It was not possible to sample the response rate jointly (taking into account the correlation) in the absence of patient data for other treatments.

2. HAQ for responders and non-responders

Wyeth estimates a regression of HAQ given PsARC and PASI (Table 9 and 10). The Assessment Group would like to request that Wyeth re-run this regression without PASI. This is for 2 reasons. First, each of the manufacturers has submitted a different model and we would like to compare estimates of parameters from different sources. Wyeth's model is the only one which uses PASI to predict HAQ. Secondly, this will enable the York Assessment Group to use Wyeth's data to inform HAQ in the York economic model.

Our model included Pasi to predict HAQ given the possible correlation between HAQ and Pasi. A full regression model, including different covariates was estimated initially. Non-significant covariates were then excluded (sig level of 0.05). Pasi was found to be a significant predictor of HAQ in addition to PsARC. Pasi explain thus part of the variance in HAQ in addition to PsARC. Removing Pasi would remove part of the explained variance in HAQ. Our method was also justified by the absence of relationship between Cost, HAQ and PASI

However, as requested by the Assessment Group, regression models for HAQ without PASI were re-run (find attached).

The Assessment Group would also like to use the data on mean HAQ conditional on response from Mease 2004, which was CIC in the previous NICE appraisal. Please could you consider releasing this data from the CIC restriction?
We are in contact with our Global Medical Affairs department to clarify whether this data can be released from the CIC restriction.

3. Long term withdrawal rate from biologics

Wyeth has estimated Weibull models for the rate of withdrawal from biologics, from data published from the BSR register. The York Assessment Group is not clear what calculations were made to estimate these parameters. Please clarify how these parameters were worked out from the data?

The BSR paper (Saad et al, 2009) reported the proportion of patients on etanercept at 1 year (86%), 2 year (79%), 3 year (65%). A weibull curve was fitted to these three values by calibrating the two parameters of the weibull function (scale and shape) in order to minimise the error between the observed and predicted proportion of patients still treated with etanercept. The observed and predicted proportions of patients treated with etarnercept at 1, 2 and 3 years are reported below. The Root Mean Squared Error between the observed and predicted proportion was 0.01961

year	Observed	Predicted
-	1.00	1.00
1.00	0.86	0.88
2.00	0.79	0.76
3.00	0.65	0.66

The weibull function was assumed to follow the following equation (as defined in stata)
S(t) = EXP((-EXP(scale)*(time^EXP(shape))))

4. Utility conditional on PASI and HAQ

Wyeth has presented regression models to predict utility from HAQ and PASI. However, the Assessment Group is unable to easily compare this with the other models because each has used a different source of data and different covariates in the regression. To enable us to compare the submissions, and include estimates from different sources in the York model, we would like to request that you re-run this regression in a comparable way. We suggest the following set of untransformed covariates is included in the regression: Constant, HAQ,

*PASI, HAQ*PASI (interaction term). We would like to request the results of this regression, as: coefficients, variance-covariance matrix, number of observations, number of clusters (if appropriate), indicating the source of data.*

The regression model to predict utility from PRESTA was re-run to include HAQ, PASI and the interaction between HAQ and PASI as requested by ERG (find attached). A second model was also generated without the interaction between HAQ and PASI given the non significance of the coefficient for the interaction.

Abbott

1. Sequencing

The Abbott model allows a sequence of DMARDs after failure of biologic therapy. Is there always 10 DMARDs in this sequence? What treatment (or no treatment) is given after failure of the last DMARD in the sequence?

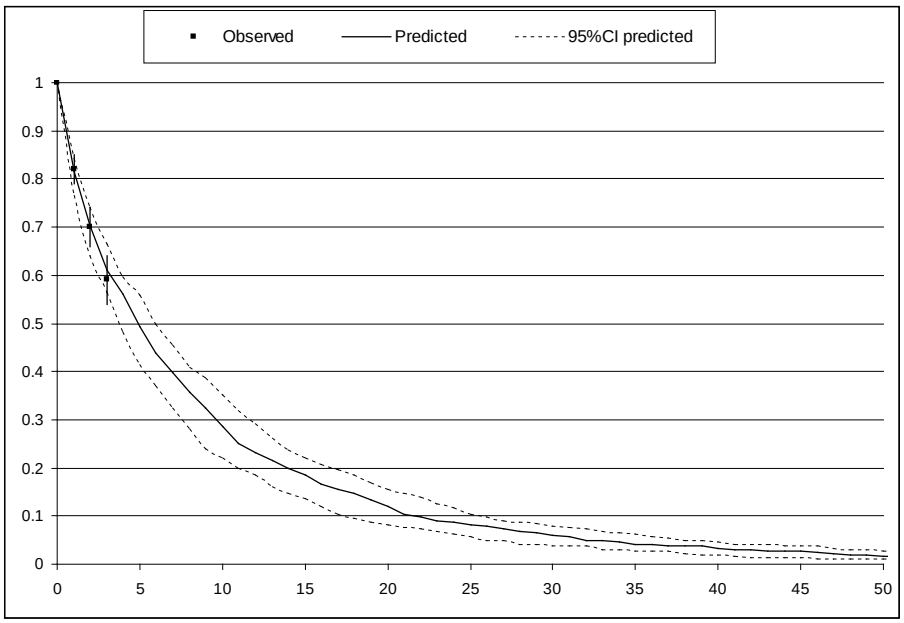
The model is structured to allow for a maximum of 10 different DMARD treatments (which includes different combinations of DMARDs). The model assumes that patients will continue to try different combinations of DMARDs rather than receive no active treatment. Consequently no response test is used for DMARD therapies, and patients withdraw from these treatments based on the long-term withdrawal rate. Once the patient reaches the last DMARD combination in the sequence, they have effectively run out of options and so will continue on that treatment until they die.

2. Long term withdrawal rate from biologics

Abbott has estimated Weibull models for the rate of withdrawal from biologics, from data published from the BSR register. The York Assessment Group is not clear what calculations were made to estimate these parameters. Please can you clarify how these parameters were worked out from the data?

A crude survival analysis is made using the reported figures in table 10.6.1 of Saad et al, 2008.[187] As can be seen in Figure 10.6.1, the analysis used survival rates reported by Saad et al. for all anti-TNFs in year 1 (0.82), in year 2 (0.70) and in year 3 (0.59). Survival rates beyond the initial three year period were modeled assuming a Weibull distribution following the shape of survival curves observed for other rheumatic diseases.[210]

Figure 10.6.1: Observed versus predicted survival for all biologics.



3. Utility conditional on PASI and HAQ

Abbott has presented a regression model to predict utility from HAQ and PASI. However, the Assessment Group is unable to easily compare your model with the others because each model has used a different source of data and different covariates in the regression. To enable us to compare the submissions, and include estimates from different sources in the York model, we would like to request that you re-run this regression in a comparable way. We suggest the following set of untransformed covariates is included in the regression: Constant, HAQ, PASI, HAQ*PASI (interaction term). We would also like to request that the results of this regression, as: coefficients, variance-covariance matrix, number of observations, number of clusters (if appropriate), indicating the source of data.

The utility regression estimates are shown in Table10.6.1, and the covariance matrix is in Table 10.6.2. It should be noted that in the ADEPT trial a proportion of patients had a HAQ score of zero. It was therefore impossible for these patients to experience an improvement in their HAQ score. In order to ensure the utility regressions truly capture the impact a change in HAQ has on a patient's utility score, these patients have been excluded from the analysis.

Table10.6.1: Utility regression estimates

Parameter	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Intercept	0.8862	0.0182	0.8506	0.9217	48.82	<.0001
HAQ	-0.2317	0.0248	-0.2803	-0.1831	-9.35	<.0001
PASI	-0.0025	0.0015	-0.0054	0.0004	-1.69	0.0906
HAQ*PASI	-0.0039	0.002	-0.0079	0	-1.94	0.0523
Number of observations used: 386						
Number of clusters: 138						

Table 10.6.2: Covariance matrix for utility regression

Covariance Matrix				
	Intercept	**HAQ**	**PASI**	**HAQ*PASI**
Intercept	0.0003295	-0.000292	-0.000014	0.0000126
HAQ	-0.000292	0.0006146	0.0000129	-0.000033
PASI	-0.000014	0.0000129	2.1946E-06	-0.000001607
HAQ*PASI	0.0000126	-0.000033	-0.000001607	4.0944E-06

4. Correlation between outcomes

There is no evidence presented to support the correlation across outcomes. How large are the correlations? What were the data restrictions that meant a trivariate analysis could not be completed? Can the data be presented?

Spearman correlations have been calculated using patient level data from the ADEPT clinical trial. There is a positive correlation between the two measures of the arthritis component of the disease (PsARC and ACR) indicating that a PsARC responder is also likely to be an ACR responder although this correlation is not as strong as would be expected if these two measures were truly interchangeable (Table 10.6.3). As can be seen in Table 10.6.4, approximately 80% of PsARC responders were ACR 20 responders at week 12 in the treatment group in the ADEPT trial, with a Kappa coefficient of 0.56 (moderate agreement)

Table 10.6.3: Spearman correlation between response measures of the arthritis component of the disease

		Treatment*	
PsARC	**ACR†**	**Adalimumab (n=151)**	**Placebo (n=162)**
PsARC (week 12)	ACR 20 (week 12)	0.57 (p<0.0001)	0.57 (p<0.0001)
PsARC (week 24)	ACR 20 (week 24)	0.64 (p<0.0001)	0.69 (p<0.0001)

*correlation coefficient (significance)
† <20 / 20-50 / 50-70 / 70+

Table 10.6.4: Kappa agreement correlation between ACR 20 and PsARC response in the Adalimumab treatment group

Week 12 PsARC	Week 12 ACR 20	
	Non responders N (%)	Responders
Non responder	45 (77.5%)	13 (22.4%)
Responders	19 (20.4%)	74 (79.5)
Kappa Coefficient	0.56 (Moderate agreement)	

As can be seen in Table 10.6., there is a significant and positive correlation between all three outcomes observed between week 12 and week 24. This is particularly high for ACR 20 response rates, and is stronger in the adalimumab arm than in the placebo arm of the trial. It is anticipated that the lower correlation in the placebo arm is due to the fact that these patients may be classed as responders by chance rather than because they are actually responding to treatment. The probability that patients in the placebo arm who respond to treatment at week 12 are still responding to treatment at week 24 is therefore lower than for those patients in the adalimumab arm. Correlations are higher between ACR responses at week 12 and week 24 when compared to PsARC response rates indicating that the ACR is a more robust measure of response than the PsARC.

Table 10.6.5: Spearman correlation between outcomes over time

		Treatment*	
12 weeks	**24 weeks**	**Adalimumab (n=151)**	**Placebo (n=162)**
PsARC	PsARC	0.61 (p<0.0001)	0.37 (p<0.0001)
ACR†	ACR†	0.79 (p<0.0001)	0.33 (p<0.001)
12 weeks	**24 weeks**	**Adalimumab (n=69)**	**Placebo (n=69)**
PASI^	PASI^	0.64 (p<0.0001)	0.39 (p<0.0001)

*correlation coefficient (significance)
† <20 / 20-50 / 50-70 / 70+
^ <50 / 50-75 / 75-90 / 90+

The correlations presented in Table 10.6.6 indicate that there is a weak correlation between skin response, and arthritis response. This suggests that patients who observe improvements in their skin symptoms may not observe similar improvements in their arthritis symptoms. Table 10.6.7 indicates that approximately 62% of ACR 20 responders were also PASI 75 responders at week 12 in the ADEPT trial, with a Kappa coefficient of 0.31 (fair agreement). When interpreting this data, it is important to remember that only a subset of patients in the ADEPT trial were eligible for PASI assessment thus reducing the statistical power of the analysis.

Table 10.6.6: Spearman correlation between response criteria for the skin and arthritis components of the disease

		Treatment	
Arthritis response measure	**Skin response measure**	**Adalimumab (n=69)**	**Placebo (n=69)**
PsARC (week 12)	PASI^ (week 12)	0.49 (p<0.0001)	0.13 (p=0.2969)
PsARC (week 24)	PASI^ (week 24)	0.36 (p=0.0023)	0.26 (p=0.304)
ACR† (week 12)	PASI^ (week 12)	0.42 (p=0.0004)	0.23 (p=0.0614)
ACR† (week 24)	PASI^ (week 24)	0.38 (p=0.0014)	0.23 (p=0.0612)

*correlation coefficient (significance)
† <20 / 20-50 / 50-70 / 70+
^ <50 / 50-75 / 75-90 / 90+

Table 10.6.7: Kappa agreement correlation for the skin and arthritis components in the Adalimumab treatment group

Week 12 ACR 20 response	Week 12 PASI 75 response	
	Non responders N (%)	Responders
Non responder	19 (70.3%)	8 (29.6%)
Responders	16 (38%)	26 (61.9%)
Kappa Coefficient	0.31 (Fair agreement)	

A trivariate analysis could not be completed for several reasons. Firstly, in the ADEPT trial, PASI was measured only in patients with BSA ≥ 3% meaning that PASI, PsARC and ACR response data was only available for 43.2% of patients (n=69). Excluding those patients with no PASI scores would have meant discarding most of the data on arthritis response thus significantly reducing the power of the analysis. Including these patients would result in an error and the model would not be able to run due to the absence of PASI scores.

A further barrier to conducting a trivariate analysis is the computational burden required for such a complex analysis. For example, the model examining the relationship between ACR 20 at 12 weeks and at 24 weeks took approximately 5 hours to compile; for the fixed-effects model it took a total 50 hours to run 3 chains while for random-effects models it took 500 hours. Expanding to a trivariate analysis would require many times this. It is therefore not possible to present the results of a trivariate analysis.

Schering-Plough

Regression of Quality of Life on HAQ and PASI

NICE request – 2009-09-29

NICE requested a linear regression of quality of life on the following covariates:

- Intercept
- HAQ
- PASI
- HAQ x PASI interaction term

Two options are available for estimating the QoL data:

1. SF-36 to EQ5D via Gray algorithm
2. EQ5D

The data source used here is the IMPACT 2 study (Excel files from Ewen's emails 2009-03-21). EQ5D was converted to a QoL index score using the published UK tariffs (Brazier algorithm).

Results

Patients with missing values for baseline EQ5D, HAQ or PASI have been removed from both analyses. Multiple observations in the same patient were treated as independent observations, no cluster-based analysis was used. Sample size in both cases: N=740 observations.

Using the SF-36 data via Gray algorithm

Covariate	Mean	Variance-Covariance matrix			
		Intercept	HAQ	PASI	HAQ x PASI
Intercept	8.712e-01	5.978e-07	-4.215e-07	-3.698e-08	2.632e-08
HAQ	-2.490e-01	-4.215e-07	5.107e-07	2.679e-08	-3.024e-08
PASI	-2.485e-03	-3.698e-08	2.679e-08	9.536e-09	-6.684e-09
HAQ x PASI	5.928e-05	2.632e-08	-3.024e-08	-6.684e-09	6.405e-09

Using the EQ5D data

Covariate	Mean	Variance-Covariance matrix			
		Intercept	HAQ	PASI	HAQ x PASI
Intercept	7.862e-01	9.233e-08	-6.510e-08	-5.712e-09	4.065e-09
HAQ	-1.437e-01	-6.510e-08	7.888e-08	4.139e-09	-4.670e-09
PASI	-2.648e-03	-5.712e-09	4.139e-09	1.437e-09	-1.032e-09
HAQ x PASI	9.927e-04	4.065e-09	-4.670e-09	-1.032e-09	9.893e-10

10.7 Reviews of cost-effectiveness studies and checklists

Review of Olivieri, et al. The psoriatic arthritis cost evaluation study: a cost-of-illness study on tumour necrosis factor inhibitors in psoriatic arthritis patients with inadequate response to conventional therapy[173]

Overview

This is a before and after study which evaluated the costs and benefits of biologics (as a group) compared to no biologics. The study was undertaken in Italy and included 107 patients from nine tertiary referral centres. Both NHS and societal costs were included and HRQoL was measured using the EQ-5D. Results were expressed using a third party payer and a societal perspective.

Summary of effectiveness data

The following outcomes were collected before and after biologics treatment: laboratory parameters, tender/swollen joint count, numbers of digits with dactylitis, MASES, BASDI, BASFI, occipult to wall distance, chest expansion, modified Schober's test, VAS, duration of morning stiffness, PASI, HAQ, EQ-5D, SF-36, demographic characteristics, clinical characteristics, surgical procedures, use of healthcare resources, days off work due to illness and caregiver time. Patients were interviewed using a structured electronic case report form. This was administered and completed by a physician. Resource use and HRQoL were collected for the 6 months proceeding biologics treatment, at baseline, 6-months and 12-months that followed initiation of treatment.

Both the EQ-5D (VAS and utility) and the SF-36 were used to evaluate HRQoL. Only the EQ-5D utility scores were used in the cost-effectiveness analysis. The EQ-5D utilities were converted to QALYs by computing the difference between average per patient utility at enrolment (before biologics) and average utility after initiation of treatment. This difference was then multiplied by 0.5 (6 months).

At the end of the 12-month observation period there was a gain of 0.25 in utility, equating to a 0.12 gain in QALYs.

Summary of resource utilisation and cost data

As described above, resource use was retrospectively collected from patients, for the 6 months proceeding biologics and for the 12-months after initiation of treatment. Resource use data collected were: surgical procedures, hospitalisations, visits to the physician, medications

and other non-healthcare items, including days off work, caregivers time and transport to and from hospital visits. Case record forms were designed to collect all of this information from patients. This was administered and completed by physicians.

Medical costs were calculated by multiplying the items of resource use by the associated unit costs. DRG costs were used to represent the unit costs of hospitalisations. The authors did not state the sources for other medical costs. The costs of transportation were taken directly from patients reports. Carers costs and days lost from work were costed using the human capital approach.

At the end of the 12-month follow-up direct costs increased by €5052. There were some decreases in hospitalisation costs (€142) and indirect costs (costs to the patient and carers) (€413).

Summary of cost-effectiveness
Incremental cost-effectiveness ratios were appropriately calculated using the differences in costs and QALYs described above.

The increase in costs is somewhat offset by the 0.12 increase in QALYs to produce an ICER of €40,876 for the NHS and an ICER of €37,591 for society.

The uncertainty regarding the estimates of costs and QALYs were expressed using cost-effectiveness acceptability curves, showing the probability that biologicss were cost-effective at various thresholds for a QALY gained. If a decision makers willingness to pay threshold was €45,000 the probability that biologics is cost-effective is 0.82.

Comments
All TNFs were grouped together, although the majority of patients were taking etanercept. It is therefore not possible to estimate any differences in cost-effectiveness between the biologics drugs.

The analysis has a limited length of follow up (6-months). PsA is a chronic disease and it is therefore likely that all differences in costs and outcomes between comparators can be captured in this short time frame.

Internal validity

This is a before and after study, so there may be a problem of confounding. It is possible that patients will get better over time as a result of increased monitoring as part of the study. It is not possible to disentangle these effects.

External validity

This is relatively small sample of patients recruited from a single site. Patients, however, seem fairly typical of the PsA population in terms of disease markers.

Checklist for Olivieri

✓ ✕		
Study question	**Grade**	**Comments**
1. Costs and effects examined	✓	
2. Alternatives compared	✕	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✕	Two perspective chosen. Confusing statements about which is used for costing.
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	✕	
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated		
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	✕	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✕	
11. Potential biases identified (especially if data not from RCTs)	✕	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
Costs		
13. All the important and relevant resource use included	✓	
14. All the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✕	
16. Unit costs reported separately from resource use data	✕	
17. Productivity costs treated separately from other costs	✓	
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	✕	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	
20. Methods to value health states and other benefits are stated	✓	
21. Details of the individuals from whom valuations were obtained are given	✓	
Decision modelling		

22. Details of any decision model used are given (e.g. decision tree, Markov model)	N/A	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	N/A	
24. All model outputs described adequately.	N/A	
Discounting		
25. Discount rate used for both costs and benefits	N/A	
26. Do discount rates accord with NHS guidance?	N/A	
Allowance for uncertainty		
Stochastic analysis of patient-level data	✓	
27. Details of statistical tests and confidence intervals are given for stochastic data	✓	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	✓	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	✓	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	N/A	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	N/A	
32. Are the probability distributions adequately detailed and appropriate?	N/A	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	N/A	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)		No deterministic sensitivity analysis performed.
35. The choice of variables for sensitivity analysis is justified		
36. The ranges over which the variables are varied are stated		
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	
39. Applicable to the NHS setting	✗	Biologicss not evaluated separately. Problems with internal validity.

Review of Bansback, et al. Estimating the cost and health status consequences of treatment with TNF antagonists in patients with psoriatic arthritis[171]

Overview

This paper aimed to generate estimates of the long-term benefits, in terms of HRQoL, of biologics (etanercept) in PsA. In addition they assessed the cost-effectiveness of antiTNFs compared to conventional therapies. The model is based on that used in Wyeth submission to the previous NICE appraisal of biologic drugs[74].The HAQ-DI was used to measure benefit and linked to utilities to generate QALYs. A third party payer perspective was used for the analysis.

An individual sampling model was used to simulate costs and benefits over a 10-year time horizon, using data from a variety of sources, including RCTs, open label and observational data. The authors do not state which software was used to program to model.

Sequencing of three comparators following failure on conventional DMARDs was evaluated. Etanercept was compared with combination therapy on methotrexate and ciclosporin or leflunomide.

Summary of effectiveness data

To estimate the initial (3-month) effect of etanercept, patient level data from a phase III randomised trial was obtained (Mease et al 2004[53]). HAQ was measured at 4, 12 and 24 weeks after which patients were invited to join and open label extension of the trial and treated with etanercept. The randomised data was used within a multivariate regression model to predict 3-month HAQ change. The open label extension data was used to estimate HAQ progression beyond 3 months.

A cohort study containing moderate to severe PsA patients from the Academic unit of musculoskeletal disease at the University of Leeds[199] was used to estimate health state utilities. The relationship between health utilities and HAQ was examined by fitting linear regression models estimated by generalised estimating equation algorithms.

The dataset was also used to estimate long term progression on best standard care and to explore the effect of adding the skin component (PASI) to the prediction of health utilities. The effect of PASI was found to be very small and not statistically significant. This may have been due to the relatively homogeneous PASI scores in the Leeds dataset[199].

Withdrawal from etanercept was taken from the literature and assigned values of 34% and 42%. Patients that withdrew from treatment were assumed to worsen instantaneously by the same magnitude as they initially improved. This assumption is based on the 'rebound' effect observed in a previous economic evaluation of etanercept in RA.

Discounted 10-year QALYs were 4.49 for etanercept, 3.67 for ciclosporin and 3.84 for leflunomide.

Summary of resource utilisation and cost data

Costs included all direct costs attributable to patients with PsA, including drug costs, monitoring, administration and hospitalisation costs. The cost offsets of improving disability were also estimated using a study of patients with RA.

Total costs of etanercept over 10 years is estimated as £51,122, ciclosporin was £28,010 and leflunomode £26,822.

Summary of cost-effectiveness

An individual sampling model was used to estimate costs and benefits over 10 years. Baseline characteristics were sampled from the demographics from the Mease, 2004 trial[199]. The model tracks the decision to continue treatment at 3 monthly intervals. At each interval a decision about whether to continue treatment was randomly sampled. Biologics were assumed to halt the progression of disease whilst treatment is continued.

One way and probabilistic sensitivity analysis were used to explore uncertainties in the data and the model structure.

The results show that at 6-months etanercept gives an additional 0.4 QALYs at an additional cost of £3000, which gives an ICER of around £70,000. At 10-years the QALy benefit increased giving and ICER of £28,000 compared to ciclosporin and £38,000 compared to leflunomide.

Sensitivity analysis showed that the ICER was sensitive to the baseline HAQ and annual HAQ progression. The probabilistic sensitivity analysis showed the decision to recommend etanercept as the optimum treatment was uncertain at 10 years, with a probability that is it cost-effective of 0.58 (at a threshold of £30,000 per QALY).

Comments

This is a good quality evaluation of biologics for PsA. However, only the biologic etanercept was evaluated and therefore the study cannot inform the question as to which biologic is most cost-effective (adalimumab, infliximab and etanercept). It only addresses the question of if biologics are cost-effective compared to ciclosporin and leflunomide. In addition only data from a single phase II trial was used to determine effectiveness. More trials are now available and this evidence should be appropriately synthesised.

The skin component of PsA was not included. The effect of PASI was explored using the Leeds dataset[199] and found not to be statistically significant. However, this may have been due

to the relatively homogeneous PASI scores in the Leeds dataset[199]. Alternative datasets to explore the effect on PASI should have been explored.

Only a single scenario (rebound to gain) was used to represent the uncertainty regarding the effect of withdrawal from treatment on HAQ. Other scenarios, such as rebound to natural history were not explored.

Internal validity

There are no major issues with internal validity.

External validity

The use of a single trial to estimate the initial response to treatment may be expected to produce less robust estimates and limit generalisability. In addition the study is of little use in determining the relative cost-effective of alternative biologics, as the use of biologics was limited to etanercept. This is a major limitation to the study's generalisability.

Checklist for Bansback

✓ ✕		
Study question	**Grade**	**Comments**
1. Costs and effects examined	✓	
2. Alternatives compared	✕	Only looks at the biologics etanercept
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	✕	A do nothing (palliative care) option is not considered.
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	But limited to a single study
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	✕	Fact that the skin component not considered is not discussed.
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	
Costs		
13. All the important and relevant resource use included	✓	
14. All the important and relevant resource use measured accurately (with methodology)	✓	

15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	✗	
17. Productivity costs treated separately from other costs	✗	
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	
20. Methods to value health states and other benefits are stated	✓	
21. Details of the individuals from whom valuations were obtained are given	✓	But only limited information presented
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✗	Not clear why it was appropriate to use an individual sampling model.
24. All model outputs described adequately.	✓	
Discounting		
25. Discount rate used for both costs and benefits	✓	Also explored in the sensitivity analysis
26. Do discount rates accord with NHS guidance?	✓	
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	N/A	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	N/A	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	N/A	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	✗	Costs presented as fixed
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?		Both are presented
32. Are the probability distributions adequately detailed and appropriate?	✓	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	✓	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)	✓	
35. The choice of variables for sensitivity analysis is justified	✓	
36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✗	Compares etanercept with all other comparators not just against next best strategy.
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	
39. Applicable to the NHS setting	✗	Use of a single trail to determine effectiveness potentially limits generalisability.

Review of Bravo Vergel et al. The cost-effectiveness of etanercept and infliximab for the treatment of patients with psoriatic arthritis[172]

Overview

The aim of the study was to estimate the cost-effectiveness of etanercept and infliximab for the treatment of active and progressive psoriatic arthritis (PsA) in patients who have inadequate response to standard treatment (palliative care), including disease-modifying antirheumatic drug (DMARD) therapy. The analysis is based on the York Assessment Group model developed as part of the previous NICE appraisal of biologic therapies for PsA[74]. A probabilistic cohort model was developed in Excel used over a 10 year and 40 year time horizon. A third party payer perspective was used for the analysis.

Summary of effectiveness data

Short term trial data (Mease, et al 2000[79], Mease et al, 2004[53] and IMPACT[82]was used to model the response of patients (measured by PsARC criteria) to biologicss. A Bayesian evidence synthesis was used to link the trials via indirect comparisons methods. A WinBUGS synthesis model was also used to estimate the mean improvements in HAQ score conditional on response. The placebo effect was deducted from the estimates of effect as the comparison strategy was palliative care (do nothing). The mean HAQ change for non-responders was also estimated by the synthesis model and incorporated into the decision model for the initial 3 month period.

The absolute change in HAQ conditional on response from the Mease, et al[53, 79] and IMPACT trials[82,Antoni, 2005 #82], was obtained from the pharmaceutical companies. HAQ progression for palliative care patients was taken from the Leeds cohort study[199].

The posterior distributions estimated by the synthesis model were used to populate the decision model. In addition the probability of withdrawals from treatment was taken from Geoborek, el al[200]. Standard UK mortality rates were used and no excess mortality risk for PsA patients was assumed.

Utility data was taken from a previous cost-effectiveness analysis for biologicss in PsA (Bansback, et al[171]) in which the relationship between health state utility and the HAQ-DI was examined by fitting a regression model to the Leeds dataset[199].

The results show that infliximab is the most effective strategy in both scenarios (4.636 and 4.455 QALYs for rebound to gain and rebound to NH respectively) and etanercept the next most effective (4.514 and 4.356 for both scenarios). Palliative care is the least effective strategy.

Summary of resource utilisation and cost data

Drug costs (including acquisition, administration and monitoring) were inputted into the model as fixed costs. Drug costs were taken from the BNF. The issue of vial sharing for infliximab was explored as a sensitivity analysis. 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. These costs were assumed to include the costs of palliative care.

The results show that total mean costs were highest for infliximab in both rebound scenarios (£64,274 and £64,418 for rebound to gain and rebound to NH respectively). Etanercept is the next most costly (£44,111 and £44,169 for both scenarios) and palliative care the least costly (£10,718 and £10.679 for both scenarios).

Summary of cost-effectiveness

A modified decision tree was used to model the cohort of PsA patients over time. The model was run separately for males and females.

Patients have a probability of responding the biologics in an initial 3-month period. This response is measured using the PsARC criteria. The associated HAQ change for responders is then estimated, this accounts for the progressive nature of the disease. For responders there is an annual risk of withdrawal (for any reason) from treatment. Once patients have withdrawn from treatment they experience a worsening in HAQ.

Uncertainty regarding parameters was characterised using the posterior distributions from the evidence synthesis and by assigning probability to other parameters. Monte Carlo simulation was used to generate lifetime costs and QALYs for the three strategies. Scenario analysis was used to explore some of the other uncertainties in the model, such as the rebound for patients withdrawing from treatment (rebound equal to gain and rebound equal to natural history), time horizon, discount rate and number of vials of infliximab.

The ICERs for infliximab are unlikely to be considered reasonable at £165,363 and £205,345 compared to etanercept for rebound to gain and rebound to natural history (NH) respectively. The ICER for etanercept may or may not be acceptable depending on the threshold for cost-effectiveness and the scenario for rebound believed to be correct. The ICER for rebound equal

to gain is £26,361 and the ICER for rebound equal to NH is £30,628. Both of these ICERs are compared to palliative care.

Etanercept has the highest probability of being cost effective in the rebound equal to gain scenario (0.693 at a £30,000 threshold) whereas palliative care has the highest probability of being cost-effective in the rebound equal to NH scenario (0.554 at a £30,000 threshold).

Comments

This is a good quality evaluation of biologics for PsA. Its limitations are not considering the use of the biologics adalimumab, simply presenting the uncertainty about the rebound effect as scenarios and exclusion of the skin component.

Internal validity

There are no major issues with internal validity

External validity

The psoriasis component (measured using PASI) was not included in the model. HRQoL for PsA patients is influenced by both the arthritis component and the psoriasis component. Failure to capture the effect of treatments on the psoriasis component of disease represents a major limitation of the study.

In addition the uncertainty regarding the effect of withdrawal from treatment on HAQ, was only presented as two alternative scenarios. It is therefore difficult to determine the value of further research to reduce this uncertainty.

Checklist for Bravo Vergel

✓ ✕		
Study question	**Grade**	**Comments**
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	✓	
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✕	Does not justify why a do-nothing strategy is more appropriate than an active comparator such as other DMARDs.
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	

Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	✗	Comparability of studies not discussed Fact that the skin component not considered is not discussed.
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓	
Costs		
13. All the important and relevant resource use included	✓	
14. All the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	✗	Although further details available in HTA report.
17. Productivity costs treated separately from other costs	✗	No considered.
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	QALYs
20. Methods to value health states and other benefits are stated	✓	Fact that the skin component not considered is not discussed.
21. Details of the individuals from whom valuations were obtained are given	✗	Does reference a separate publication
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately.	✓	
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance?	✓	
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	N/A	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	N/A	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	N/A	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	✗	Costs presented as fixed
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	✓	
32. Are the probability distributions adequately detailed and appropriate?	✓	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	✓	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)	✓	
35. The choice of variables for sensitivity analysis is justified	✓	

36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	
39. Applicable to the NHS setting	✓	

Review of Abbott submission[174]

An individual sampling model is used to assess the cost-effectiveness of adalimumab compared to etanercept, infliximab and conventional DMARDs. 3rd, 4th and 5th line treatments are modelled with 4th and 5th line treatments always DMARDs. The patients included in the model were assumed to have not responded to at least two DMARDs, individually or in combination. A third party payer perspective was used for the analysis. The model is programmed in R and a lifetime time horizon is assumed.

Summary of effectiveness data

Baseline patient characteristics from the ADEPT trial[89] were used determine the baseline distribution of patients characteristics in the model.

Long term outcomes were expressed as QALYs. To generate QALYs short term and long term outcomes were estimated. These longer term outcomes were then regressed onto utilities. Short term efficacy was determined using PsARC, ACR and PASI responses. Longer term outcomes were HAQ and PASI.

In the base-case model 12 week PsARC response rates were used to determine continuation of therapy beyond the trial period. A mixed treatment fixed-effects meta-analysis was used determine response rates. The evidence synthesis was undertaken using WinBUGS and used data from 10 different sources (Mease 2000[79], Antoni 2003[82], Antoni 2005[83], Mease 2004[53], Kaltwasser 2004[63], Mease 2005[211], Mease 2006[89], Genovese 2007[84], Kavanaugh 2008[212] and Gottlieb 2009[213]) each of which compares different treatment, some of which that are not included in this appraisal. Three Bayesian bivariate analyses were conducted 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, 3) 24 week ACR response conditional on the 12 week ACR response. The joint distribution of 12 and 24 week PASI response rate is modelled independently. The associated WinBUGS code was presented. In a sensitivity analysis continuation beyond 12 weeks was estimated directly from the BSRBR and so PsARC response rates were not used to determine continuation.

Patient level data from the ADEPT[89] study were then used to estimate HAQ and PASI changes dependent on the magnitude of response. Patients who had previously failed two or more DMARDs and had a baseline HAQ greater than zero were included in the analysis. A forward stepwise regression analysis was used to select significant variables in predicting HAQ and PASI improvement, including ACR response type, HAQ at baseline, demographics, disease duration and treatment. In order to estimate the PASI the data was transformed by Log(PASI+0.5). The authors state this was done "to obtain normality". It is important to note that this log-transformation assumes that a 1% improvement in PASI will lead to a constant change in utility, regardless of the absolute change in PASI. For example, this regression assumes that a reduction in PASI score from 16 to 0 leads to the same change in HRQOL as a reduction in PASI score from 8 to 0. A linear regression on the other hand assumes that a reduction in PASI by 16 points gives twice the HRQOL benefit of a reduction in PASI by 8 points, regardless of the baseline. A similar regression was specified for HAQ at 24 weeks.

Placebo response rates from trials were used to represent the DMARD efficacy data. A common efficacy was used for all DMARDs. A reduction multiplier was applied to response rates for subsequent DMARDs (24% reduction in receiving response). Alternative reduction multipliers were examined in sensitivity analysis.

Long term progression of HAQ while on biologics was assumed to be 0.0005 per year. This was taken from a longitudinal analysis of the Bath Psoriatic Arthritis Database (reference not given). Progression on DMARDs was 0.024 per year. Progression of patients who do not respond (defined as ACR 20) is assumed to be 0.06 per year. These were both estimated using the Leeds dataset[199]. PASI is assumed to halt for responders.

The model assumes that patients withdrawn from therapy at 12-months due to inefficacy reflect the PsARC response rates in practice. Rates of withdrawal from therapy between 1 and 3 years, due to either adverse events or loss of efficacy, were estimated using data from the BSRBR registry (Saad, 2009[157]) and specified using a Weibull distribution. No differences between drugs were assumed due to selection bias. Sensitivity analysis explored differential biologics withdrawal and the use of data from Kristensen[214]. Withdrawal rates for conventional DMARDs were taken from a smaller study by Malesci[197] and were again specified using a Weibull distribution. It is unclear how the parameters for either of these Weibull distributions were derived from the referenced data. Following withdrawal from treatment patients HAQ is assumed to rebound equivalent to the initial gain and PASI rebound to the starting level. The rate of HAQ progression following stopping biologics therapy was assumed to be the same as for patients who do not respond to therapy (0.066).

Two sources of data were used to estimate the improvement in health utility through a direct linear relationship with HAQ and PASI. Base-case uses the ADEPT trial[89] of adalimumab. SF-36 was converted to EQ-5D. In a sensitivity analysis, data from Bath Psoriatic Arthritis Database was used. Functions for health utilities reported with and without skin effect. Any interaction between HAQ and PASI was not explored.

The model used psoriatic arthritis specific mortality inflators (Wong[30]) along with UK life tables.

Infliximab was associated with the highest QALYs (8.49), followed by etanercept and adalimumab (8.33) and then DMARDs (7.47)

Summary of resource utilisation and cost data
The costs of all drugs were estimated using the Monthly Index of Medical Specialties (MIMS[215]) as opposed to the BNF. Infliximab costs were calculated assuming that four vials were used per infusion, based on an average patient weight of 80kg.

Resource use associated with monitoring and administering drugs was estimated according to BSR guidelines. Assumes infliximab requires ½ day hospital visit for each infusion. A single outpatient visit is required for adalimumab and etanercept. Gives references for each unit cost used to cost these items of resource use.

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, therefore estimating the relationship between PASI. This was done for four hypothetical patients with differing PASI scores. The median responses on resource utilisation were to generate costs. A logarithmic regression was then fitted to the data points to estimate cost based on a continuous PASI scale.

The base-case results show that infliximab is the most costly strategy (£104,772)

Summary of cost-effectiveness
An individual sampling model is used to simulate the disease progression of a cohort of PsA patients over a lifetime horizon. The model is written in R with an accompanying evidence synthesis model written in WinBUGS.

Initial response to treatment is determined according to the PsARC criteria at the end of the initial 3-month period. Patients who do not respond according to PsARC take the next available treatment in the sequence. Patients who respond according to PsARC criteria remain on treatment unless they withdraw due to either loss of efficacy or toxicity. 3-monthly cycles are used.

It is assumed that patients who do not receive an biologics agent after failure of two conventional DMARDs would continue treatment with an alternative conventional DMARD.

The ICER for infliximab is unlikely to be considered acceptable given current levels for the threshold (ICER = £199,596 compared to adalimumab). Etanercept is dominated by adalimumab. Adalimumab has an ICER of £29,827 compared to a DMARD.

Probabilistic sensitivity analysis was conducted and shows that there is considerable uncertainty regarding the optimum strategy. Adalimumab had a probability of less than 0.5 of being cost-effective at thresholds up to £30,000. This rose to around 0.7 at thresholds greater than £60,000.

Multiple univariate sensitivity analysis were conducted to assess the models sensitivity to effectiveness parameters, withdrawal rates, disease progression estimates, utilities, costs, rebound effect, characteristics of patients and discounting. Results were sensitive to many of the changes in parameters, in particular the stopping rule for BSRBR withdrawal rates and the rebound assumption. The impact on decision uncertainty using alternative parameter assumptions was not presented.

Comments

This is a comprehensive evaluation of biologics for the treatment of PsA. There are, however, a number of limitations. In particular, the model assumes that after failing biologics, patients will receive another DMARD, or combinations of DMARDs. This is un-realistic as patients have previously failed two or more DMARDs. Placebo response rates from trials were also used to represent the DMARD efficacy data. This means that DMARDs will have no effect but will incur costs, biasing against DMARDs. The authors do not give a clear rationale for not choosing palliative care as the comparator to biologics.

Withdrawals were calculated using data from a single dataset. There are other potential registry datasets available which could have been synthesised with the data by Saad. In addition, parameters for a Weibull distribution were derived using longitudinal data from three time points, and the data were assumed to be independent. This assumption is incorrect, because the same patients contribute data to the probability of survival at 2 years as 1 year. Only one scenario was used to determine HAQ following rebound, this was that patients will rebound equivalent to the initial gain.

Internal validity

There are no major issues with internal validity.

The model results have been checked and verified by the assessment team. There are some issues with the cost estimates used in the model. These cannot be ratified with the costs presented in the report. In particular the drug, monitoring and administration costs in the model differ from those presented in the report.

External validity

The use of DMARDs as a comparator to biologics is a major limitation. As discussed, DMARDs are unlikely to be considered for patients withdrawing from biologic treatment, as this cohort of patients will have previously failed two or more DMARDs.

In addition, the evidence synthesis uses all available evidence to generate estimates of effect, using data from 10 different sources. However, some of these data sources relate to treatments not included as comparators in the model, such as Golimumab. It is not clear if the relative treatment effects can be transferred from one biologic to another.

Checklist for Abbott submission

✓ ✕		
Study question	**Grade**	**Comments**
1. Costs and effects examined	✓	
2. Alternatives compared		
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	✕	Biologics compared to DMARDs and no palliative care.
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✕	Does not describe what the series of DMARDs are.
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		

7. The choice of form of economic evaluation is justified in relation to the questions addressed.	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	✗	Limitations of using registry data not discussed
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓	Evidence synthesis model is not well annotated and thus is difficult to interpret.
Costs		
13. All the important and relevant resource use included	✓	
14. All the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	✓	
17. Productivity costs treated separately from other costs	N/A	
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	✗	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	
20. Methods to value health states and other benefits are stated	✓	
21. Details of the individuals from whom valuations were obtained are given	✓	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	Do not give adequate justification for why an individual sampling model is used.
24. All model outputs described adequately.	✗	Calculate of withdrawal rates is not clear
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance?	✓	
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	✓	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	✓	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	✓	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	✓	Costs are fixed
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	✓	Both
32. Are the probability distributions adequately detailed and appropriate?	✓	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	✓	
Deterministic analysis		

34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)	✓	
35. The choice of variables for sensitivity analysis is justified	✓	
36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	
39. Applicable to the NHS setting	✓	

Review of Schering-Plough submission[175]

A cohort model was developed to assess the cost-effectiveness of four treatment alternatives: adalimumab, etanercept, infliximab and DMARDs (assumed to represent palliative care) for psoriatic arthritis patients. Sequential use of biologics was not considered. The report states that a sequence of DMARDs was considered.

The model was programmed in Excel with evidence synthesis undertaken in WinBUGS. A third party payer perspective was used for the analysis.

Summary of effectiveness data

The primary outcome was QALYs, estimated using both HAQ and PASI. An evidence synthesis model was used to determine the response to biologics and the associated HAQ and PASI change for responders. The evidence synthesis model used to generate initial HAQ and PASI changes and the data used are presented. In many cases results from the York model were used as priors. Data from the previous York model[172] along with IMPACT[82], IMPACT 2[83], Mease 2000[79], Mease 2004[53], GO-REVEAL[176], Genovese 2007[84] and ADEPT[52] were used in the evidence synthesis model. As change in absolute PASI was modelled, absolute changes in PASI were inferred form relative changes reported in trials. It is also assumed that the average HAQ change in non-responders can be used when data are not reported by responders/non-responders. From this HAQ for responders can be inferred from the aggregate data.

At the end of the first cycle (12-weeks) patients where categorised as responders or not responders according to their PsARC response. Responders continued with treatment whereas non-responders discontinued treatment and instead received palliative care. The results of the evidence synthesis showed that PASI was not different in individuals with and without a PsARC response. This was concluded using data for golimumab but assumed for all drugs. All patients start with the same PASI score. PASI change is not assumed to be correlated with baseline score.

The same HAQ and PASI change is assumed for the two 12-week cycles for responders. In addition a HAQ reduction is also assumed for the 3rd cycle [redacted] The HAQ reductions for the 2nd and 3rd cycles are taken from the GO-REVEAL trial[176] (this is a trial of golimumab which is not included in the appraisal, however relationships observed in this trial were assumed across all biologics). For non-responders the HAQ and PASI change is only applied for the first cycle. The placebo effect is then subtracted from the treatment effect (on HAQ) estimated by the evidence synthesis model, however palliative care in this model is DMARDs (active treatment). This will not bias the comparison between biologicss but may affect the comparison with palliative care.

HAQ is not assumed to progress for patients responding to treatment and is not correlated with initial HAQ change. A sensitivity analysis is conducted assuming that progression for responders is the same as natural history. Patients on palliative care (in this case actually DMARDS) will progress in line with natural history (0.0719 annual). This is estimated from the Leeds NESPAR study[199]. The distribution placed on this assumes that the value can only be non-negative. The natural history of PASI was assumed to be flat, based on expert opinion (source for this is not stated). Following rebound patients rebounding are assumed to return to their original PASI score.

Two alternative methods to generate utilities were explored: the Gray algorithm (selected as the base-case) and the Brazier algorithm. The Gray algorithm converts SF-36 to EQ-5D then EQ-5D to utilities whereas the Brazier algorithm estimates utilities directly from SF-36. Explanatory variables used in the model were: HAQ, PASI, HAQ squared and PASI squared. Interaction between PASI and HAQ was not explored. The GO-REVEAL data was used to estimate the regression.

Annual withdrawals from treatment were taken from the Geborek study[200] and are 11.4% per annum. The same withdrawal rate was applied to all strategies. After withdrawal patients will go onto palliative care. Patients also have an annual risk of death. PsA specific mortality multipliers are also included (Wong et al[30]).

The results show that palliative care is the strategy associated with the lowest QALYs in all base-case scenarios (5.79 to 6.68 depending on the group of patents). Infliximab is the most effective strategy for all base-case scenarios, for all patients as a group and psoriasis patients (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).

Summary of resource utilisation and cost data

Resource use associated with treatment, administration and monitoring was taken from the previous York model. Costs associated with adalimumab were assumed to be the same as etanercept. The BNF[178] was used to cost medications. Costs for infliximab were calculated using 60, 70 and 80kg weights for patients in addition to the use of 4 and 3.5 vials.

Ongoing costs as a function of HAQ were derived from the Kobelt, 2002 study[42]. Patients on treatment only incur 85% of these costs, whilst those withdrawing from treatment incur 100%. [redacted]

The base-case results for all patients produce 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 patterns were observed for minimal psoriasis and psoriasis patients separately.

Summary of cost-effectiveness

An initial 2 cycles of 12 weeks were modelled followed by annual cycles. Half cycle correction is applied. In the first cycle, patient's response to PsARC is assessed and their associated HAQ and PASI change determined. PsARC responders on continue with current treatment whereas those do not respond will move onto palliative care. PsARC responders will then experience an annual risk of withdrawal from treatment with an associated HAQ loss. Two scenarios were modelled for the rebound: rebound equal to gain (followed by NH after 3-months) and rebound equal to NH.

For approximately 1/3 of patients with no clinically significant psoriasis component to their disease (estimated from the IMPACT and IMPACT 2 trials) only the change in HAQ is modelled. The PASI impact on QoL is not included for these patients. Costs and QALYs are reported separately for psoriasis and non-psoriasis patients as well as the group as a whole.

The base-case results are presented for 60kg, 70kg and 80kg patients and for patients with psoriasis, minimal psoriasis and all patients. For a 60kg patient infliximab is the most cost-effective strategy for all patients and for psoriatic patients, dominating etanercept and

extendedly dominating adalimumab. For a 70kg patient etanercept is the most cost-effective strategy for all patients and for psoriatic patients, with an ICER of £12,696 compared to adalimumab (however this is extendedly dominated so should be compared to palliative care which gives an ICER over £16k) for psoriatic patients and £12,606 for all patients. For an 80kg patient etanercept is again the most cost-effective strategy for all patients and for psoriatic patients, with ICERs of £12,696 and £12,606 compared to adalimumab. For all patient weights, etanercept is the most cost-effective with an ICER of £12,432 compared to adalimumab for non-psoriatic patients.

A number of univariate sensitivity analyses were conducted: reduction in the baseline HAQ, HAQ reduction beyond week 12, non-zero HAQ progression for responders after week 12, reduction in the baseline PASI score, 20-year time horizon as opposed to lifetime, exclusion of phototherapy costs, reduction in annual withdrawals from 11.4% to 5.7%, reduction of natural history progression to 0.036 annually and using the Brazier algorithm to calculate utilities. Vial optimization is not considered in the sensitivity analysis.

Results for the sensitivity analysis are presented as ICERs versus palliative care and ICERs versus other biologics. It is not clear from the results if these results are for psoriasis, non-psoriasis or all patients. The results of the sensitivity analysis appear sensible given the changes in parameter assumptions made, for example increasing the lifetime of the model makes all biologics more cost-effective.

Biologics appear to be robust to the sensitivity analysis compared to palliative care, apart from changing the algorithm for estimating QoL. This generated ICERs greater than £36,000 for all biologics compared to palliative care. For patients with a body weight of less than 70kg infliximab remained the most cost effective strategy compared to other biologics, apart from when the baseline HAQ is reduced from 1.14 to 0.90, no HAQ change beyond 1st cycle is assumed and HAQ of responders to etanercept, infliximab and adalimumab progress at the same rate as natural history after initial HAQ improvement.

Probabilistic sensitivity analysis is also conducted. This shows a great deal of decision uncertainty for the optimum strategies given each of the base-case assumptions.

Comments

This is a good quality evaluation of the relevant biologics for the treatment of PsA. There are, however, a number of issues that are of concern. In particular, the use of data from a trial of golilimumab to inform a number of model parameters, the use of DMARDs to represent the

comparator, the addition of HAQ gains beyond the initial cycle and the use of a single data source to estimate withdrawals.

Internal validity

There are no major issues with internal validity.

We were able to replicate the deterministic results. The probabilistic results could not be replicated, however, differences were small and the interpretation of results was the same in terms of ordering of strategies.

External validity

Data from a number of sources were used to estimate benefits of treatments. However data from the [redacted] a trial of golilimumab was also used to inform a number of parameters, in particular HAQ and PASI changes. This biologics was not included in the model and it is unclear if the relationships observed in this trial can be assumed to transfer across to other biologics. In addition, the estimated placebo effect has been subtracted from the treatment effect (on HAQ), however palliative care in this model is actually DMARDs (active treatment). This will not bias the comparison between biologics but may affect the comparison with palliative care.

Withdrawals were also estimated from a single data source, and it is unclear if this is a representative data source. It is of concern that identification of studies to generate withdrawal rates was not more systematic.

Checklist for Schering-Plough submission

✓ ✕		
Study question	**Grade**	**Comments**
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	✓	
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		

9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	✗	Potential biases of using registry/ survey data not discussed
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓	WinBUGS code presented
Costs		
13. All the important and relevant resource use included	✓	
14. All the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	
16. Unit costs reported separately from resource use data	✓	
17. Productivity costs treated separately from other costs	✓	
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	
20. Methods to value health states and other benefits are stated	✓	
21. Details of the individuals from whom valuations were obtained are given	✓	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately.	✓	Not clear why PASI was predicted for PsARC responders and non-responders
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance?	✓	
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	N/A	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	N/A	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	N/A	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	✓	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	✓	
32. Are the probability distributions adequately detailed and appropriate?	✓	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	✓	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)	✓	
35. The choice of variables for sensitivity analysis is justified	✓	

36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	
39. Applicable to the NHS setting	✓	

Review of Wyeth submission[152]

[redacted]

[redacted]

[redacted]

Summary of effectiveness data

[redacted]

[redacted]

[redacted]

[redacted]

Summary of resource utilisation and cost data

[redacted]

Summary of cost-effectiveness

[redacted]

[redacted]

[redacted]

[redacted]The results appear to make sense in terms of the changes made to parameters assumptions. For example increasing the rate of HAQ progressin whilst receiving biologics increases costs slightly and decreases QALYs for adalimumab, etanercept and infliximab.

[redacted]

Comments

This is a good quality evaluation of biologics for the treatment of PsA. There are, however, a number of issues that may cause concern.[redacted]

[redacted]

[redacted]

[redacted]

Internal validity

There are no major issues with internal validity.

It was not possible to replicate the deterministic model results as there was a runtime error in the visual basic macro. Given this, and the anticipated 24 hour + simulation time, we did not attempt to replicate the results of the probabilistic model.

External validity

[redacted] Although data were included from a number of trials in the adalimumab MTC the original review used to identify trials to populate this MTC was restricted to a review of clinical trials including adalimumab as an intervention.

As discussed above the use of ciclosporin as a comparator to biologics as opposed to palliative care, is unlikely to be appropriate given that the patients relevant for treatment with biologics will have failed at least two previous DMARDs.

Checklist for Wyeth submission

✓ ✗	

Study question	Grade	Comments
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	×	Ciclosporin used as comparator not palliative care.
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	N/A	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	×	Does not discuss the bias associated with using registry and survey data.
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	✓	
Costs		
13. All the important and relevant resource use included	×	Does not include the costs of PASI as these are used to predict HAQ.
14. All the important and relevant resource use measured accurately (with methodology)	✓	
15. Appropriate unit costs estimated (with methodology)	✓	Unclear how the costs of HAQ have been used in the model
16. Unit costs reported separately from resource use data	✓	
17. Productivity costs treated separately from other costs	N/A	
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	✓	
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	PASI incorrectly used to predict HAQ
20. Methods to value health states and other benefits are stated	✓	
21. Details of the individuals from whom valuations were obtained are given	✓	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	×	The need to use an individual sampling model was not justified sufficiently.
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	
24. All model outputs described adequately.	✓	
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance?	✓	
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and confidence intervals are given for stochastic data	✓	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	✓	

29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	✓	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	✓	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	✓	
32. Are the probability distributions adequately detailed and appropriate?	×	Not clear how the uncertainty in HAQ costs is propagated.
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	✓	
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)	✓	
35. The choice of variables for sensitivity analysis is justified	✓	
36. The ranges over which the variables are varied are stated	✓	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	
39. Applicable to the NHS setting	✓	

10.8 Critique of the manufacturers models

Choice of comparator(s)

The submission by Schering-Plough compares etanercept, infliximab and adalimumab with palliative care. Wyeth and Abbott use DMARDs as the comparator to the biologics. [redacted] Abbott uses a series of unspecified DMARDs as comparators with 4th and 5th line treatments always being DMARDs. Although Wyeth and Abbott compare biologics to DMARDs, they assign effectiveness estimates from the placebo arms of trials. Therefore the effectiveness of biologics is likely to be artificially inflated.

Patient characteristics

The Schering-Plough model uses a homogeneous cohort of patients considered representative of the groups of patients eligible for biologic therapies to treat PsA; that is, patients who have failed two or more conventional DMARDs.

[redacted] and Abbott, however, model [redacted] Both of the individual sampling models are difficult to critique and require a significant time to run probabilistic sensitivity analysis. [redacted] comparing etanercept and placebo. [redacted] In the Abbott submission, baseline patient characteristics from the ADEPT trial [89] were used to determine the baseline distribution of patients characteristics in the model. The ADEPT trial [89] compared adalimumab with placebo. Only patients who had failed at lease two DMARDs were included in the analysis. Patients' characteristics that were included were: age, disease duration, gender, presence of psoriasis, % on methotrexate, PASI and HAQ score.

Adjustment for placebo effect

A placebo adjustment accounts for any overestimate of the *absolute* response rates in both placebo and treatment groups, compared with what would be expected in general practice. There may be a need to adjust for the placebo effect observed in the clinical trials if the placebo effects in the trials are assumed not to occur in usual practice (see Appendix 10.9).

[redacted] and Abbott [redacted] In other words, these models assume that DMARDs are no more effective than placebo in these patients.

In the Schering-Plough model, the placebo effect is subtracted from the treatment effect (on HAQ) for responders and non-responders on biologics, estimated by the evidence synthesis model. However, palliative care in this model is DMARDs (active treatment). As an inactive treatment is not actually included in any of these three models, the use of a placebo adjustment should have little impact on the results or their interpretation. It will also not bias the comparison between biologics but may overstate the effectiveness of biologics.

Sequencing

None of the four models consider the use of sequential biologics in the base-case scenario. The Abbott model uses a series of unspecified DMARDs, following failure of treatment with any biologic (up to 5th line), but the use of subsequent DMARDs for patients who have previously failed two or more DMARDs is unlikely in practice. A reduction multiplier is applied to response rates for subsequent DMARDs (24% reduction in receiving response in the base-case). This reduction is justified using estimates from the BSRBR of the percentage of patients that withdraw on their 2nd biologic at year 1 compared to the first course. A reference for these figures is not given.

The sequential use of biologics is likely to be feasible in practice; however a lack of data on the effectiveness of biologics beyond 1st line, limits the possibilities to consider such an analysis.

Outcomes of the evidence synthesis

Each of the three industry models, use an evidence synthesis component (implemented in WinBUGS) to generate estimates of treatment effect (see section 5.2.2).

[redacted] The need for an evidence synthesis component is primarily because of the lack of head-to-head data from trials for the three biologics, thus there is a need to use a mixed treatment comparison model. Each model, however, generates different parameters using different data.

[redacted]

Schering-Plough estimates PsARC at 12 weeks for responders and non-responders. In the subgroup with >3% body skin area PASI change from baseline at 12 weeks by PsARC response/no response was estimated. The prediction of PASI change by PsARC response is somewhat questionable. Schering-Plough also determine HAQ change at 12 weeks by PsARC response /no response and treatment drug was also estimated. In many cases the results from the previous York model were used as priors. Abbott use a mixed treatment fixed-effects meta-analysis was used determine: 1) joint distribution of 12 week PsARC and ACR response rates, 2) 24 week PsARC response conditional on the 12 week PsARC response, 3) 24 week ACR response conditional on the 12 week ACR response. The joint distribution of 12 and 24 week PASI response rate is modelled independently.

Decision to withdraw depending on initial response(s)

All of the industry models assume that patients are withdrawn from treatment if they are PsARC non-responders at 12 weeks, irrespective of PASI response. In addition the [redacted] Abbott conduct a sensitivity analysis in which continuation beyond 12 weeks is estimated directly from the British Society for Rheumatology Biologics Register (BSRBR) [157], and so PsARC response rates are not used to determine continuation. None of the industry models consider the possibility of different scenarios for discontinuation, for example the possibility that there may be a response on either PsARC or PASI or both.

Initial change in HAQ for responders and non responders

Schering-Plough predicts HAQ by PsARC response and treatment from the evidence synthesis. The latest available endpoints for HAQ were used to reflect short-term benefits. The same HAQ change is assumed for the two initial 12-week cycles for responders. In addition, a HAQ reduction is also assumed for the 3rd cycle [redacted]. The HAQ reductions for the 2nd and 3rd cycles are taken from the [redacted]. For non-

responders, the HAQ change is only applied for the first cycle after which a natural history progression is assumed.

Abbott predicts HAQ at 12 and 24 weeks as a function of ACR response (20, 50 etc), baseline HAQ, age, gender, baseline PSA duration, concomitant MTX and if receiving biologic drugs(ADEPT[89]). HAQ does not differ by biologic drug.

[redacted] Despite the justification given in the report for using PASI to predict HAQ, the use of the skin component of PsA to predict the arthritis component of the disease is of doubtful 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*.

HAQ progression while responding on a biologic therapy
As in the earlier York Assessment Group model, [redacted] and Schering-Plough [redacted] The Schering-Plough model incorporates a slight improvement in HAQ over the first year. The Abbott model assumes that HAQ will worsen by 0.0005 per year. This figure was taken form a longitudinal analysis of the Bath Psoriatic Arthritis Database (reference not given).

The Abbott model also the subgroup of patients where ACR <20 separately and uses a HAQ progression rate of 0.066 per year from the Leeds cohort [199].

HAQ progression when on DMARD
In the Schering-Plough model the comparator is palliative care, and thus progression is assumed to be that of natural history (0.066 per year)[199]. For the Abbott and [redacted]. Abbott uses an annual rate of progression of 0.024 from the Leeds cohort study[199]. Wyeth uses a similar rate of 0.028 from Sokoll (reference not given).

HAQ progression while not on biologic therapy
All of the industry models use the Leeds cohort study[199] data to estimate HAQ progression while not on biologic therapy (also called natural history progression). Abbott estimates this

as a 0.066 increase in HAQ per year, [redacted] and Schering-Plough 0.071 increase per year. It is not clear why the same data source appears to generate three slightly different estimates but these differences are unlikely to have major impacts on the cost-effectiveness results.

The Leeds dataset is, however, small, including only 24 patients. In addition patients surveyed do not meet the requirements for this analysis in that many have not failed at least 2 previous DMARDs. It is also not clear if patients met the current guideline criteria for initiating biologics for PsA (3 tender and 3 swollen joints).

Initial change in psoriasis severity while on biologic therapy

Each of the models uses a different approach to estimate the initial change in psoriasis severity after treatment with a biologic. [redacted] Schering-Plough estimates the PASI change from baseline to 12 weeks for PsARC responders/non-responders in their evidence synthesis model. As change in absolute PASI was modelled, absolute changes in PASI were inferred form relative changes reported in trials. It is not clear why PASI change was estimated for PsARC responders and non-responders and not for PASI responders. Abbott predict the initial (12 week) change in PASI, using baseline PASI and proportion who are PASI 50, 75 90 responders. Abbott also predicts this at 24 weeks.

Correlation between PASI and PsARC responses

Biologics are intended treat both joint disease and psoriasis. Clinical response at 3 months is measured using the PsARC for joints and PASI 75 for skin conditions for these two aspects respectively. The PsARC and PASI 75 responses are not necessarily independent (see Appendix 10.10).

Each of the industry models uses a different approach to account for any correlation between PASI and PsARC responses. The Wyeth model assumes PASI is a predictor of HAQ (see Appendix 10.8 for further detail), which is unlikely. Abbott assumes that they are independent and thus models them separately (see Appendix 10.8 for further detail). The Schering-Plough model predicts PASI by PsARC response, thus generating a different PASI change for PsARC responders and non responders; by drug.

Psoriasis progression on and off biologic therapy

Each of the models assumes that psoriasis will not progress on or off treatment, that is psoriasis will not worsen over time. This assumption is justified quoting clinical opinion, although this is not referenced.

HAQ rebound after discontinuation of biologic therapy

Following withdrawal from treatment, either due to adverse events or loss of efficacy, it can be expected that there will be some change in patients' HAQ scores. The previous York model[172] looked at two possible scenarios for this: rebound by the same amount as initial gain and rebound back to natural history progression (see Appendix 10.11). The models from Wyeth and Schering-Plough also explore these two scenarios. [redacted]. The Abbott model only uses the rebound to initial gain scenario as it states that rebound to natural history is unlikely to be possible as halting joint destruction does have an impact on long-term disability.

Psoriasis rebound when stopping therapy

Each of the industry models assume that following withdrawal from treatment, patients PASI score will rebound by the original gain. As PASI is not assumed to progress whilst receiving treatment, the rebound will be to the original PASI score. Clinical opinion is cited as the source of this evidence but no reference is given.

Withdrawal rates

To estimate the probability of withdrawal whilst receiving biologics, due to either loss of efficacy or adverse events, Schering-Plough employs the same rates as used in the previous York model (0.11 per year from Geborek [200] beyond the initial 12 week period) for biologics. As the comparator is palliative care (in active treatment) no withdrawals were seen in the comparator arm.

[redacted]and Abbott [redacted]

[redacted] On seeking clarification from Abbott they confirmed that the reported figures in table 2 of Saad et al, 2009[187]. These are slightly lower than the values fitted in the Wyeth analysis. A diagram showing observed versus predicted durvival was presented. [redacted] No further details of this study were presented.

There are a number of issues with the Wyeth and Abbott approach. Firstly, no justification was given for the choice of Weibull distributions rather than other parametric distributions. It may be that other distributions offered a better fit. Secondly, the 1 year rates from the BSBDR are likely to include non-responders to biologics in addition to those who withdraw due to loss of efficacy or adverse events after the initial 3-month period. As these initial withdrawals are already counted as non-responders, there is a degree of double counting. Thirdly, this approach assumes that the data points are independent, which is unlikely.

Utility estimates

Each of the industry models uses different methodologies and datasets to link changes in HAQ and PASI to utilities, in order to generate QALYs (see Table 10.8.1).

The Wyeth model uses the relationship between HAQ and EQ-5D observed in the PRESTA dataset (a clinical of etaneracept including 752 patients)[216] [redacted]

The Schering-Plough model explores two alternative methods to generate utilities: the Gray algorithm [217] and the Brazier algorithm[218]. The Gray algorithm converts SF-36 profiles to EQ-5D profiles and then EQ-5D profiles to utilities. The Brazier algorithm estimates utilities directly from SF-36. The Gray algorithm was used in the base-case analysis. The GO-REVEAL [176] trial data were used in a multiple regression model using HAQ, PASI, HAQ squared and PASI squared, with no interaction terms, as explanatory variables. The Abbott

model uses the ADEPT trial [89] of adalimumab versus placebo to estimate utility through a direct linear relationship with HAQ and PASI collected in the trial. The base-case uses the SF-36, collected in the trial, converted to EQ-5D. In a sensitivity analysis, data from the Bath Psoriatic Arthritis Database was used (no reference given). Again any interaction between HAQ and PASI was not explored.

There is some uncertainty regarding which of the industry regression models is appropriate to generate utilities.

Table 10.8.1: Utilities used in the cost-effectiveness models

	Regression estimates
[redacted]	[redacted]
Schering-Plough[1]	Intercept = 0.6442260 (SE = 0.0115177) sHAQ = -0.1610008 (SE = 0.0087963) sPASI = -0.0375632 (SE = 0.0132345) $sHAQ^2$ = -0.0050072 (SE = 0.0067073) $sPASI^2$ = 0.0051515 (SE = 0.0030365)
Abbott[2]	Intercept = 0.9144 (SE = 0.0186) HAQ = -0.2512 (SE = 0.0189) PASI_t = -0.0355 (SE = 0.0096)

Mortality

All of the industry models, use UK life tables along with PsA specific mortality multipliers (Wong[30]) to estimate mortality. Each also uses the same mortality rate for all treatments and no treatment (i.e. there is not differential impact of the alternative therapies on mortality). This assumption is reasonable, although there may be a beneficial effect of biologics on mortality; however, data to quantify this is not available.

Costs of treatment, start-up, administration and monitoring

Each of the industry model present information, to differing degree on the resource use and unit costs used to cost drug treatment, administration of drugs and monitoring of patients. Of concern is the fact that in the Abbott model the total costs given in the report could not be replicated in terms of the resource use items and unit costs presented. These also appear to differ from the costs used in the model, where drug costs are split by direct and indirect with no accompanying definition provided in the report.

[1] Estimates from Brazier algorithm and split by psoriasis and non psoriasis also available.
[2] Also reports for a model not including PASI

The BNF[178] was used to cost medications in the [redacted] and Schering submission. MIMS[215] was used in the Abbott submission. However, unit costs are consistent across the industry models, £419.62 per vial of infliximab, £89.38 per vial of etanercept and £357.50 per vial of adalimumab. Despite the consistency in unit costs, there are some differences in the medication costs for the industry models (see Table 10.8.2). There are a number of differences in costing methodology that explain this: Firstly, different assumptions were made regarding the use of vials and patient weight for infliximab. Abbott assumes that four vials were used per infusion, based on an average patient weight of 80kg. [redacted] Schering-Plough explore various scenarios to cost infliximab, using 60, 70 and 80kg weights for patients in addition to the use of 4 and 3.5 vials. All models assume that 5mg infliximab is given per kg. Secondly, there are some differences in the number of vials used for the biologics in the different time periods. Schering-Plough and Abbott assume that three doses of infliximab are given in the initial 3-month period (at 0, 2 and 6 weeks). This is followed by doses every 8 weeks. Wyeth [redacted] Thus 4 doses are given in the initial 3 month period, as opposed to three in the Schering-Plough and Abbott models. All three industry models assume that 6 vials of adalimumab are given in the first period. Abbott then assumes 7 vials are given in months 3-6 followed by 6.5 vials in subsequent three month periods. [redacted] Schering-Plough assume 6 vials for the 3-6 month period followed by 6.5 vials for subsequent 3-month periods. All three models assume 24 vials of etanercept are given in the initial 3-month period. [redacted] Schering-Plough give 24 vials for months 3-6 followed by 26 for subsequent 3-month periods. Abbott gives 28 vials in the 3-6 month period followed by 26 vials in all subsequent periods.

Table 10.8.2: Costs used in the industry models

	Drug costs	Administration costs	Monitoring costs	Total costs
Abbott[3]	From report: 0-12 weeks Etanercept = £2324 Adalimumab = £2324 Infliximab =£4196 DMARD = £70.5 12-24 weeks Etanercept = £2324 Adalimumab = £2324 Infliximab =£4196 DMARD = £70.5 24 weeks + (3-month costs) Etanercept = £2324 Adalimumab = £2324 Infliximab = £2727.5 DMARD = £70.5 From model code: 0-12 weeks Etanercept = £2145.12 (direct), £2239.64 (indirect) Adalimumab = £2145 (direct), £2239.52 (indirect) Infliximab = £5035.44 (direct),£5319 (indirect) DMARD = £65.15 (direct),£85.49 (indirect)	From report: 0-12 weeks Etanercept = £194.5 Adalimumab = £194.5 Infliximab =£1263 DMARD = £363.5 12-24 weeks Etanercept = £194.5 Adalimumab = £194.5 Infliximab =£1263 DMARD = £363.5 24 weeks + (3-month costs) Etanercept = £152 Adalimumab = £152 Infliximab = £1018.5 DMARD = £328 From model code: 0-12 weeks Etanercept = 236.73 Adalimumab = 236.73 Infliximab = 1507.73 DMARD = 399.07 12-24 weeks Etanercept = 151.98 Adalimumab = 151.98 Infliximab = 1018.48		[4]0-12 weeks Etanercept = £2518.5 Adalimumab = £2518.5 Infliximab = £5459 DMARD = £434[5] 12-24 weeks Etanercept = £2518.5 Adalimumab = £2518.5 Infliximab = £5459 DMARD = £434 24 weeks + (3-month costs) Etanercept = £2476 Adalimumab = £2476 Infliximab = £3746 DMARD = £398.5

[3] Do not give administration and monitoring costs separately and cannot derive using unit costs and resource use in report. The costs calculated do not tally with those used in the model. Drugs costs defined as direct and indirect in the R code but no definition of what these are is given in the report.
[4] Using costs presented in the paper
[5] Abbott used a weighted average of the DMARDs used in the University of Toronto database to calculate drug, monitoring and administration costs for DMARDs.

	12-24 weeks Etanercept = £2502.64 (direct), £2597.16 (indirect) Adalimumab = £2502.5 (indirect),£2597.02 (indirect) Infliximab = £3356.96 (direct),£3546 (indirect) DMARD = £76.01 (direct),£93.96 (indirect) 24 weeks + (3-month costs) Etanercept = £2323.88 (direct), £2418.40 (indirect) Adalimumab = £2323.75 (direct),£2418.27 (indirect) Infliximab = £2727.53 (direct), £2881.13(indirect) DMARD = £70.58 (direct),£87.60 (indirect)	DMARD = 328.04 24 weeks + (3-month costs) Etanercept = 151.98 Adalimumab = 151.98 Infliximab = 1018.48 DMARD = 328.04		
Schering[6]	0-12 weeks Infliximab 4 vials = £5035 Infliximab 3.5 vials = £4406 Infliximab 3 vials = £3776 Etanercept = £2145 Adalimumab = £2145 12-24 weeks Infliximab 4 vials = £3356 Infliximab 3.5 vials = £2937 Infliximab 3 vials = £2517 Etanercept = £2145 Adalimumab = £2145	0-12 weeks Infliximab = £372 Etanercept = £394.09 Adalimumab = £394.09 12-24 weeks Infliximab = £248 Etanercept = £0 Adalimumab = £0 24 week + (3-month costs) Infliximab = £201.5 Etanercept = £0 Adalimumab = £0	0-12 weeks Infliximab = £225.78 Etanercept = £225.78 Adalimumab = £225.78 12-24 weeks Infliximab = £50.39 Etanercept = £90.40 Adalimumab = £90.40 24 week + (3-month costs) Infliximab = £54.59 Etanercept = £97.93 Adalimumab = £97.93	0-12 weeks Infliximab = £4374.36[7] Etanercept = £2764.99 Adalimumab = £2764.87 12-24 weeks Infliximab = £2816.11[3] Etanercept = £2235.52 Adalimumab = £2235.40 24 week + (3-month costs) Infliximab = £2301.74[3] Etanercept = £2421.81 Adalimumab = £2421.68

[6] Doesn't appear to include costs of methotrexate
[7] Assuming 3 vials

	24 week + (3-month costs) Infliximab 4 vials = £2727.53 Infliximab 3.5 vials = £2386.58 Infliximab 3 vials = £2045.65 Etanercept = £2323.88 Adalimumab =£2323.75			
Wyeth[8]	[redacted]	[redacted]	[redacted]	[redacted]

[8] Administration and monitoring costs were not reported separately but these have been calculated using resource use and unit costs given

All of the three submissions state that they use the BSR guidelines to determine the resource use associated with administering drugs and monitoring patients, however there are differences in the estimates of administration and monitoring costs in the various time periods.

Abbott assumes that etanercept and adalimumab were self-administered and incur the cost of a single outpatient visit (£115) in the initial 3-month period. This assumption was also made in the [redacted] and Schering-Plough models; however an outpatient visit is assigned a cost of £222.71 in the Schering-Plough model and a cost of £71 in the Wyeth model. Schering-Plough also assumes an additional 4 hours of staff nursing time for follow up (£150.58).

In the Abbott model infliximab has a half day-care hospital cost assigned for each infusion (£462 time by 3 infusions). This cost is taken from NHS Reference Costs 2007/08 for a day case for inflammatory Spine, Joint or Connective Tissue Disorders without complications. Wyeth also assume a hospital cost for each infusion of infliximab, however this is much lower at £115.23 for ½ day for each infusion at taken from published hospital costs[219]. Schering-Plough uses a cost of £124 per ½ day, citing results of a MTA.

In terms of monitoring costs, for the initial 3 month period Schering-Plough assumes a 2nd outpatient visit for all biologics at £135.71 per visit. In addition there is £90.07 of lab costs. This includes the cost of a Full Blood Count (FBC), Erythrocyte Sedimentation Rate (ESR), Liver Function Test (LFT), Urea and Electrolytes (U&E), Chest-X ray, TB Heaf test, Antinuclear antibodies (ANA) and DNA binding (ds DNA). Outpatients visits are then reduced to 0.23 of a visit for infliximab and 0.46 for etanercept and adalimumab in the 3-6 month period. Lab costs are also reduced to £19.07 for all biologics. In periods beyond 6-months infliximab patients are assume to require 0.25 of an outpatients visits and etanercept and adalimumab patients 0.5 of a visit. Lab costs are £20.66 for all biologics.

[redacted] Abbott assume all biologics patients will receive 2 CBCs at £15.19 each, 2 ESRs at zero cost, 2 LFTs at £8.43 each, 2 CMP at £8.43 each and 1 chest x ray at £27.25 in the first 3 months. In the subsequent 3-month periods patients will receive tests at the same intensity but will not require a chest X-Ray.

Costs depending on HAQ and costs of psoriasis

Each of the models estimates the ongoing costs of PsA in relation to HAQ and PASI scores (see Table 10.8.3). Abbott estimates the relationship between HAQ score and disease-related hospital costs using data on resource use by HAQ from the Norfolk Arthritis Register (NOAR) database. It is difficult to assess the validity of this approach as the NOAR report used in the Abbott submission was not made available to the Assessment Group on request. As the NOAR data did not include any measure of uncertainty in the mean estimates of resource use, the estimates of the standard errors of mean costs in the Abbott submission cannot be valid. Schering-Plough derives these estimates from the UK data of a study by Kobelt, 2002 [42], which was used in the previous York Assessment Group model. The Kobelt data includes the costs of RA drugs, primarily DMARDs. As per the previous York model, patients on biologic treatment only incur 85% of these costs, whilst those withdrawing from biologic treatment incur 100%. [redacted] and regression results from THIN were reported. However prediction errors from the BSREB/THIN regression were not included in the first regression of predicted HAQ values onto the observed costs. As such the goodness of fit and uncertainty estimates do not reflect all of the uncertainty in the prediction. The costs used in the Wyeth submission are difficult to interpret and costs by HAQ score are not presented. It is also not clear how estimates of uncertainty were derived.

Abbott and Schering-Plough both conduct separate physician surveys to assess the ongoing costs of psoriasis in relation to PASI. Abbott uses four hypothetical patients with differing PASI scores to generate costs. A logarithmic regression was then fitted to the median responses to estimate 6-month costs based on a continuous PASI scale. It is not clear how many physicians were surveyed. Schering-Plough sample from 20 dermatologists to determine NHS costs associated with various PASI scores. The report does not say how the responses were synthesised. [redacted] Each of the industry models relies on survey data to estimate the costs associated with psoriasis. This could be associated with a number of biases.

Table 10.8.3: Costs associated with PsA as a function of HAQ and PASI used in each of the models

	HAQ costs	PASI cost
Abbott	By HAQ score[9]: 0.0 <0.5 = £121 (59-173) 0.5 <1.0 = £77 (43-109) 1.0 <1.5 = £269 (141-382) 1.5 <2.0 = £388 (206-550) 2.0 <2.5 = £909 (459-1295) 2.5, 3.0 = £1945 (958-2778)	PASI state 1: score=1.5 (1.5, 2.7) = £153.68[10] PASI state 2: score=9 (7, 11.2) = £933.62 PASI state 3: score=15 (12.6, 16.8) = £859.35 PASI state 4: score=40 (32.4, 43.2) = £1002.83
Schering	Constant: mean = £1325, SE = £466 Slope: Mean = £401, SE = £259	[redacted]
Wyeth	[redacted]	-

Patient subgroups

Schering-Plough report results separately for psoriasis and non-psoriasis patients. For approximately 1/3 of patients with no clinically significant psoriasis (estimated from the IMPACT [82] and IMPACT 2 [83] trials) only the change in HAQ is modelled. The PASI impact on health-related quality of life is not included for these patients. They do not consider variation in baseline HAQ.

The Wyeth and Abbott models use the variation in baseline disease severity (measured using both HAQ and PASI) to explore the cost-effectiveness of treatments for subgroups. This is preferred to the approach used by Schering-Plough as it allows the comparison of a greater number of sub-groups, defined not only by the presence or absence of psoriasis but also by their severity of disease according to PASI and HAQ.

[9] Costs by HAQ score required for the model. Direct costs estimated by fitting an exponential line to the midpoint of each HAQ band.

[10] For 6-months

10.9 Generalising the results of RCTs to general practice

Introduction[11]

Section 5.2 showed that biologic drugs are much more effective than placebo controls in the experimental setting. The RCT is generally accepted as the best method to estimate an unbiased measure of the relative effectiveness of the treatment, in this case versus a placebo control, whether that relative effect is measured on a proportionate scale, such as an odds ratio, or as a difference in means between groups. However, RCTs are not necessarily predictive of the absolute effectiveness of the intervention in general practice.

Any medical intervention can be thought of as a complex set of factors, of which the active pharmaceutical ingredients are only one component, albeit usually an important one. Other components of the intervention might include the relationship between the doctor and patient, interventions by other health professionals, and the patient's expectations, all of which to a greater or lesser extent, and for better or worse, contribute towards the overall outcome. Selection effects, or 'regression to the mean', may also play a part. These 'non-pharmacological' components of the intervention can be thought of as acting equally in the intervention and placebo arms of clinical trials, assuming that both doctors and patients are blinded as to the treatment arm. In these circumstances, the effect observed in the placebo arm of the trial measures the effectiveness of these non-pharmacological components, while the 'treatment difference' measures the independent effectiveness of the pharmacological component of the intervention.

Predicting the absolute effectiveness of the intervention in general practice requires some assumption to be made about whether the protocols, procedures and general 'quality of care' of the RCT are similar to general practice. A Cochrane Review[220] found little evidence that using a placebo improved symptoms, with the exception of pain relief. However, the key question is not whether the 'placebo effect' is operating in every case, but whether outcomes associated with non-pharmacological components of the treatment are generalisable from RCTs to clinical practice. In other words, it matters less how the treatment works than whether it works[185].

This generalisability would not matter too much if the decision model were comparing 'placebo' with 'biologic therapy', as both groups would experience the same non-pharmacological components of therapy. However, NICE will not compare an active therapy

[11] With thanks to Neil Hawkins for an early sight of his draft paper on placebo effects

with a placebo, even if it were shown to be effective: it compares active therapies with 'standard practice' which in this case is assumed to be palliative care only. Adding the doctor's caring to the medical care component of biologic therapy might affect the patient's experience of treatment and may, for example, reduce pain and affect outcome. The 'no treatment' group might or might not receive equivalent non-pharmacological care.

We can represent these possibilities as two scenarios.

- Scenario 1: the 'no treatment group' receives similar care (with similar mean outcomes) to the placebo arm in an RCT
- Scenario 2: the 'no treatment group' receives less care than the placebo arm in an RCT, and does not achieve the response rate of the placebo arm in an RCT

Conceptual framework

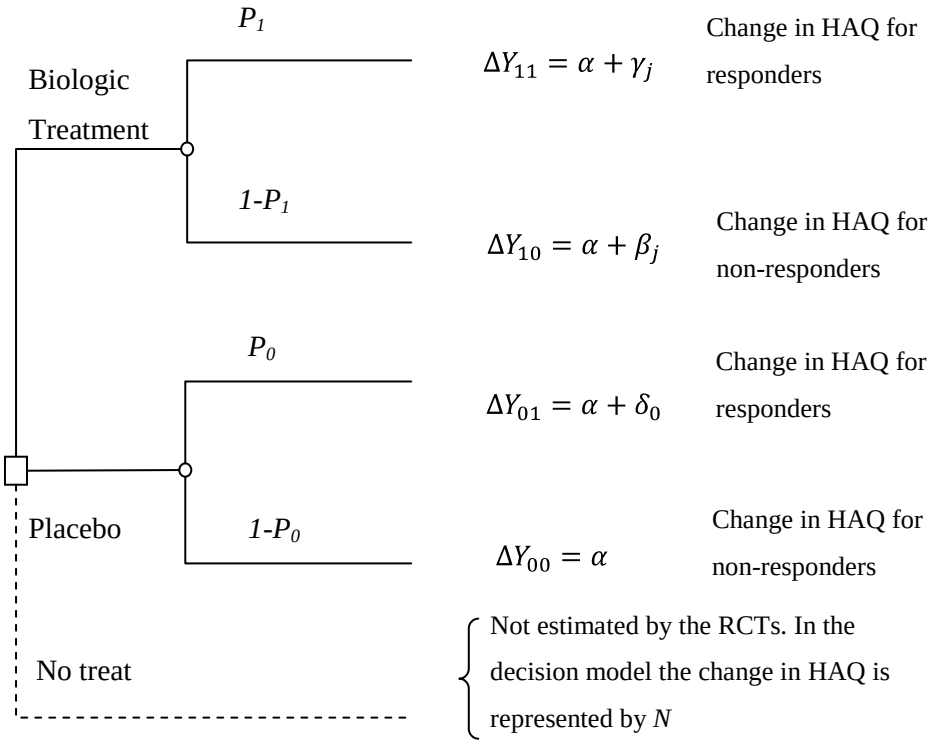
Figure 10.9.1 shows the mean change in HAQ ΔY_{jr} from 0 to 12 weeks in the RCTs in the treatment group *j=1* and placebo group *j=0*, depending on response *r=1,0*. These parameters were estimated in the evidence synthesis in Chapter 5. Variable α represents the change in HAQ over 3months if there is no response for patients with placebo. Variable δ represents the mean difference in the change in HAQ between placebo non-responders and placebo responders. Variable β_j represents the mean difference in the change in HAQ between placebo non-responders and non responders with treatment j. Variable γ_j represents the mean difference in the change in HAQ between placebo non-responders and responders with treatment j.

The average change in HAQ (over responders and non-responders) in the placebo arm is

$\Delta Y_0 = (p_0(\alpha + \delta_0) + (1 - p_0)\alpha)$

$= \alpha + p_0\delta_0$

Figure 10.9.1 Change in HAQ from 0 to 12 weeks in treatment groups estimated by RCTs



We can represent these scenarios by our beliefs about the relationship between the natural history (ie the change in HAQ *N* in three months observed in general practice with no treatment) and the change in HAQ for non-responders in a placebo group (α), if both 'placebo' and 'no treatment' were compared in general practice.

Scenario 1: Results with 'no treatment' in practice are similar to placebo arms of RCTs
If *N* is approximately equal to $\alpha+p_0\delta$ (the average change in HAQ in the placebo group), this represents a scenario where we think the results obtained in a group given placebo, averaged across responders and non-responders, would be the same as what would have been observed if no treatment had been given.

In scenario 1, the absolute difference in the change in HAQ between treatment *in practice* and no treatment (difference in difference) can be estimated by substituting $N = \alpha + p_0\delta$ into the parameters shown in Figure 10.9.1 and so the difference-in-difference for responders is estimated to be $(\alpha + \gamma_j) - N = \alpha + \gamma_j - (\alpha + p_0\delta) = \gamma_j - p_0\delta,$ and for non responders is estimated to be $\beta_j - p_0\delta$.

Scenario 2: the 'no treatment group' in practice gets worse outcomes than the placebo arm in an RCT
In this scenario, patients with no treatment would not achieve the response rates observed in the placebo arms of RCTs. It is assumed that they would have the same outcomes as patients with 'no response' in the placebo group of an RCT. This implies that *N* is approximately equal to α. In this scenario, if placebo were to be given in practice, there would be some lasting average benefit over and above natural history equal to: $(\alpha + p_0\delta) - N = \alpha + p_0\delta - \alpha = p_0\delta$.

This might imply a lasting psychological benefit of the act of taking medication or due to beneficial interactions between the doctor and patient that occur both in trials and in the regular clinical setting. By extension, this 'placebo effect' would also partly explain the results in the treatment group, and would be expected equally in the trials and in general clinical practice. Therefore we would expect that if biologic therapy and no treatment were compared in general practice, the absolute difference in the change in HAQ between treatment and no treatment (difference-in-difference) would be $\alpha + \gamma_j - N = \gamma_j$ for responders and β_j for non responders.

It is difficult to test these alternative hypotheses, because the scenarios represent our hypothetical beliefs about a counterfactual argument: what would happened if 'no treatment', 'placebo' and 'treatment' were compared in general practice.

Conclusion

We conclude by setting out the implications for predicting the HAQ score in the decision model under each scenario.

In the decision model, variable *N* (the long term natural history in the untreated patients) is informed by observational evidence independent of the RCTs and is assumed to be constant over time. Therefore in either scenario the HAQ score in the untreated group at time *t* after the start of the model is calculated as *N*t.*

If responders on treatment are assumed not to progress (worsen) over time, then the *HAQ(t,j)* score at time t for responders while still on treatment *j* is:

Scenario 1: Results with 'no treatment' are similar to average in placebo arms of RCTs *($N=\alpha+p_0\delta$)*

$$HAQ(t,j) = \alpha + \gamma_j = N - p_0\delta + \gamma_j$$

Scenario 2: the 'no treatment group' achieves worse outcomes than the average in placebo arms of RCTs *($N=\alpha$)*

$$HAQ(t,j) = \alpha + \gamma_j = N + \gamma_j$$

We assume scenario 1 is the basecase, consistent with the assumptions made in the previous AG model [172], and scenario 2 is a sensitivity analysis.

10.10 Estimation of probability of achieving both PsARC and PASI 75 response

Introduction

Biologic therapy may be indicated to treat both joints disease and psoriasis. Clinical response at 3 months is measured using the PsARC for joints and PASI 75 for skin conditions. Because there are two response variables, there are 4 possible outcomes at 3 months: skin response only, joints response only, response of both, response of neither. Furthermore, the PsARC and PASI 75 responses are not necessarily independent.

The meta-analysis in Chapter 5 estimated the marginal probability of each type of response. However, this analysis did not estimate the bivariate probability, that is, the probability of observing both a response on arthritis and skin disease together.

This appendix shows how the bivariate probability density function (pdf) of PASI 75 and PsARC was estimated from the clinical trial evidence, to be used in the decision model for patients who have both skin and arthritis involvement at baseline, and were assessed for PASI and PsARC responses at 3 months.

Estimate of correlation between PASI 75 and PsARC outcomes in the ADEPT trial[52]

No published papers reported the correlation between PsARC and PASI 75. The AG requested this from the manufacturers. One manufacturer (Abbott) provided this data based on the ADEPT trial, comparing adalimumab with placebo. In this appendix, we use the estimate of the correlation coefficient derived from the ADEPT trial and the estimates of the marginal pdfs of each type of response from the meta-analysis to estimate the bivariate pdf.

Table 10.10.1. Outcomes of ADEPT at 12 weeks for patients in the adalimumab group, for patients with at least 3% body skin area affected by psoriasis at baseline (n=66)[52]

PsARC (x)	PASI 75 (y)	N	f(x,y)
0	0	18	0.27
0	1	5	0.08
1	0	14	0.21
1	1	29	0.45

Table 10.10.1 shows the outcomes of the ADEPT trial, in the 66 patients who were assessed for both outcomes at 12 weeks. We refer to PsARC as variable *x* and PASI 75 as variable *y*. The responses are dichotomous, where zero represents no response and one represents a response. To distinguish between the results of the meta-analysis and the results of the ADEPT trial, we label the pdfs from the ADEPT trial as *f(x)* and *f(y)* and the corresponding pdfs for the population estimated from the meta-analysis as *Pr(x=1)* and *Pr(y=1).* Similarly,

the joint pdf from the ADEPT trial is *f(x,y)* and the (predicted) joint pdf for the population as *Pr(x=1,y=1)*

The correlation coefficient $\rho = cov_{x,y} / s_x s_y$ ***(Equation 1)***

Where the trial estimate of $cov_{x,y} = E(XY) – E(X)E(Y) = f(x=1,y=1) – f(x=1)f(y=1)$
And the trial estimate of $s_x = SD(X) = \sqrt{ (f(x=1)(1-f(x=1)))}$

From the ADEPT trial, $cov_{x,y}$ = (29/66 – (34/66)(43/66)) = 0.103
$s_x = \sqrt{(43/66)(1-43/66)} = 0.500$
$s_y = \sqrt{(34/66)(1-34/66)} = 0.476$

ρ = 0.103 / (0.5*0.476) = 0.436

This value of ρ is significant at the 5% level (t=3.31 with 65 d.f., p=0.0015)
The standard error is $SE(\rho) = \sqrt{[(1-\rho^2)/(N-2)]}$=0.112, and t is distributed according to a student-t distribution with *N-2* d.f

The ADEPT trial found that responses were uncorrelated for the placebo group, with an estimated correlation coefficient of 0.02 (table 10.10.2) (t=0.16, 67 d.f, p=0.87).

Table 10.10.2. Outcomes of ADEPT at 12 weeks for patients in the placebo group, for patients with at least 3% body skin area affected by psoriasis at baseline (n=69)[52]

PsARC (x)	PASI 75 (y)	N	f(x,y)
0	0	49	0.72
0	1	2	0.03
1	0	17	0.24
1	1	1	0.01

Estimate of joint probability density function of PsARC and PASI 75 in the population
We can use these relationships to estimate the bivariate probability of PASI 75 and PsARC in the population *Pr(x=1,y=1).*

We assume the correlation coefficient ρ between response types from the ADEPT trial is an unbiased estimate for all biologics in the population. This represents the correlation between outcomes in the population, and is a measure of *variability* not *uncertainty*. The definition of ρ is

$\rho = cov_{x,y} / s_x s_y$

where s_x and s_y are estimates of variability of *X* and *Y* in the population, and not the uncertainty σ_x and σ_y in the mean *E(X)=Pr(x=1)* and *E(Y)=Pr(y=1).* An estimate of s_x in the population is $SD(X) = \sqrt{[Pr(x=1)(1-Pr(x=1))]}$

From the definition of the covariance[12]

$cov_{x,y} = E(XY) - E(X)E(Y) = Pr(x=1,y=1) - Pr(x=1)Pr(y=1)$ ***Equation 2***

Rearranging Equation 2 gives

$Pr(x=1,y=1) = cov_{x,y} + Pr(x=1)Pr(y=1)$ ***Equation 3***

Rearranging Equation 1 and substituting in Equation 3 gives

$Pr(x=1,y=1) = \rho\, s_x\, s_y + Pr(x=1)Pr(y=1)$

$= \rho \sqrt{\{Pr(x=1)Pr(y=1)(1-Pr(x=1))(1-Pr(y=1))\}} + Pr(x=1)Pr(y=1)$ ***(Equation 4)***

The conditional probabilities of a PASI 75 response, given PsARC outcomes, are:
$Pr(y=1 | x=1) = Pr(x=1, y=1)/Pr(x=1)$
$Pr(y=1 | x=0) = Pr(y=1, x=0)/Pr(x=0) = (Pr(y=1) - Pr(x=1,y=1)) / (1-Pr(x=1))$

Given $Pr(x=1) \geq 0$ and $Pr(y=1) \geq 0$, there are constraints on $Pr(x=1,y=1)$:

$Pr(x=1,y=1) \leq Pr(x=1)$ and
$Pr(x=1,y=1) \leq Pr(y=1)$ and
$Pr(x=1,y=1) \geq 0$ and
$Pr(x=0,y=0) \geq 0$ and
$-1 \leq \rho \leq 1$

By substituting Equation 4 in these constraints and rearranging, this implies that

[12] $E(XY) = Pr(x=1,y=1)*1 + Pr(x=0,y=1)*0 + Pr(x=0,y=1)*0 + Pr(x=0,y=0)*0 = Pr(x=1,y=1)$

$Max[-\sqrt{\{odds(x=1)*odds(y=1)\}};-\sqrt{1/\{odds(x=1)*odds(y=1)\}}] \leq \rho \leq$
$Min[\sqrt{\{odds(y=1)/odds(x=1)\}};\ \sqrt{\{odds(x=1)/odds(y=1)\}}]$
where
$odds(a) = Pr(a)/(1-Pr(a))$

Implications for the decision model

We show an example of the implications of these assumptions for the decision model. For illustrative purposes, assume that the probability of PsARC for treatment *j* is estimated to be $Pr(x=1)$ =0.80, and the probability of PASI 75 is $Pr(y=1)$ = 0.5.

In this example, $odds(x=1)$ = 0.8/0.2 = 4 and $odds\ (y=1)$ = 0.5/0.5=1. Given $Pr(x=1)$ and $Pr(y=1)$, the constraints on ρ are:

$-0.5 \leq \rho \leq 0.5$

If we assume there is no correlation between these outcomes $\rho=0$, then

$Pr(x=1,y=1) = Pr(x=1)Pr(y=1) =$ 0.8*0.5=	0.4
$Pr(x=1,y=0) = Pr(x=1)- Pr(x=1)Pr(y=1)$=0.8-0.4 =	0.4
$Pr(x=0,y=1) = Pr(y=1)- Pr(x=1)Pr(y=1)$= 0.5-0.4=	0.1
$Pr\ (x=0,y=0)= (1-Pr(x=1))(1-Pr(y=1))$ = 0.2*0.5 =	0.1

If we estimate that the correlation between *X* and *Y* is ρ=0.5, then

$Pr(x=1,y=1)$ = 0.5*$\sqrt{}$(0.8*0.2*0.5*0.5)+ 0.8*0.5=0.1+0.4=	0.5
$Pr(x=1,y=0) = Pr(x=1)- Pr(x=1)Pr(y=1)$=0.8-0.5 =	0.3
$Pr(x=0,y=1) = Pr(y=1)- Pr(x=1)Pr(y=1)$= 0.5-0.5=	0
$Pr\ (x=0,y=0)$= 0.1+0.1 =	0.2

10.11 The elicitation exercise

A number of parameters within the model either did not have adequate evidence or did not have any evidence at all with which to populate them. This latter issue, in particular, poses a potential problem. One option would be to assign un-informative priors to these. However this un-informative prior may does not truly represent the current level of knowledge regarding these parameters. Alternatively elicitation techniques can be used to quantify unknown parameters in the absence of actual data[221].

An elicitation exercise was designed to generate prior estimates of the unknown parameters in the model, the effect of withdrawal from anti-TNFs, along with two other parameters for which evidence may be poor.

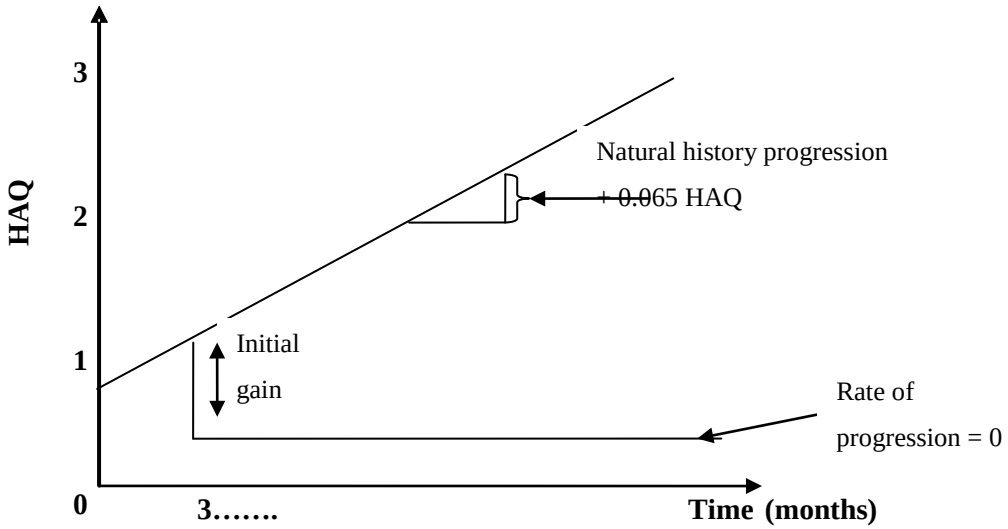
The following sections, first describe the uncertainties and then go onto describe the elicitation exercise used to generate prior information to characterise these uncertainties. Finally the results of the elicitation exercise are presented.

10.11.1 Uncertainties in the PsA model

10.11.1.1 The rate of disease progression beyond the initial HAQ change

The rate of progression following a response to etanercept or infliximab is uncertain. In the original York model an assumption was made that beyond the initial HAQ gain, disease progression will stop (rate of progression = 0 in Figure 10.10.1) following response to anti-TNFs. There is some uncertainty, however, about the extent to which this truly reflects the longer-term efficacy of anti-TNFs. Colloquial evidence suggests that patients may either improve their disease following a response to anti-TNFs or may experience some disease progression at a slower rate than the natural history of the disease. Recent observational evidence from national biologics registers suggests that HAQ and health utility remain stable for PsA patients while on biologics. Gulfe (2009) analysed data from 574 patients in South Sweden between May 2002 and December 2008, and found health utilities remained largely unchanged for PsA over 7 years. [redacted] The limitation of these registry data for the purposes of the decision model is that the data do not distinguish between outcomes for patients who persisted with their initial biologic, and those who withdrew or switched to another drug.

Figure 10.11.1: Natural history of PsA measured using the HAQ



In the original York model progression following a response was simply assigned a fixed value of 0 and no scenarios were specified for this assumption. It is therefore not possible to determine the sensitivity of the model to this assumption.

10.11.1.2 The rebound effect

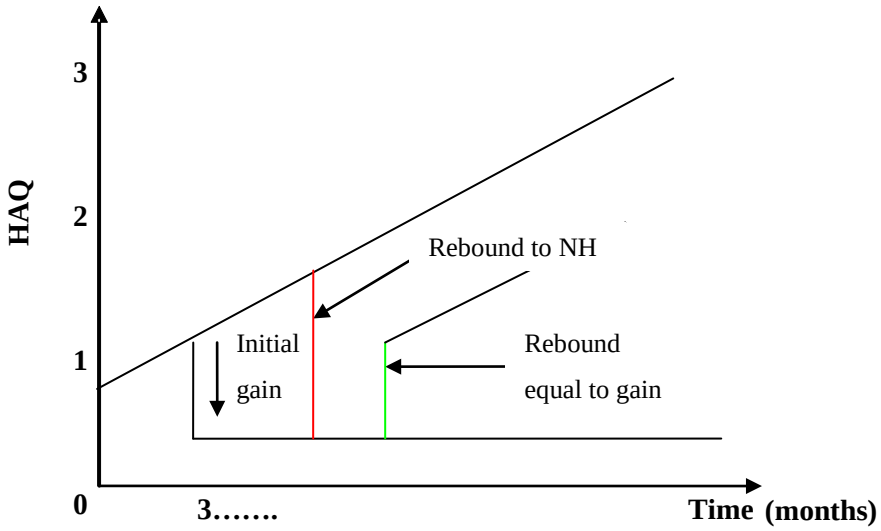
As described above, patients that withdraw from anti-TNF treatment, due to either adverse events or loss of efficacy, will then have some worsening in HAQ score (the 'rebound').

There are no data on the rate of disease progression for the 3-month period immediately following withdrawal from treatment (given an initial response on the PsARC criteria). Clinical opinion suggests that there will be some kind of rebound (back up to natural history progression) but the degree of rebound is unknown. In the original York model two rebound scenarios were, therefore, considered (see Figure 10.11.2):

1. When patients fail therapy (after initially responding), their HAQ score deteriorates by the same amount by which it improved when patients initially responded to therapy (rebound equal to gain in Figure 2).

2. When patients fail therapy, their HAQ score returns to the level and subsequent trajectory it would have been had they not initially responded to therapy (rebound to natural history (NH) in Figure 2).

Figure 10.11.2: Disease progression following treatment failure



The two rebound scenarios for progression following relapse produced two different estimates of the cost-effectiveness of etanercept and infliximab. By specifying the rebound as equal to natural history progression, the ICER for etanercept increases from £26,361 to £30,628 in the 10-year model compared to the rebound equal to initial gain. This increase in the ICER may be sufficient to change the adoption decision, if the threshold is greater than £26,361 but less than £30,628.

10.11.1.3 The rate of disease progression beyond the rebound effect

The original York model assumed that following a change in HAQ after withdrawing from anti-TNFs (the rebound effect) patients would immediately return to the natural history progression rate. Clinical opinion suggests that this might not be the case. That is when withdrawing from treatment, having received, and responded to anti-TNFs alters the course of the disease for a given period of time after withdrawal. This issue was not explored in the previous York model.

10.11.2 Methods of the elicitation

The parameters described above were elicited form multiple experts individually, followed by appropriate synthesis. Clinical opinion suggests that the first two uncertain parameters may be correlated. That is the degree of rebound following relapse is conditional upon the extent of gain when responding. In addition clinical opinion also suggested that extent of gain when responding may be conditional upon the extent of initial HAQ change following a PsARC response. The exercise, therefore, incorporates these relationships when eliciting data from experts.

To enable experts to express the extent of gain when responding conditional upon the extent of initial HAQ change following a PsARC response, this HAQ change was also elicited from experts during the exercise. These data are not used directly in the decision model, which takes estimates of initial HAQ gain from the evidence synthesis in Chapter 5.

10.11.2.1 Format and content of elicitation

A spreadsheet (Excel) based, interactive elicitation exercise was designed to generate estimates of initial HAQ change, disease progression while responding to treatment, disease progression for the three-months following a relapse and longer term disease progression following withdrawal. An interactive format was used as the elicitation exercise was also designed to incorporate any correlation between the first three parameters. To build in the correlation between parameters, responses for some questions were conditional upon responses to previous questions. This method is an appropriate way to incorporate conditional dependence suggested by Garthwaite, 2005[222].

In accordance with good elicitation practice, background to the elicitation was presented at the start of the exercise along with a guide to completion[223]. The background information presented can be seen below. Experts were told the rationale for the elicitation exercise, to obtain data on unknown parameters to inform a decision-analytic model, and reminded of the HAQ scoring method and expected natural history progression (progression without treatment). Experts were presented with an illustration of the trajectory of disease progression without treatment and change in HAQ score. Experts were given examples of the question format and invited to complete practice questions.

The histogram approach[224] is used in this elicitation. For each question, a discretised numerical scale was predefined and experts were asked to place 20 crosses on a frequency chart, representing their beliefs about the distribution of a particular quantity. Each cross represents 5% of the distribution.

Once the expert had read through the supporting material and completed the example questions, they were asked to start the elicitation questions. Experts were then taken to a separate worksheet where the four questions were arranged into sections which they were asked to complete sequentially.

Initial HAQ gain following treatment with etanercept, infliximab or adalimumab
Experts were asked to provide an estimate of the known parameter (HAQ gain) following treatment with infliximab, etanercept or adalimumab. Experts could choose to group all three anti-TNFs together or complete separate histograms for each anti-TNF.

Experts were asked for their estimates of HAQ score following treatment (3-month response) and were asked to place 20 crosses on a grid running from 0 to +3.

Rate of progression whilst still responding to treatment
Experts were asked to provide an estimate of disease progression for patients who have responded to treatment on etanercept, infliximab or adalimumab. Again experts could choose to group all three anti-TNFs together or complete separate histograms for each anti-TNF. In addition experts were asked if they believed that the rate of progression whilst responding was related to the initial HAQ gain (separately for each anti-TNF if appropriate). If experts responded yes they were requested to complete grids for each of the 0-25, 25-50, 50-75 and 75-100th percentiles from the WinBUGS output of HAQ score for infliximab, adalimimab and etanercept (see section 5.2.2). If experts responded no, they completed a single grid assuming no relationship between the two parameters.

Again experts were asked to place 20 sets of crosses on each grid. Experts were reminded prior to answering these questions that we estimated the natural history rate of progression of HAQ (progression without treatment) to be +0.016 per 3 months [171].

Rate of progression in the 3-month period after withdrawal from treatment
Experts were asked to provide an estimate of disease progression for the 3-months following a treatment failure (after an initial response); this was termed the 'rebound'. Again experts could choose to group all three anti-TNFs together or complete separate histograms for each anti-TNF. In addition experts were asked if they believed that the rate of progression after withdrawal from treatment was related to the rate of progression whilst responding (separately for each anti-TNF if appropriate). If experts responded yes they were requested to complete grids for each of the 0-25, 25-50, 50-75 and 75-100th percentiles. These ranges were generated by sampling from the responses to question 2, given the likelihood of observing a particular conditional HAQ gain (question 1). The likelihood of observing particular ranges for HAQ gain was again taken from the WinBUGS output of the current York model. If experts responded no, they completed a single grid assuming no relationship between the two parameters.

Rate of progression following the 3-month rebound

Experts were asked to provide an estimate of disease progression for period following the 3-month rebound. Again experts were reminded that this was for patients who had previously responded to anti-TNFs using the PsARC criteria but had now withdrawn from treatment either due to adverse effects or loss of efficacy.

Experts were asked, for each of the three anti-TNFs, if they believed that the rate of progression would return to natural history. If they answered yes the questionnaire was complete. If they answered yes they were asked to complete a grid (for each anti-TNF separately if appropriate) expressing their belief about the progression rate following the rebound period. They were then asked for the number of months they would expert to observe this progression rate before patients retuned to natural history.

10.11.2.2 Study sample

Sixteen experts were sent the questionnaire. These experts were chosen to represent a range of clinical opinion nationally. Experts were chosen on the basis of the clinical advice from a 'lead expert'.

Questionnaires were sent by email along with a covering letter. This format was chosen because of the wide national distribution of experts in the original sample of 16. Experts where then sent a reminder email inviting them to complete the questionnaire. A number of experts expressed a desire to be guided through the questionnaire by telephone. The remainder completed the questionnaire independently and returned via email.

Questionnaire responses were received from five experts. A large number of the remaining 11 experts expressed a conflict of interest that prevented them from taking part in the exercise. Others stated that due to other commitments they were unable to participate. Experts are anonymised here and are referred to as experts 1-5.

10.11.2.3 Synthesis of experts' histograms

Linear opinion pooling is the synthesis method most commonly applied in expert elicitation[225]. In linear pooling experts' probabilities or weights are aggregated using simple linear combinations. If $p(\theta)$ is the probability distribution for unknown parameter θ in linear pooling experts' probabilities or weights are aggregated using simple linear combination, $p(\theta) = \Sigma_i w_i * p_i(\theta)$ where w_i is expert i's weight.

This method is akin to generating a 'super' distribution by pooling the five experts' assessments. From this we can generate an arithmetic mean and associated uncertainty[226]. This method assumes that by gathering more priors (eliciting from more experts) we do not necessarily become any more certain about the rate of progression during response or relapse. The linear pooling method considers each expert's distributions as separate priors with no relationship between experts' distributions assumed. Here linear pooling was carried out using equal weights for experts.

10.11.3 Results

10.11.3.1 Questionnaire responses

Responses to the elicitation questions varied, reflecting different clinical opinion regarding treatment. The histograms for each of the, questions, for each of the 5 experts are presented below. Table 1 also shows the means and standard errors of the means for each of the elicited parameters.

None of the experts expressed any difference between the initial HAQ changes for the three drugs. Elicited means ranged from 0.39 to 1, with a mean of 0.747. This figure is not dissimilar to the initial HAQ changes generated by the evidence synthesis model (see section 5.2.2). Many of the experts believed that HAQ progression for responders would be negative, that is patients would continue to improve over time whilst receiving biologics. The elicited 'rebound' effect is neither similar to the original 'rebound to initial HAQ ain' nor the 'rebound back to natural history' scenarios. Experts believed that there was a continued effect of biologics even for patients discontinuing treatment due to either adverse events of loss of efficacy. 4/5 of the experts believed that long term progression would be equivalent to natural history.

10.11.3.2 Synthesised beliefs

Two if the experts that stated that there was a correlation between initial HAQ gain and progression whilst responding to treatment and/or progression whilst responding to treatment and progression for the 3-months after withdrawal from treatment. These correlations were, however, very small. Given the complexity in involved in building this correlation into the decision model, it was therefore decided to assume that there was in fact no correlation between elicited parameters (as expressed by the majority of experts). Table 2 shows the results from the synthesis of elicited parameters (mean (SE)) assuming no correlation between parameters.

The synthesised progression whilst responding rate is very close to zero at 0.002 (SE = 0.022). The rebound progression is 0.13 (SE = 0.14) increase in HAQ for 3-months. Again this is somewhat different to the initial HAQ gain, contradicting the 'rebound to initial gain' assumption. It is further still from the 'rebound to natural history' assumption.

10.11.3.3 Using the elicited data in the decision model

The elicitation was designed to inform the following three parameters in the decision model:
1. The rate of change of HAQ for patients on biologic therapies (*HAQ1.d*)
2. The change or rebound in HAQ in the 3 month period immediately after withdrawing from biologic therapy (*loss.w*)
3. The rate of change in HAQ in the long term after withdrawing from biologic therapy (*HAQ1.w)*

The base-case decision model will assume that the mean value of HAQ1.d is zero (SE 0.02), consistent with the elicitation and the limited observational evidence from biologics registers.

For convenience, the decision model expresses the value of parameter *loss.w* relative to baseline HAQ. Its magnitude can be estimated as the difference between the absolute initial gain and the rebound. A value of zero means that the rebound is equal in absolute terms to the initial gain on starting biologics, a positive value means the rebound is between the initial gain and 'natural history', and a negative value means the rebound is less in absolute terms than the initial gain (see Figure x.1). The results of the elicitation (Table x.2) suggest that *loss.w* is negative. Mean (initial HAQ gain) +Mean (progression in 3m after withdrawal) = -0.75+0.13 = -0.62 (SE = 0.29). Given the limitations of the exercise and some uncertainty about whether this accurately represents the views of the experts, we assume the basecase mean value of *loss.w* is zero, with a normal distribution with a wide standard error of 0.5 to indicate the considerable uncertainty. We use the mean value of *loss.w* = -0.62 as a sensitivity analysis.

The experts were almost unanimous that the long term rate of change of HAQ after withdrawal would be equal to the rate of change of HAQ of patients who never used biologics (the natural history). We therefore set these parameters to be equal in the decision model.

10.11.4 Discussion

There are a number of issues with the elicitation exercise that are worth noting. Firstly it is likely that there is a degree of heterogeneity between experts. Possible reasons are: clinical knowledge, clinical experience (types of patients seen and/or drugs used), interpretation and

understanding of elicitation questions and true underlying heterogeneity about the treatment effect. Unfortunately it is not possible with five experts to incorporate these factors, as covariates, into a model. To do this would require many more experts to have any power to detect any difference[227].

Secondly the selection of experts for the elicitation questionnaire was undertaken by a single lead expert and the number of experts available to complete the questionnaire was very limited. Whilst this number reflects was is commonly observed in elicitation exercises conducted to inform HTA decision models we cannot be sure that the sample of experts included is representative of the current level of knowledge.

Perhaps the most striking conclusion from the elicitation exercise, is that the 'rebound' effect is neither similar to the original 'rebound to initial HAQ gain' nor the 'rebound back to natural history' scenarios. Experts believed that there was a continued effect of biologics even for patients discontinuing treatment due to either adverse events of loss of efficacy. The majority of experts then believed that patients would return to a natural history rate of progression beyond this rebound period. It is possible that experts did not truly comprehend the longer term implication of their expressions of rebound effect and the fact that by assuming that patients only return to natural history rate of progression after this period meant that the progression of patients no longer on treatment would never return to the natural history line of progression (Figure 10.11.1). It is possible that the complexity of the exercise made it difficult for experts to express their beliefs accurately and perhaps a visual expression of the resulting line of progression may have helped. Therefore there may well be a trade off between obtaining information on specific model parameters, the complexity of the exercise and cognitive burden on experts.

Table 10.11.1: Responses to elicitation questionnaire (mean change in HAQ in 3 months (SE))

Expert	HAQ gain			Progression while responding			Progression in 3m after withdrawal			LT progression after withdrawal		
	E	I	A	E	I	A	E	I	A	E	I	A
1	-1 (0.18)	-1 (0.18)	-1 (0.18)	-0.0035 (0.007)	-0.0035 (0.007)	-0.0035 (0.007)	0.08 (0.016)	0.08 (0.016)	0.08 (0.016)	0.016	0.016	0.016
2	-0.805 (0.135)	-0.805 (0.135)	-0.805 (0.135)	-0.009 (0.007)	-0.009 (0.007)	-0.009 (0.007)	0.393 (0.006)	0.393 (0.006)	0.393 (0.006)	0.016	0.016	0.016
3	-0.72 (0.16)	-0.72 (0.16)	-0.72 (0.16)	-0.017 (0.01)	-0.017 (0.01)	-0.017 (0.01)	0.013 (0.007)	0.013 (0.007)	0.013 (0.007)	0.02 (0.01)	0.019 (0.008)	0.02[13] (0.008)
4	-0.82 (0.24)	-0.82 (0.24)	-0.82 (0.24)	-0.0017 (0.014)	-0.0017 (0.014)	-0.0017 (0.014)	0.037 (0.034)	0.037 (0.034)	0.037 (0.034)	0.016	0.016	0.016
5	-0.39 (0.17)	-0.39 (0.17)	-0.39 (0.17)	0.04 (0.011)	0.04 (0.011)	0.04 (0.011)	0.12 (0.007)	0.12 (0.007)	0.12 (0.007)	0.016	0.016	0.016

Table 10.11.2: Results from synthesis of elicited parameters (mean (SE)) (assuming no correlation between parameters)

HAQ gain			Progression while responding			Progression after relapse			LT progression		
E	**I**	**A**	**E**	**I**	**A**	**E**	**I**	**A**	**E**	**I**	**A**
-0.747 (0.268)	-0.747 (0.268)	-0.747 (0.268)	0.002 (0.022)	0.002 (0.022)	0.002 (0.022)	0.13 (0.14)	0.13 (0.14)	0.13 (0.14)	0.0168 (0.004)	0.0166 (0.003)	0.0168 (0.004)

[13] This effect lasts for 6-months post rebound

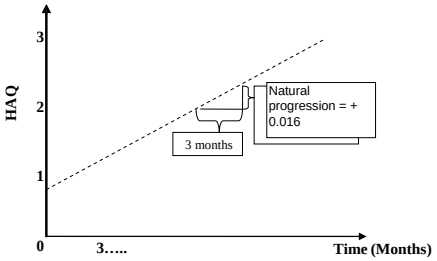
Background information presented to experts

Background information

In this questionnaire you are asked about the intial impact of anti-TNFs (etanercept, infliximab and adalimunab) on HAQ, the change in disease progression whilst responding to anti-TNFs, initial (3-month) progression of disease after withdrawal from treatment and longer term progression of disease after withdrawal.

The diagram opposite shows progression of PsA for untreated patients (natural history) using the Health Assessment Questionnaire (HAQ). The HAQ is a well validated tool in the assessment of PsA. It focuses on two dimensions of health status: physical disability (8 scales) and pain, generating a score of 0 (least disability) to 3 (most severe disability). A change in HAQ toward 0 is interpreted as a "HAQ gain" and a change toward 3 a "HAQ loss".

The questions we will ask you assume that the natural progression of disease is as shown in this diagram and can be represented using the HAQ. For the purposes of this questionnaire, baseline HAQ score for PsA patients is 1.16, with a 3-monthly natural rate of progression of



You will move through the questionnaire by right clicking (with your mouse) the question boxes. Some of the buttons may take a few seconds to move onto the next questic
For some of the questions you wil be asked to answer a simple yes/no. For some of the questions you will give your answer using a grid (see Figure 1 below).
Each value along the horizontal axis represents a possible value for that particular question. The vertical axis represents frequency.
We have given you 20 crosses per grid and we would like you to place all of these in some or all of the columns to represent your current belief and uncertainty about that particular question. You place a cross in the grid by left clicking (with your mouse) on a cell.

Please begin by placing 2 of the crosses at the upper and lower limits of your belief about the piece of data. You should then place the remaining 18 crosses so as to express your remaining uncertainty about the particular piece of data (see Figure 2 shown below). In red we show you how many crosses you have left.

If you change your mind about where you want to put your crosses simply press the CLEAR button and all crossess will be moved from the grid.
You can also remove an indidual "x" by clicking on it a second time. Once you are happy with your grid please press the 'submit your answer' button.

Figure 1: Example uncompleted grid

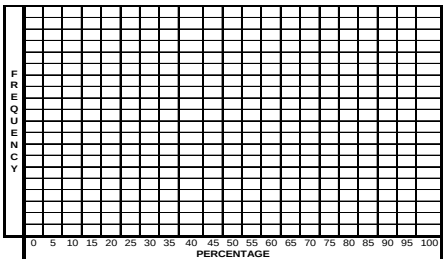
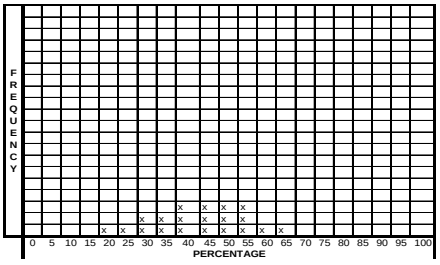


Figure 2: Example completed grid



Proceed to 'Examples'

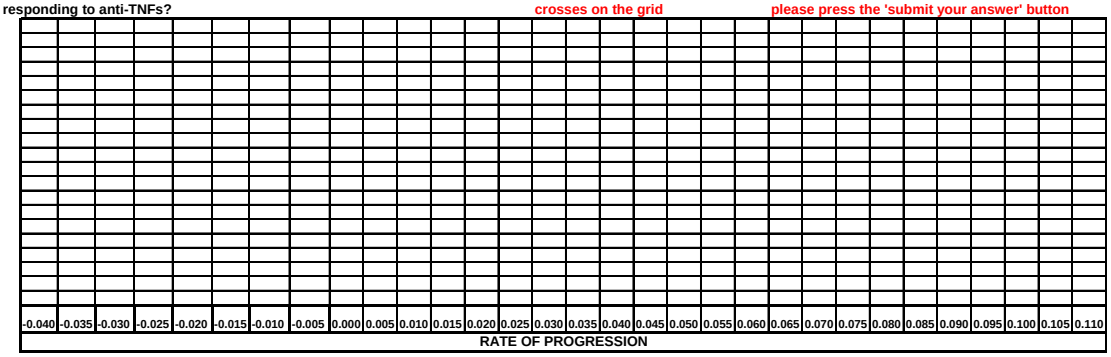
Back to introduction

Example of histogram used

What will the 3-month rate of HAQ progression be for patients responding to anti-TNFs?

Please place 20 crosses on the grid

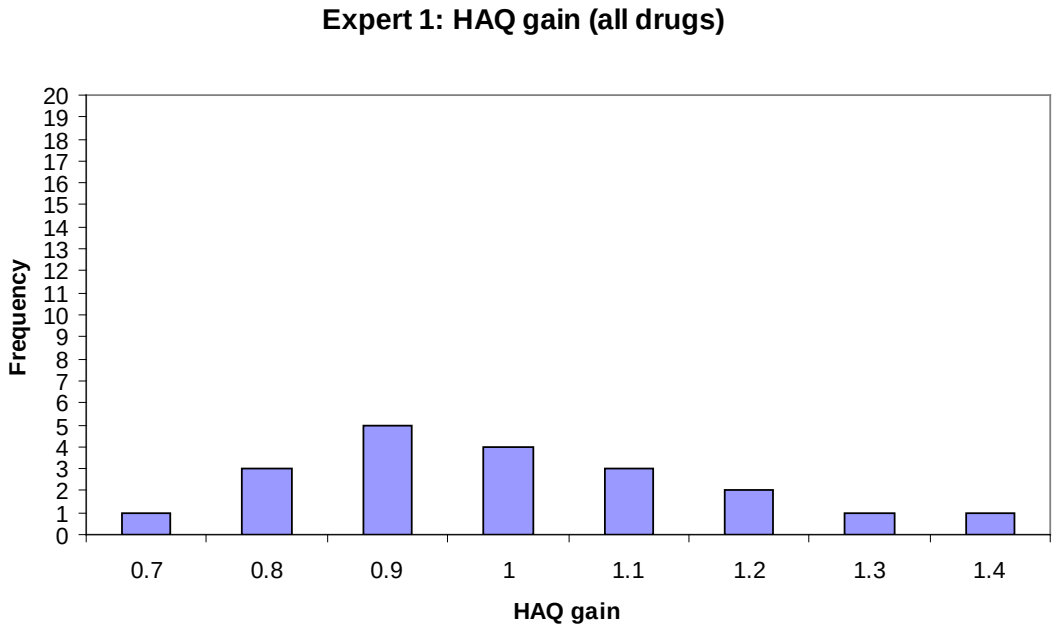
Once you are happy with your answer please press the 'submit your answer' button

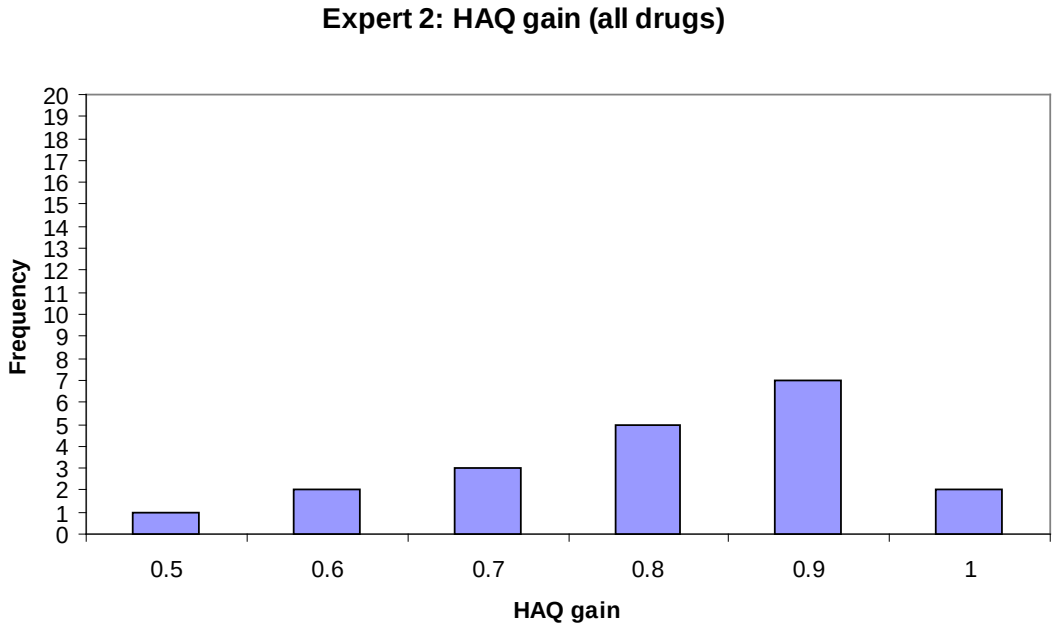


Clear grid

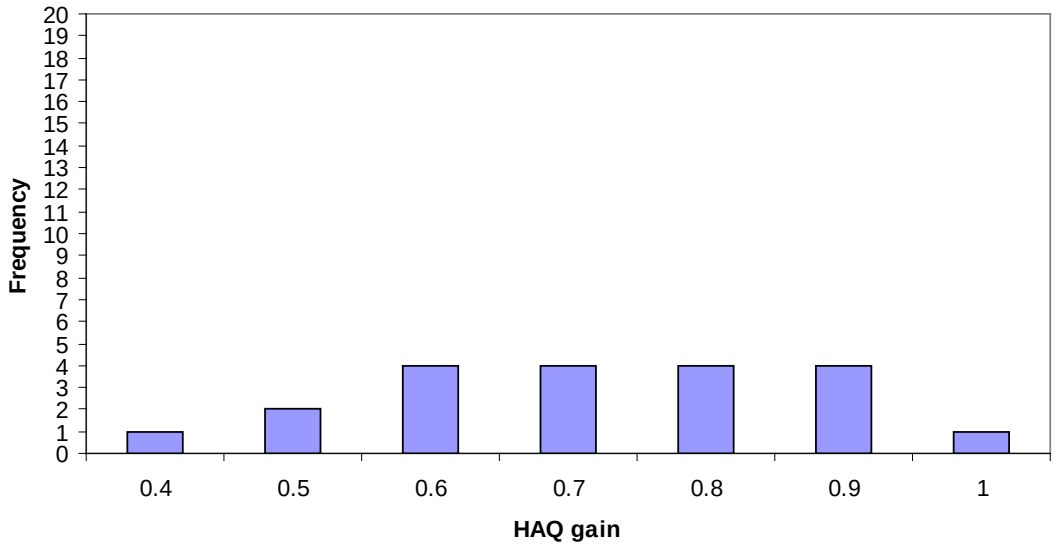
Submit your answer

Elicited histograms

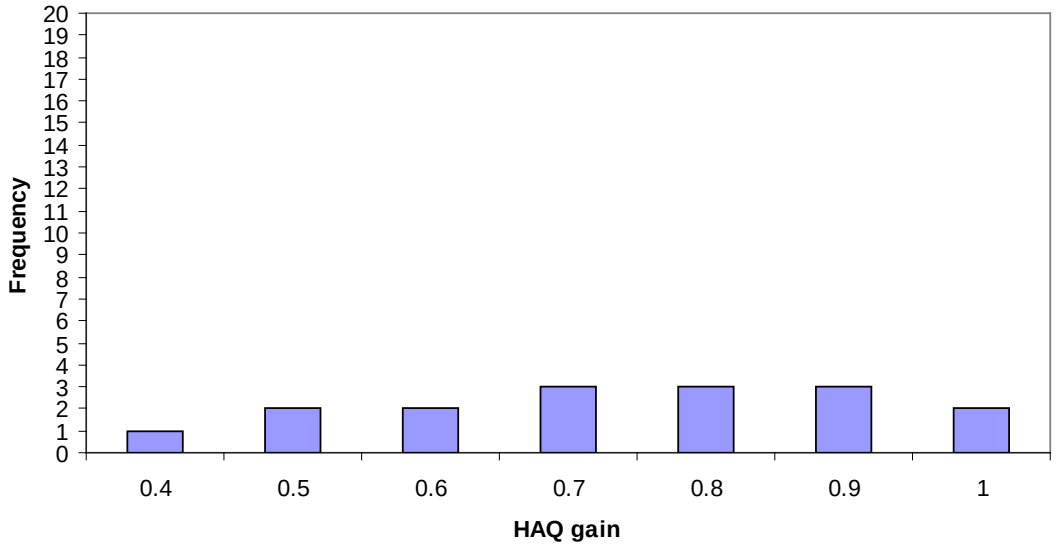




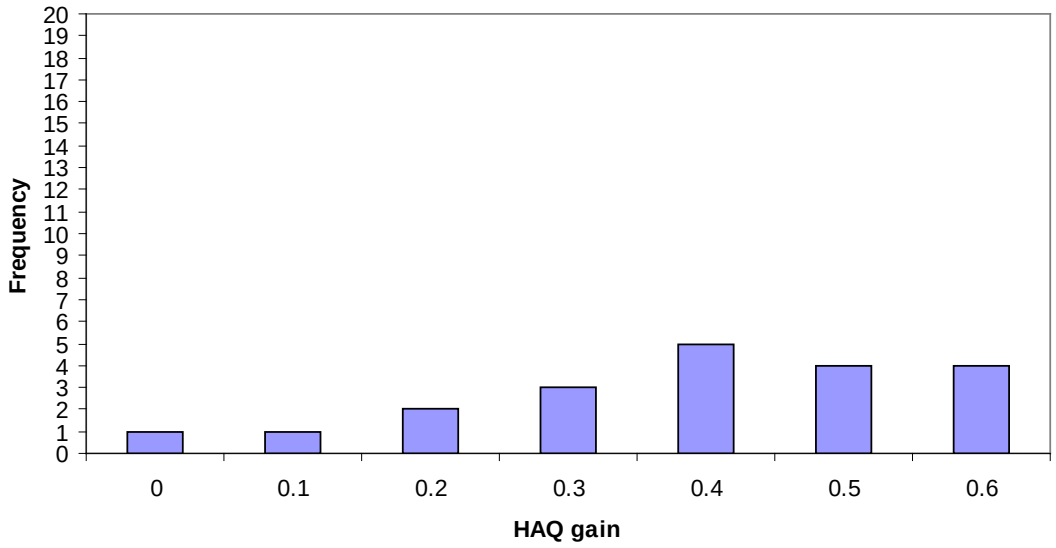
Expert 3: HAQ gain (all drugs)



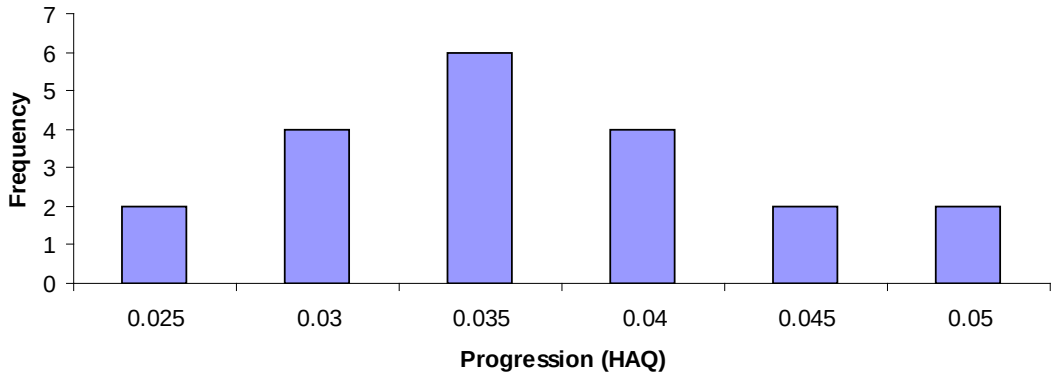
Expert 4: HAQ gain (all drugs)



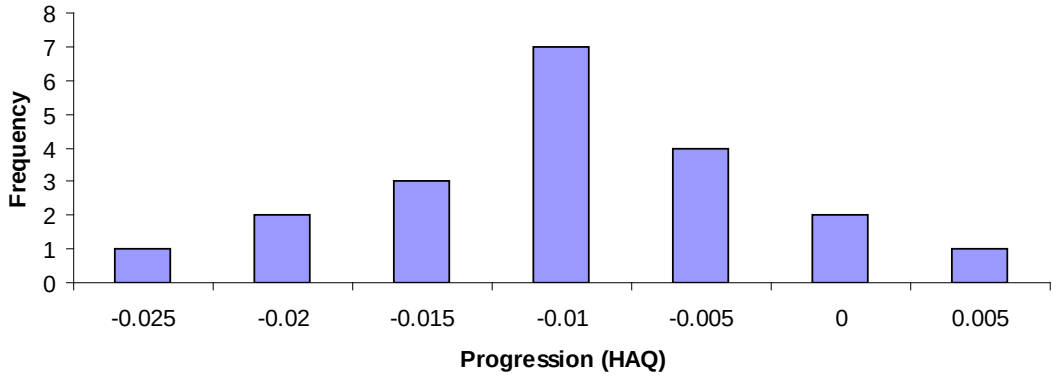
Expert 5: HAQ gain (all drugs)



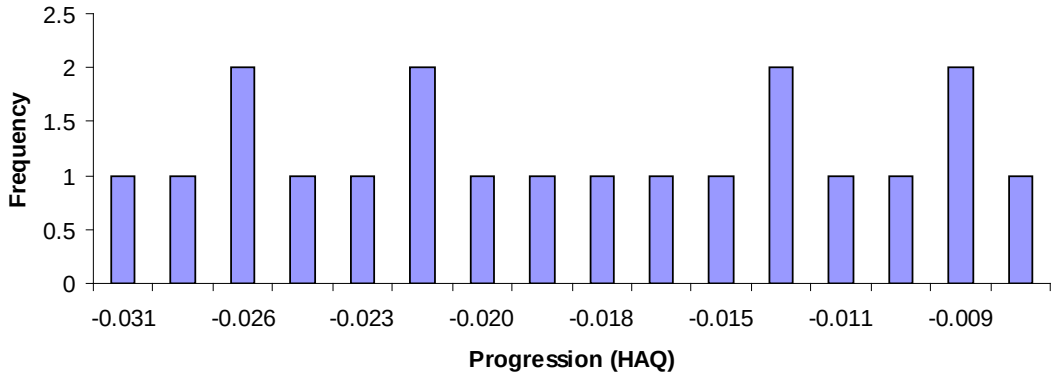
Expert 1: Progression whilst reponding



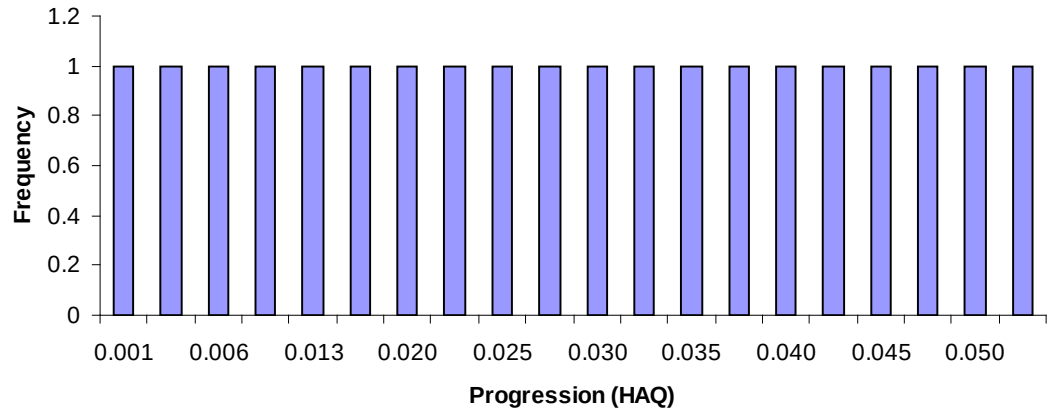
Expert 2: Progression whilst reponding



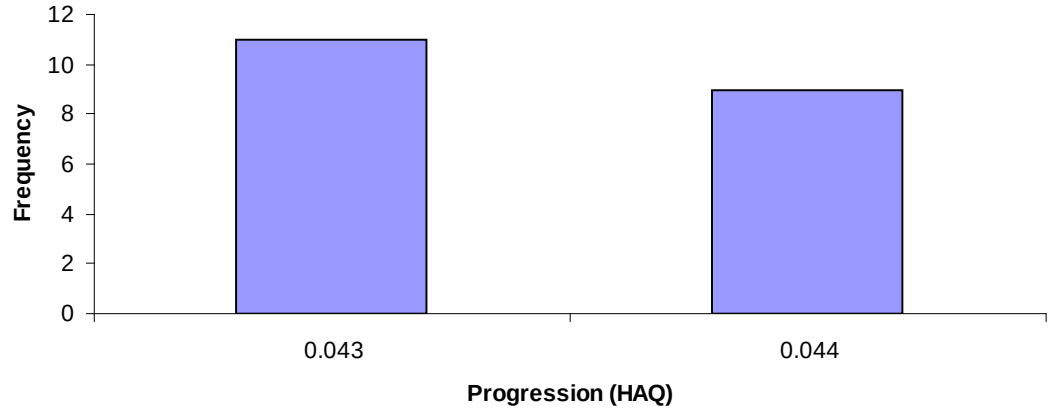
Expert 3: Progression whilst responding



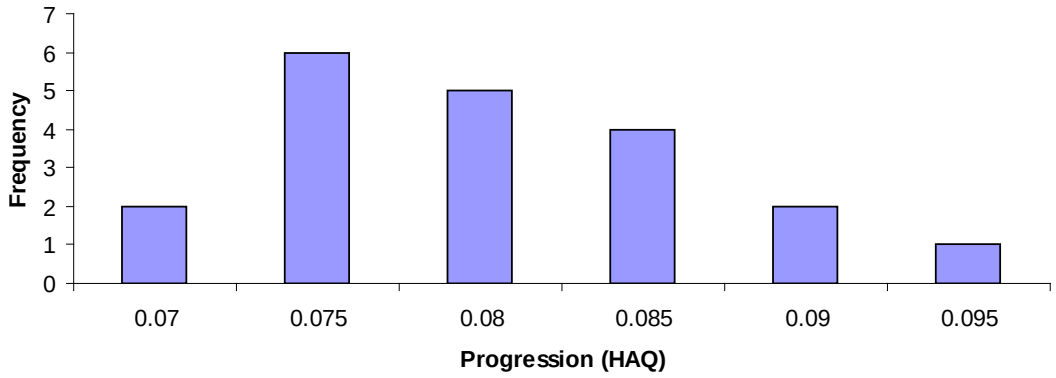
Expert 4: Progression whilst responding



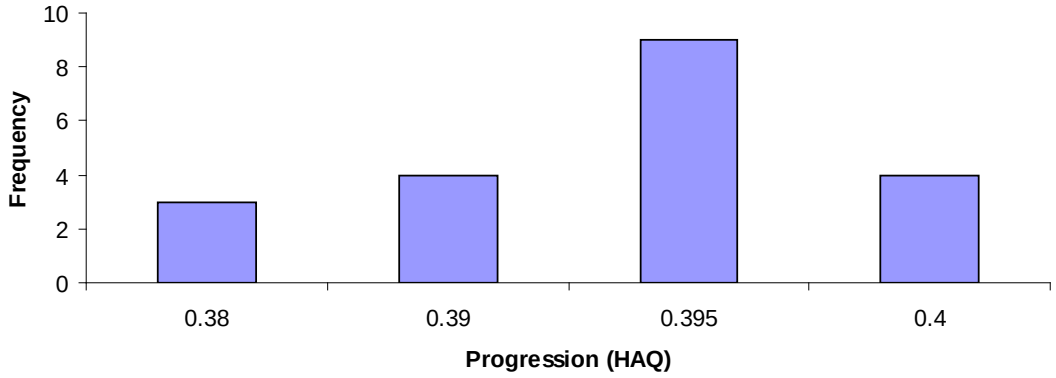
Expert 5: Progression whilst responding



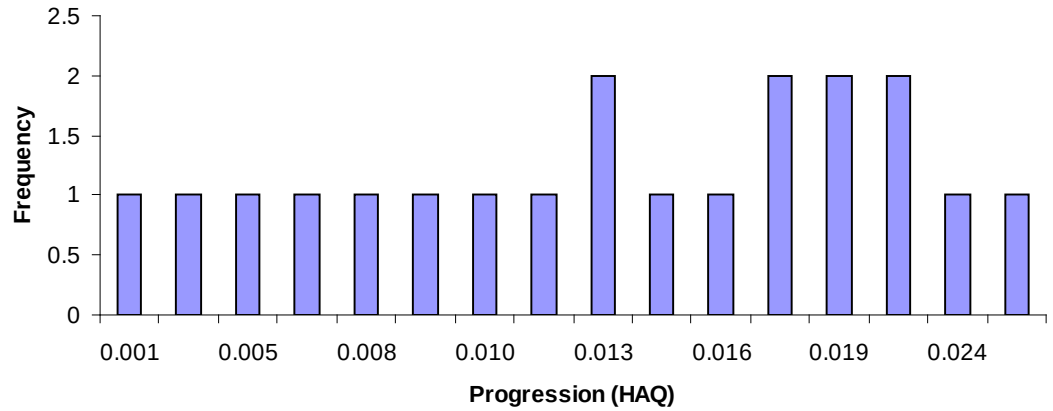
Expert 1: Progression during rebound period



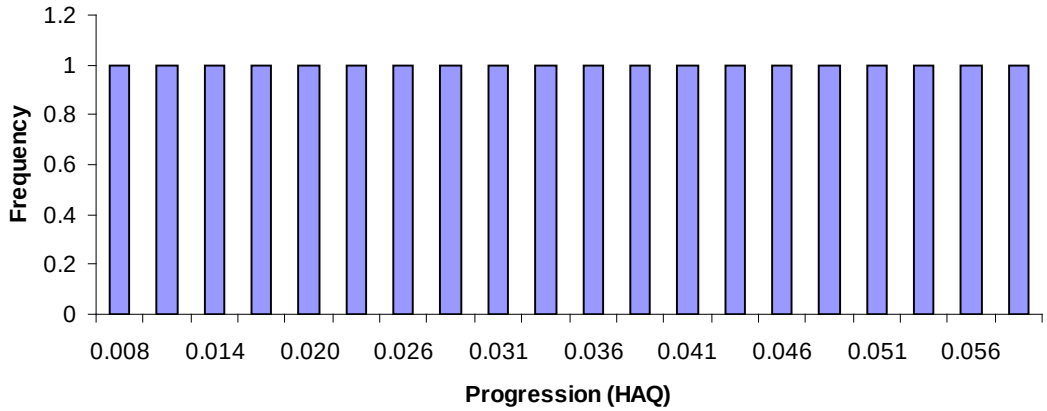
Expert 2: Progression during rebound period



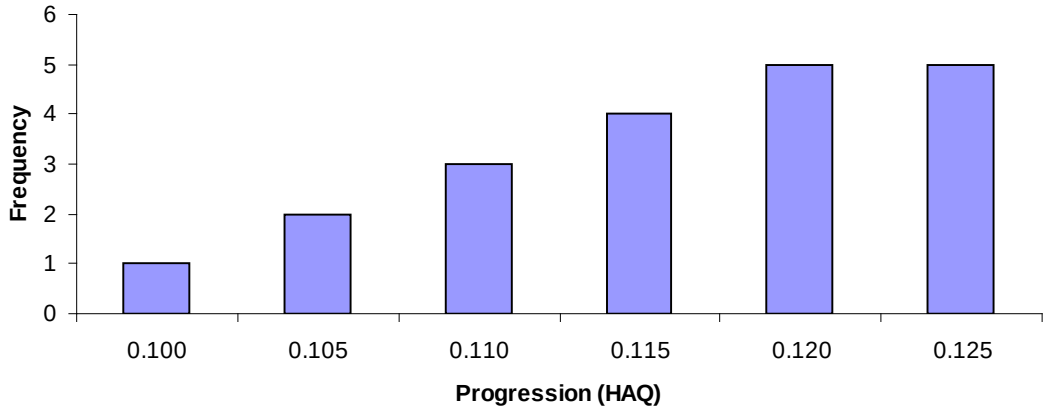
Expert 3: Progression during rebound period



Expert 4: Progression during rebound period



Expert 5: Progression during rebound period



10.12 Withdrawal rates from biologic therapies in patients with psoriatic arthritis

10.12.1 Introduction

This paper estimates persistence with initial anti-TNF therapies in patients with psoriatic arthritis. There are now registers in several countries that follow the progress of patients using biologic therapies and record the time to discontinuation. This paper undertakes a review of relevant registries to identify papers reporting drug discontinuation rates (or related data). A synthesis of relevant evidence is then undertaken, in order to estimate the rate of withdrawal from initial biologic therapy. The paper considers whether this rate may vary over time, and whether there may be differences in withdrawal rates between etanercept, infliximab and adalimumab. All evidence is drawn from national biologic registers and is based on published summary data only. As withdrawal rates of patients with psoriatic arthritis are different from other types of chronic arthritis, all patients in this analysis have a diagnosis of psoriatic arthritis.

The estimates from the evidence synthesis will be used in a decision model, and extrapolated beyond the horizon of the studies to predict withdrawal over the patient's lifetime.

10.12.2 Methods

10.12.2.1 Literature search

A literature search was carried out to identify published papers from biologics registers of patients with PsA that reported survival probabilities of remaining on first biologic therapy at 3 months or more, and number of patients at risk or confidence intervals to estimate the uncertainty in the parameters. The search strategies can be seen in the Annex at the end of this section.

This search identified 154 publications of registry data that were potentially relevant. In total, 130 of these were excluded based on the abstract as they were found not to be relevant, therefore leaving 24 publications that were considered in full. Of these 24 publications the information available can be summarised as:

Reports rate of drug withdrawals, n=8
Reports 2nd line success given reason for 1st line failure, n=4
Reports HAQ progression, n=14

Reports PASI progression, n=1

Of the eight publications reporting rates of drug withdrawals just six of these reported rates for PsA patients separately and in a format that could be used in the analysis. Data from patients registered between 2000 and 2006 in NOR-DMARD were published by Heiburg 2008 and Heiburg 2007. The latter was excluded as a majority of patients are likely to be included in both publications. Thus five publications were included in the analysis. These were Kristensen 2008[214], Gulfe 2009[186], Gomez 2006[228], Saad 2008[157] and Heiburg 2008.[229]

10.12.2.2 Included studies

In the five papers included in the analysis, the majority report the average unadjusted Kaplan-Meier probabilities of survival, apart from Kristensen 2008, who reported results stratified by use of concomitant MTX. Only one of the publication includes UK patients (Saad 2008). Kristensen 2008 and Gulfe 2009 include Swedish patients, Gomez 2006 Spanish patients and Heiburg 2008 Norwegian patients. A brief summary of the papers is given in Table 10.12.1.

Table 10.12.1: Summary of included studies

Author	Year	Register	Condition	No. patients at baseline	Biologic treatment?	Parameter(s)
Gomez-Reino[228]	2006	BIOBADASER	PsA	289	Yes	One year drug survival 1st and 2nd line Reasons for withdrawal
Kristensen[214]	2008	SSATG	PsA	261	Yes	~5 year drug survival for etanercept Risk of withdrawal relative to infliximab
Heiberg[229]	2008	NOR-DMARD	PsA	172	Yes	One year drug survival
Saad[157]	2008	BSRBR	PsA	566	Yes	One, two and three year drug survival, Reason for withdrawal Reported by individual drug
Gulfe[186]	2009	SSATG	PsA	344	Yes	~5 year drug survival for etanercept Risk of withdrawal relative to infliximab

Kirstensen 2008 (study 1) included 161 patients starting first biologic between April 1999 and Sept 2006 in the SSATG registry. Gülfe 2009 (study 2) included 344 patients starting first biologic between May 2002 and December 2008 from the SSATG. We included data from

both these publications in the evidence synthesis on the assumption that a minority of the patients would be included twice.

Table 10.12.2 shows the number at risk at the start of each follow up and the probability of surviving on first biologic therapy until at least the end of the period.

Table 10.12.2 Data used in the evidence synthesis

	Observational period 1					**Observational period 2**					**Observational period 3**					**Observational period 4**				
Study	*Start*	*End*	*N*	*S*	*St|St-1*	*Start*	*End*	*N*	*S*	*St|St-1*	*Start*	*End*	*N*	*St*	*St|St-1*	*Start*	*End*	*N*	*St*	*St|St-1*
1	1	12	161	0.82	0.820	13	24	103	0.72	0.878	25	36	54	0.6	0.833	37	48	17	0.5	0.833
2	1	3	344	0.902	0.902	4	6	216	0.81	0.898	7	12	144	0.699	0.863	13	24	136	0.598	0.856
3	1	12	289	0.87	0.870															
4	1	12	566	0.82	0.820	13	24	422	0.7	0.854										
5	1	12	172	0.773	0.773															

Start, End: Start and end of observation period (months from start of the study)

St: Probability of survival up to end of the period

St|t-1 : Probability of survival up to end of the period, given survival up to the start = *St / St-1*

N: Number at risk at start of period

Study 1 is Kristensen 2007 (South Sweden, patients with concomitant MTX), 2 is Gulfe 2009 (South Sweden), 3 is Gomez 2006 (Spain), 4 is Saad 2009 (UK), 5 is Heiburg 2008 (Norway)

Study 1 survival probabilities are read from a graph. Study 1 reported the number of patients at risk at 10 month intervals. Numbers at risk at the start of each year were interpolated from the data in the paper by estimating the average rate of censoring during the study and assuming this rate was constant throughout the study.

10.12.2.3 Synthesis of registry data

The evidence synthesis is carried out using Monte Carlo Markov Chain estimation. The model is based on a method for meta-analysis at multiple follow up times by Lu et al (2007)[230].

We define an 'event' as withdrawal from initial biologic therapy. The literature tends to report survival probabilities at a series of follow up times, $Pr(T_j > t_{u'}) = S(t_{u'})$, and the number observed at the start of each period $N_{ju'}$.(Table X.1) Unconditional survival probabilities are difficult to synthesise as probabilities reported at successive time points in the same dataset are correlated.

We therefore define the conditional probability of an event occurring between time u´ and u in trial j for those who do not have an event up to time u as $F_{ju'u}$. If T_j is the withdrawal time of patients in study j then

$$F_{ju'u} = Pr(t_{u'} < T_j < t_u \mid T_j < t_{u'}) = 1\text{-}S(t_u)/S(t_{u'})$$

where $t_{u'}$ is the beginning of segment u' and t_u is the endpoint of segment u. The data $F_{ju'u}$ are conditionally independent. We index the time segments 1-3 months, 3-6 months, 6-12 months, 12-24 months, 24-36 months and 36-48 months by u = 1,2,3,4,5,6. The observation periods are, therefore, made up of adjacent time segments, of unequal length. Not all studies report the same observation periods. For example, Saad 2009 reports survival probabilities at 12 and 24 months, while Gulfe 2009 reports survival probabilities at 3,6,12 and 24 months.

We assume that $F_{ju'u}$ is drawn from a normal distribution with mean $p_{ju'u}$ and variance $F_{ju'u}*(1\text{-}F_{ju'u})/N_{ju'}$. Other versions of the model might consider other distributions, such as the beta.

The hazard h_{ju} represents the failure rate of patients in trial j during segment u. The rate of withdrawal may vary over time. This might be represented in the model in various ways, such as a piece-wise constant hazard, or as a fully parametric function such as a Weibull distribution. The guidelines for the use of biologic therapies in psoriatic arthritis state that an assessment should be made at 3 months of whether the patient has responded on the PsARC and PASI 75 scales, and that drugs should be withdrawn or switched if there is no initial response (Kyle 2005). Discontinuation after 3 months is likely to be a function of adverse events and/or continued response. It is therefore likely that the rate of withdrawal in the first 3

months is different from later time periods. Given we only have a few studies there is probably insufficient data to model changes in the hazard after the first 3 months. We therefore specify a piece-wise hazard that is constant after the first 3 months.

If an observation period spans segments *u'* to *u*, for a piecewise constant hazard

$p_{ju'u} = 1\text{-}exp(-(H_{ju'} + \ldots H_{ju})$
$= 1\text{-}exp(-(c_{u'}h_{ju'} + ..+c_u h_{ju}))$

The meta-analysis is undertaken on the log-hazard scale.

$h_{ju} = exp(\theta_{ju})$

$\theta_{ju} = \mu_j + vI(u=1)$

Parameter μ_j takes random effects, and v is a constant in the base-case model. $I(u=1)$ is an indicator function that takes value 1 if u=1 and 0 otherwise. Parameter v represents the additive effect of the first 3months on the log-hazard scale. The prior of v is a non-informative normal, but in principle might be informed by non-response rates at 3 months estimated by the evidence synthesis in Section 5.2.

10.12.2.4 Differences in withdrawal between anti-TNF drugs

We conducted a meta-analysis of hazard ratios for differences in withdrawal rates between anti-TNFs, assuming fixed treatment effects. Data were included from studies identified in the literature search that reported hazard ratios for withdrawal for one biologic compared to another and its standard error or confidence interval. This analysis was conducted in STATA 10 using the 'metan' command.

10.12.3 Results

Results from the WinBUGS model are shown in Table 10.12.3

Table 10.12.3 Results from the synthesis of withdrawal rates

Description	*Mean*	*SE*
Mean annual hazard in month 1 exp(MU+v)	0.320	0.071
Mean annual hazard in month m≥2 (exp(MU))	0.165	0.031
Between study standard error (log scale) (se)	0.332	0.229

Note: the model constrains the hazards in study j in periods m≥2 to be equal

The model predicts the pooled mean hazard is 0.17 per year across all studies and all drugs. The hazard is double in the first 3 months, and the predicted probability of withdrawal in the first 3 months is 1-exp(-0.32x3/12) = 0.077

Two studies identified in the literature review[214,157] reported hazard ratios between therapies for discontinuation from first anti-TNF for any reason for PsA patients. Both studies adjusted for other factors using multiple regression in a Cox proportional hazards model. The data and results of the meta-analysis are shown in Table 10.12.4. Data from Kristensen 2008 have been read from a graph. The authors declined our request to provide the precise hazard ratios and confidence intervals (personal communication, P Geborek, 22/9/09)

Table 10.12.4. Hazard ratios for discontinuation from first anti-TNF for PsA patients

Comparison	*Study**	*Mean HR***	*Lower 2.5%*	*Upper 97.5%*
Etanercept vs Adalimumab				
	Kristensen 2008	1.0	0.3	3.0
	Saad 2009	1.00	0.66	1.43
	Pooled	1.00	0.68	1.46
Etanercept vs Infliximab				
	Kristensen 2008	0.5	0.3	0.9
	Saad 2009	0.36	0.27	0.47
	Pooled	0.38	0.30	0.49

*Data from Kristensen 2008 have been read from a graph

**A HR of 1 indicates withdrawal rates are lower for etanercept than the comparator biologic

10.12.4 Conclusions

- This study synthesises data on time to withdrawal from first biologic in patients with a diagnosis of psoriatic arthritis from national registries.
- The estimated rate of withdrawal after the first 3 months is 0.17 per year. This value will be used as the long term withdrawal rate in the base-case of the decision model
- This rate is rather higher than the rate estimated in the previous appraisal of these drugs (0.11 per year), which was obtained from a longitudinal study of RA patients in South Sweden enrolled between March 1999 and November 2000.
- This analysis finds that, according to this observational data, on average 7.7% of patients withdraw in the first 3 months
- This is much lower that the non-response rate on the PsARC scale recorded in the RCTs (about 16%). This might suggest that, in clinical practice, some patients remain on drug even though they might not have achieved PsARC response at 12 weeks.
- This might be because of improvement in the skin condition (not captured by PsARC) and/or the clinician's belief that response might be achieved later than 12 weeks
- There does not appear to be any difference in withdrawal rates between etanercept and adalimumab. Infliximab appears to have a significantly higher withdrawal rate than etanercept.
- However, these hazard ratios between drugs may not be reliable
- The hazard ratios were estimated over the whole follow up time, and do not distinguish between the first 3 months and later periods. Early withdrawal is a function of initial response, while later withdrawal is a function of continuing response and adverse effects
- Estimates of differences between drugs may be biased because infliximab was the first antiTNF to be marketed and may have been used on severe patients with low expectation of maintaining drug therapy

Limitations

- As with all observational data, results may be subject to selection bias and confounding
- Observed withdrawal rates are likely to depend on the options available to the clinician for switching patients to other biologics.
- The two studies from the South Sweden register may include some of the same patients

- We assumed a normal distribution for probabilities. This should not be a problem if probabilities are not close to 0 or 1 and N is large
- Withdrawal rates may be lower in patients receiving concomitant MTX. In this synthesis, one study (Kristensen 2008) did not report average survival probabilities but only reported results stratified by use of concomitant MTX or not. Excluding data from Kristensen 2008 increased the estimate of the withdrawal rate after 3 months from 0.17 (SE 0.03) to 0.20 (SE 0.72) per year, but the parameters failed to converge correctly.

Annex

Search strategy

Information was identified during a number of stages:

1. The endnote library *psoriaticarthritic2009-MASTER.enl* containing all the records identified by the searches was in itself searched for records containing the words 'register' or 'registry'. This identified 25 records.

2. A search of MEDLINE OvidSP (1950 to July Week 2 2009) was carried out on 16 July 2009. The search strategy consisted of: Arthritis, Psoriatic/ OR (psoria$ adj2 (arthrit$ or arthropath$)).ti,ab. AND (register$ or registr$).ti,ab. The results were scanned for relevance and 16 potentially relevant records were identified.
3. A search for named registries was carried out on 17 July 2009 on MEDLINE OvidSP (1950 to July Week 2 2009); the named registries identified by the previous stages. This approach identified 112 additional records.

WinBUGS code

```
#Estimate parametric withdrawal rate from biologic therapy
#David Epstein Sept 2009
#PSA version 10

model{
#study, time
for (j in 1:12){
                    F[ID[j],t[j]]<-1-S[j]#Conditional failure at follow up t, given survival
up to end of t-1
                    Prec[ID[j],t[j]]<-N[j]/(F[ID[j],t[j]]*(1-F[ID[j],t[j]]))#precision of F
```

```
                    F[ID[j],t[j]]~dnorm(p[ID[j],t[j]],Prec[ID[j],t[j]]) #Likelihood for
failures
}#loop j

#h are hazards, indexed i=study 1..4, m=time periods 1..up to 6
#time periods m are of different lengths of time:
#period 1 is 3months,  2 is 3months,  3 is 6months,  4,5 and 6 are all 12m
#each study might report survival probs at different set of follow up times
p[1,1]<-1-exp(-h[1,1]*0.25-h[1,2]*0.25-h[1,3]*.5) #ie follow up1 in study 1 is at 1 year
p[1,2]<-1-exp(-h[1,4]*1)#follow up 2 in study 1 is at 2 years
p[1,3]<-1-exp(-h[1,5]*1)#follow up 3 in study 1 is at 3 years
p[1,4]<-1-exp(-h[1,6]*1)#f up 4 in study 1 is at 4 years
p[2,1]<-1-exp(-h[2,1]*.25) #follow up 1 in study 2 is at 3months
p[2,2]<-1-exp(-h[2,2]*.25)#follow up 2 in study 2 is at 6 months
p[2,3]<-1-exp(-h[2,3]*.5)#follow up 3 in study 2 is at 1 year
p[2,4]<-1-exp(-h[2,4]*1)#follow up 4 in study 2 is at 2 years
p[3,1]<-1-exp(-h[3,1]*.25-h[3,2]*.25-h[3,3]*.5)# f up 1 in study 3 is at 1 yr
p[4,1]<-1-exp(-h[4,1]*.25-h[4,2]*.25-h[4,3]*.5)#f up 1 in study 4 is at 1 yr
p[4,2]<-1-exp(-h[4,4]*1)#f up 2 in study 4 is at 2 yrs
p[5,1]<-1-exp(-h[5,1]*0.25-h[5,2]*0.25-h[5,3]*.5) # follow up 1 in study 5 is at 1 year

for (i in 1:5)  {# 5 studies
        for (m in 1:6) {#6 time points
                #step(e) = 1 if e >= 0; 0 otherwise. Acts like an 'if..then..else' statement
                theta[i,m]<-mu[i]+v*step(1-m)#fixed effect for v
                #theta[i,m]<-mu[i]+v[i]*step(1-m)#random effect for v
                h[i,m]<-exp(theta[i,m])
}}

for (i in 1:5)  {#5 studies
#mu[i]~dnorm(0,0.0001)#fixed study baseline
mu[i]~dnorm(MU,PREC)#random study baseline
#v[i]~dnorm(MU.V,PREC.V)#random study v
}

MU~dnorm(0,0.0001)#pooled value for mu
```

```
PREC<-pow(se,-2)
se~dunif(0,10)

v~dnorm(0,0.0001)#additional log-hazard in first 3months
#MU.V~dnorm(0,0.0001)#random v
#PREC.V<-pow(se.v,-2)
#se.v~dunif(0,10)

out[1]<-exp(MU+v) #mean hazard in month 1
out[2]<-exp(MU) #mean hazard in other months
out[3]<-se #between study variation in MU

}#end model

inits
list(MU=0,se=1,v=0,mu=c(0,0,0,0,0))#fixed v
list(MU=0,se=1,MU.V=0,se.v=1,mu=c(0,0,0,0,0),v=c(0,0,0,0,0))#random v

#data
#S[] is the conditional Pr(survival from t| given survival up to t)
#ie S[T>t|T>t-1) = S[T>t]/S[T>t-1]
#study 1 is Kristensen 2008 with MTX, 2 is Gulfe 2009, 3 is Gomez 2006, 4 is Saad 2009,5 is Heiburg 2008, 6 is Heiburg 2007 (not used)
#kristensen estimates read from a graph
ID[] N[] S[]  t[]
1       161     0.82    1
1       103     0.878   2
1       54      0.833   3
1       17      0.833   4
2       344     0.902   1
2       216     0.898   2
2       144     0.863   3
2       136     0.8555  4
3       289     0.87    1
4       566     0.82    1
4       422     0.8537  2
5       172     0.77    1
```

10.13 Costs used in the York model

Each of the industry models presents different resource use assumptions and unit costs which are used to cost drug treatment and administration and monitoring of patients. Different assumptions are used regarding the dosing of drugs and resource use for administration and monitoring (see Section 6.3). The current York model sought to generate appropriate costs for each of the treatment options using clinical advice and BSR guidelines to determine the resource use associated with administering drugs and monitoring patients. These items are valued using recently published unit costs and prices. The following sections describe the assumptions made in costing, the associated resource use assumptions, unit costs and cost inputs for the decision model.

Resource use

The current York model assumes that infliximab vials cannot be shared and adopts separate scenarios regarding the use of 3 or 4vials per patient. Infliximab is given at 0, 2 and 6 weeks followed by every 8 weeks. Six vials of adalimumab are given in every 3-month cycle. Twenty four vials of etanercept are given in the first cycle followed by 26 vials for all subsequent cycles. These assumptions were made in consultation with an expert pharmacist (personal communication Carolyn Davies).

The York model also assumes a ½ day in-patient hospital cost for each infusion of infliximab. A single outpatient (OP) visit is assumed for etanercept and adalimumab in the initial 3-month period, followed by a review visit between 3 and 6months and every 6 months thereafter.

In the York model it is assumed that, at baseline (in the initial 3-month period), patients will require a Full Blood Count (FBC), Erythrocyte Sedimentation Rate (ESR), Liver Function Test (LFT)LFT, Urea and Electrolytes (U&E)U&E, chest X-Ray, Tuberculosis (TB) Heaf test TB Heaf test, antinuclear antibody (ANA) and a double-stranded (ds) DNA test. All of these resource use assumptions are taken from the previous York model following the BSR guidelines for the use of biologics.

The resource use assumed as part of drug use, administration and monitoring for the various treatment options are shown in Table 10.13.1. All resource use was validated by clinical input.

Table 10.13.1: Resource use associated with drug administration and monitoring

0-12 weeks	*Drugs*		*Administration*		*Monitoring*							
	Vials per visit	Doses	OP visit	Infusion cost	FBC	ESR	LFT	U&E	Chest X Ray	TB HEAF test	ANA	ds DNA
Etanercept	1	24	1	0	2	2	2	2	1	1	1	1
Adalimumab	1	6	1	0	2	2	2	2	1	1	1	1
Infliximab (4 vials)	4	3	0	3	2	2	2	2	1	1	1	1
Infliximab (3 vials)	3	3	0	3	2	2	2	2	1	1	1	1
12-24 weeks	*Drugs*		*Administration*		*Monitoring*							
	Vials per visit	Doses	OP visit	Infusion cost	FBC	ESR	LFT	U&E	Chest X Ray	TB HEAF test	ANA	ds DNA
Etanercept	1	24	1	0	0.5	0.5	0.5	0.5	0	0	0	0
Adalimumab	1	6	1	0	0.5	0.5	0.5	0.5	0	0	0	0
Infliximab (4 vials)	4	2	0	2	0.5	0.5	0.5	0.5	0	0	0	0
Infliximab (3 vials)	3	2	0	2	0.5	0.5	0.5	0.5	0	0	0	0
24 weeks +	*Drugs*		*Administration*		*Monitoring*							
	Vials per visit	Doses	OP visit	Infusion cost	FBC	ESR	LFT	U&E	Chest X Ray	TB HEAF test	ANA	ds DNA
Etanercept	1	24	0.5	0	0.5	0.5	0.5	0.5	0	0	0	0
Adalimumab	1	6	0.5	0	0.5	0.5	0.5	0.5	0	0	0	0
Infliximab (4 vials)	4	1.625	0	1.625	0.5	0.5	0.5	0.5	0	0	0	0
Infliximab (3 vials)	3	1.625	0	1.625	0.5	0.5	0.5	0.5	0	0	0	0

*** assuming no vial sharing, 5mg/kg and patient weight of 70-80kg ** assuming no vial sharing, 5mg/kg and patient weight of 60kg**

Unit costs

All drug costs were taken from the recent version of the BNF[178]. The costs of inpatient hospital visits were taken from the 2007/2008 NHS reference costs[231] and is for an elective excess bed day for inflammatory Spine, Joint or Connective Tissue Disorders without complications. An in-patient day is assigned a cost of £144 per ½ day. The cost of an outpatient visit is also taken from NHS reference costs and is for a follow up visit in rheumatology. Each outpatient visit costs £116. Costs associated with laboratory tests relating to the monitoring of patents, were taken from the previous York model[172] updated to reflect 2009 prices.

All unit costs used in the current York model are shown below in Table 10.13.2.

Table 10.13.2: Unit costs used in the York model

	£(2009)	Source
Drugs		
Infliximab (100mg vial)	419.62	BNF 58
Etanercept (25mg syringe)	89.38	BNF 58
Adalimumab (40mg syringe)	357.5	BNF 58
Hospital costs		
½ Inpatient day	£144	NHS reference costs 2007/2008 – elective inpatient excess bed day for inflammatory Spine, Joint or Connective Tissue Disorders without complications
Outpatient rheumatology, first attendance	£205	NHS reference costs 2007/2008 - Rheumatology outpatient first attendance
Outpatient rheumatology, follow-up attendance	£116	NHS reference costs 2007/2008- Rheumatology outpatient follow up
Laboratory tests		
Full Blood Count (FBC)	£2.74	
Erythrocyte Sedimentation Rate (ESR)	£2.71	
Liver Function Test (LFT)	£0.69	
Urea and Electrolytes (U&E)	£1.27	
Chest-X ray	£24.04	York NHS Trust – 2005 costs updated to 2009
TB Heaf test	£8.01	NHS Reference costs 2003 updated to 2009
Antinuclear antibodies (ANA)	£4.27	
DNA binding (ds DNA)	£4.27	York NHS Trust – 2005 costs updated to 2009

Costs used in the current York model

The resource use items presented in Table 1 were multiplied by the unit costs in Table 2 to generate cost inputs for the decision model. Costs were calculated for the initial 3-month period, 3-6 month period and all subsequent 3-month periods. These costs are presented below in Table 10.13.3.

Table 10.13.3: Costs used in the York model

0-12 weeks	*Drugs*	*Administration*	*Monitoring*	*Total*
Etanercept	2145.12	116.00	55.43	2316.55
Adalimumab	2145.00	116.00	55.43	2316.43
Infliximab (4 vials)	5035.44	432.00	55.43	5522.87
Infliximab (3 vials)	3776.58	432.00	55.43	4264.01
12-24 weeks	*Drugs*	*Administration*	*Monitoring*	*Total*
Etanercept	2145.12	116.00	3.71	2264.83
Adalimumab	2145.00	116.00	3.71	2264.71
Infliximab (4 vials)	3356.96	288.00	3.71	3648.67
Infliximab (3 vials)	2517.72	288.00	3.71	2809.43
24 weeks +	*Drugs*	*Administration*	*Monitoring*	*Total*
Etanercept	2145.12	58.00	3.71	2206.83
Adalimumab	2145.00	58.00	3.71	2206.71
Infliximab (4 vials)	2727.53	234.00	3.71	2965.24
Infliximab (3 vials)	2045.65	234.00	3.71	2283.36

10.14 The natural history of PsA patients eligible for biologic therapy

Introduction

This Appendix was written by David Epstein, University of York; Suzanne Verstappen, University of Manchester and Deborah Symmons, University of Manchester.

The decision model estimates long term outcomes in terms of HAQ and PASI for patients with and without biologic therapy. As NICE would not recommend a placebo, the comparator is 'natural history', a counterfactual state where no biologic therapy is available.

Previous decision models of PsA have estimated what the change in HAQ would have been if no biologic therapy had been offered. Bansback et al (2006) [171] used data from a long-term open-label follow up of 35 patients who had originally been entered in a clinical trial comparing methoxretrate with and without ciclosporin in the Leeds Musculoskeletal Unit. These patients had previously not been controlled on methotrexate alone. 24 responses were received to a postal questionnaire. At the end of the trial, their mean HAQ was 1.13. After 'some 4.2 years follow up' (it is not stated if this is the maximum, minimum, mean or median), mean HAQ was 1.4, a mean annual change of 0.07 (SD 0.03).
Possible limitations of this analysis for the purposes of the current decision modelling are:

- Small sample size
- Possibility of selection bias among responders to the postal questionnaire
- Patients have failed one DMARD (methotrexate) rather than two as required by NICE guidelines
- It is not stated in the paper if patients met the current guideline criteria for initiating anti-TNFs in PsA (3 tender and 3 swollen joints)

No other published estimates were found of long term outcomes in patients who had been uncontrolled on DMARDs. Morgan et al (2007)[232] investigated outcomes in patients enrolled in NOAR between 1990 & 1994 with and without psoriasis. The median HAQ score for n=79 patients with inflammatory polyarthritis plus psoriasis at baseline was 0.625 (IQR 0.25-1.375) and was 0.75 (IQR 0.125 – 1.75) at 5 years, indicating a very small annual change in HAQ (0.025 per year). However, these data are not in patients who are necessarily uncontrolled with DMARD.

The NOAR data was re-analysed by the ARC Epidemiology Unit at the University of Manchester to estimate HAQ change in patients who are uncontrolled (with 3 tender joints

and 3 swollen joints) and have previously tried two or more DMARDs. This paper describes how HAQ progression was estimated and used in the decision model.

Methods

The NOAR database is a primary care based cohort of patients with inflammatory polyarthritis (IP). NOAR has been recruiting patients since 1990. Not all variables were assessed and recorded at follow ups for the cohort registered between 1995 and 2000 and so this cohort was excluded from the analyses. HAQ and other outcomes are recorded at annual follow ups. Baseline is the visit when the patient was first seen by the research nurse to be included into the NOAR register. NOAR did not record a diagnosis of PsA. As patients with IP plus psoriasis are thought to have similar prognosis to those who are sero-negative without psoriasis, patients who were rheumatoid factor negative at baseline were selected from the NOAR register. At each time point (baseline, year 1, year 2, year 3 and year 5) we evaluated whether patients fulfilled the following criteria:

- 3 tender joints (TJC) and 3 swollen joints (SJC) using the 51 joint count
- Previous use of 2 or more DMARDs, implemented as all patients who had used two DMARD(s) or were still using two DMARDs for at least 30 days

These criteria are intended to select patients who would be eligible for use of anti-TNFs. The BSR recommend that the 78-tender and 76-swollen joint count is used[150], but this was not available in NOAR. The annual change in HAQ over the following two years was estimated from the time when a patient first fulfilled the criteria. The total score is based on the inclusion of all patients who fulfilled the criteria at different time points and their change in HAQ-score since that time point. For example, from the data in Table 10.14.1, there were 216 patients in total =24 patients at baseline + 50 patients at year 1 +46 patients at year 2 + 52 patients at year 3 + 44 patients at year 5. It is therefore possible that some patients are accounted for multiple times in the total score.

Results

The results are shown in Table 10.14.1. For all patients regardless of when they first became eligible for biologics, the data suggests that there was little change in HAQ over two years (Mean annual change 0.00, SD 0.228) (n=216).

For patients who met the eligibility criteria at baseline, their mean HAQ score at baseline was 1.55 (SD 0.84), and the mean change in HAQ over 2 years was -0.060 per year (SD 0.279) (n=24). These patients had a median of 2.72 years from first onset of symptoms of disease

until entry to NOAR. As a higher HAQ score represents worse disability, a negative change is an improvement.

For patients who met the eligibility criteria 3 years after entry to NOAR, the mean change in HAQ over 2 years was 0.077 per year (0.228) (n=52), that is, a worsening of disability. These patients had a median of 3.9 years from first onset of symptoms of disease until meeting the eligibility criteria for anti-TNFs.

The following sensitivity analyses were carried out:

- Patients who (had) used a DMARD(s) for more than 90 days at time of assessment were included in the analyses. In addition, patients who had used≥2 DMARDs for at least 30 days were also included in the analyses.
- All patients who had used a DMARD(s) or were still using a DMARD, irrespective of duration and number of DMARDs, were eligible at that time point.
- Tender and swollen joints assessed using the 28 joint count (DAS-28)
- Patients with a nurse-assessment of psoriasis as baseline

The same trends observed in the primary analysis were also found in the sensitivity analyses.

Table 10.14.1. Change in HAQ for all patients who had used two DMARD(s) or were still using two DMARDs for at least 30 days

Years from baseline until patient first fulfils criteria	Median symptom duration at baseline	Mean (SD) HAQ-score at baseline	Number of patients fulfilling criteria with one year follow-up HAQ-score data available	Mean (SD) annual change in HAQ-score measured over subsequent year	Number of patients fulfilling criteria with two year follow-up HAQ-score data available	Mean (SD) annual change in HAQ-score measured over subsequent two years
Baseline	2.72	1.55 (0.84)	27	-0.046 (0.513)	24	-0.060 (0.279)
One year	0.99	1.52 (0.72)	53	-0.104 (0.427)	50	-0.019 (0.236)
Two years	0.69	1.41 (0.73)	68	0.029 (0.352)	46	-0.053 (0.214)
Three years	0.90	1.52 (0.73)	56	0.045 (0.389)	52	0.077 (0.228)
Five years	0.91	1.51 (0.74)		NA[1]	44	0.018 (0.180)
Total score			204	-0.011 (0.408)	216	0.00 (0.228)

Note 1. HAQ was not recorded 6 years after baseline, therefore the change from year 5 to year 6 could not be estimated

Discussion

This paper has estimated the change in HAQ from the time at which RF-negative patients with IP would have been eligible for biologics under current BSR guidelines. It finds that overall there is little or no change in HAQ over one or two years.

- For patients with symptoms for less than about 3 years before they became eligible for biologics, the data suggest that HAQ tends to improve over the following one or two years.
- For patients who have had symptoms of IP for more than about 3 years before they became eligible for biologics, the data suggests that HAQ tends to worsen over the following one or two years.

These analyses have several limitations:

- The dataset cannot identify patients with a consultant diagnosis of PsA
- Biologics were licensed around the year 2000. Patients whose arthritis was not considered adequately controlled after this date would probably have been assessed against the criteria for anti-TNFs. In this study, we excluded patients who used a biologic agent at any time. Therefore the patients who did not use biologics are likely to be those whose disability was less severe or progressed more slowly.
- The criteria for commencement of anti-TNFs require patients to satisfy 3 tender and 3 swollen joints twice at least a month apart, and in these data we only have a single measure

- The criteria of 3 TJC and 3 SJC in some cases will be only moderate disease, and the patient and clinician might not consider that a failure. Patients in NOAR who satisfy the 3 TJC and 3 SJC criteria might go on to try other options such as increasing the dose of DMARDs, combination therapy or steroid injections.
- Patients in NOAR seem to satisfy the 3 TJC and 3 SJC criteria having been treated with ≥ 2 DMARDs for starting biologic therapy much earlier than patients in RCTs. This may be because RCTs tended to recruit patients who may have worse disease than the minimum entry criteria in the license

Conclusion

The York decision model will use as its base-case the mean progression of HAQ for patients not using anti-TNFs estimated in the NOAR data in patients with long-standing disease (about 3 years since onset of symptoms), that is, 0.077 per year (SE = 0.228/sqrt(52) = 0.032). This value is very similar to that estimated by Bansback et al }[171](mean change per year 0.07). Sensitivity analyses will estimate model results at the upper and lower confidence interval of this parameter.

10.15 Impact of HAQ on health service costs

Introduction

This appendix reviews the published literature to estimate the impact of changes in functional status and disability, as measured by the HAQ, on health service and personal social services costs. These estimates will be used in the decision model to predict health service costs over the patients' lifetimes.

Methods

This is a very broad literature, and an exhaustive review was beyond the time constraints of this project. Instead, a rapid review was undertaken of the following sources

- evidence presented to previous NICE appraisals of psoriatic arthritis treatments,
- the manufacturers' submissions to the current appraisal,
- Pubmed in October 2009 with the search string: "costs health assessment questionnaire arthritis".

Relevant cost data for the economic model must satisfy the following criteria:

- The data should be relevant to patients with psoriatic arthritis. There are few cost data specifically measured in this disease, but many studies have analysed the relationship between HAQ and costs in other forms of chronic arthritis. It is assumed here that these data are generalisable to PsA. The cohort should include patients across the full spectrum of HAQ scores from mild to severe disability
- The data must show a causal relationship from HAQ to subsequent health service utilisation and costs. Ideally, the analysis should exclude potential bias from confounding (the effect of other factors on both HAQ and costs) and endogeneity (the use of health services on subsequent disability). A retrospective or cross-sectional analysis, where patients are asked about their current disability and previous use of health services, might not capture the correct causal relationship. For example, surgery may improve function and so reduce HAQ. A prospective study design is therefore preferred, where HAQ is measured first and the costs are those accrued over the following period.
- The data should report mean costs conditional on HAQ and measures of sampling uncertainty. If the data are longitudinal, and individuals HAQ and subsequent cost are measured more than once during the study, then the analysis should properly account for the auto-correlation between repeated measures.

- The data should measure costs not charges or prices.
- Preferably data would be taken from the UK. Where this is not possible, it is important to assess whether studies from other countries are likely to be generalisable to the UK, particularly countries with mixed public/private financing such as the US.
- The data should measure all direct healthcare costs in the hospital, outpatient and community. Productivity losses should be reported separately. The base-case model excludes productivity losses in accordance with the NICE reference case
- The data should estimate the costs of DMARDs and anti-TNF separately from those of other health services. The economic model includes these costs separately from the effect of HAQ on costs.
- The study should have collected both HAQ and subsequent resource use as primary data and not use a proxy, such as expected HAQ predicted from other variables
- The data should state the price year, the currency and other data to allow adjustment to the UK in 2009.

Papers were excluded if a rapid review of their title or abstract showed they did not meet one or more of the above criteria. The remainder were examined in more detail.

Results

The PubMed search identified 149 papers. There were 3 submissions by manufacturers to the current appraisal, and 3 submissions from the same manufacturers to previous NICE appraisals of anti-TNFs for PsA. Excluding duplicates, 5 papers were reviewed in more detail and their results are described below.

The estimates of costs used in the Wyeth submission to the current appraisal was excluded because the individual patient data did not include HAQ, and the analysis used 'predicted HAQ' as a proxy. Section 6.1 gives more details of this study.

Kobelt et al 2002

The Wyeth economic model for the previous NICE appraisal of psoriatic arthritis[180] estimated the direct costs as a function of HAQ based on data in Kobelt et al (2002) [42]. The same source was used by the York Assessment Group to populate the economic model for the previous NICE appraisal [180], and by Schering-Plough [175] in their submission to the current NICE appraisal. The data published by Kobelt are shown in Table 10.15.1.

The UK study began in 1987 and the cost component included 916 RA patients with between 5 and 9 years of follow up. Direct health care resources were collected prospectively for all patients for hospitalisations, surgical interventions, and RA medications. Outpatient visits and

community services which were collected retrospectively in a subsample of 107 patients. All observations for patients in a given state, at any year in the follow up, were used to calculate the mean annual cost for each state. The paper states that few patients were in the worst HAQ state, and no surgery was undertaken in these patients. The authors warn that results for this group may not represent general practice and should be treated with caution.

The analysis has several limitations. The paper does not explain the method of analysis used to estimate the costs in Table 10.11.1 in much detail. It is not clear if repeated measures on the same patients were included in the analysis (as their HAQ evolved). As outpatient costs were only collected for a subsample of patients, it is not clear if imputation was used to estimate these costs in the other patients in the study. No indication is given of uncertainty in the primary data such as standard errors or confidence intervals. The price year used in the analysis is not stated, though is likely to be 1999 or 2000. Table 10.15.1 shows the mean annual direct costs in 1999 US$ and 2008 UK pounds assuming purchasing power parity index of US$ = 0.6542 GBP (OECD[233]), and the UK health sector pay and prices inflation factor from 1999 to 2008 is 1.36 (PSSRU[234])

Table 10.15.1. Mean annual direct and indirect (productivity) costs estimated as a function of HAQ, in US dollars. [42, 188]

HAQ score range	Proportion of patients(*)	Direct (1999 US$)	Indirect (1999 US$)	Total (1999 US$)	Direct (2008 £)
0-0.6	0.35	1,228	148	1,376	1,094
0.6-1.1	0.16	3,152	2,524	5,676	2,809
1.1-1.6	0.15	2,091	3,474	5,565	1,864
1.6-2.1	0.14	3,087	5,300	8,387	2,751
2.1-2.6	0.11	3,401	8,070	11,471	3,031
2.6-3	0.08	2,697	8,407	11,104	2,404

(*) Actual proportion of patients in the different disease states in the UK study during the longitudinal 9 year follow up

Bansback 2002

Based on the data in Table 10.15.1, Bansback et al (2006) [171]carried out a linear regression and reported the coefficients as

Annual direct cost = £358*HAQ + £1182

Standard errors £231 £416

R-sq =0.37

The study does not give much detail of the regression method used, but it is likely that this is an ordinary least squares regression using the mid-point of the HAQ score as the independent variable and direct cost as the dependent variable, with six data points. If so, then the standard

errors estimated in the regression do not correctly reflect the uncertainty in the mean of costs in the population, as each of these six data points is a sample mean conditional on HAQ score and has been measured with sampling error.

The assumption by Bansback et al that mean costs are a linear function of HAQ across all HAQ ranges does not appear supported by the data shown in Table 10.15.1. In particular, it appears that mean direct costs increase rapidly between the first and second HAQ band, but after this, subsequent increases in HAQ do not seem to be associated with increasing direct cost, although the association seems stronger for indirect costs. However, there were few patients with severe HAQ states.

It is not clear if the regression estimates relate to the study price year 1999/2000 or have been adjusted for inflation to the price year used by Bansback et al (not stated by probably 2004 or 2005).

Kobelt (2002) [42] estimated that RA drugs such as DMARDs represent on average 13-15% of direct costs. The previous York AG model [180]reduced the means and SEs of the regression estimates by 15% to populate the decision model. This adjustment assumes that DMARD use is a constant proportion of overall direct costs for all HAQ scores. If costs are reduced by 15% to reflect expenditure on DMARDS, then mean direct health care costs per 3months in 2008 GBP are estimated as £358*0.85*0.25*1.36 = £103 (SE 67).

Abbott submission, Wiles et al (2005)

The Abbott submission to the current appraisal is based on an analysis of resource use in the NOAR register. This is a UK primary care-based cohort established in 1989. The data from the Abbott submission are shown in Table 10.15.2.

The reporting of these data has several limitations.

- The Abbott submission states that the data are taken from Wiles (2005)[235], a report commissioned by Roche as part of a previous NICE appraisal (Rituximab). However, the AG has not been granted access to the original report by Wiles et al. Therefore we cannot establish key details of how the data were collected or analysed.

- It is not stated if the cost data are prospective or retrospective, relative to when the HAQ assessment was made.

- It is not stated how many patients were included in the analysis in each HAQ range.

- It is not stated if HAQ is measured at baseline or longitudinally. If the latter, it is not clear if patients were included in the analysis more than once.
- It is not stated when the data were collected
- It is not clear over what time period the data reported in Table 10.15.2 were accrued. As the cycle length of the Abbott model is 3 months, we assume that the data in Table 10.15.2 also represent resource use and costs over 3 months
- No SEs or other measure of uncertainty are shown.

Table 10.15.2 Resource use by HAQ band [235]

HAQ band	*Inpatient days*	*Joint replacement procedures*	*Total Cost (IQR)*
0.0 -0.5	0.26	0.00	£121 (59-173)
0.5 -1.0	0.13	0.01	£77 (43-109)
1.0 -1.5	0.51	0.02	£269 (141-382)
1.5 -2.0	0.72	0.03	£388 (206-550)
2.0 -2.5	1.86	0.04	£909 (459-1295)
2.5 -3.0	4.16	0.05	£1945 (958-2778)

* Uncertainty is not reported around these estimates

Based on these resource use data and published unit costs, Abbott calculated mean costs for each HAQ band. The "IQR" estimates are based on the variability of mean unit costs between NHS hospitals in the NHS reference cost database.

Abbott fitted an exponential curve through the mean costs of the 6 HAQ bands.

Direct cost = α * *exp*(β*HAQ)

The submission states that using the IQR, estimates of the values of α and β were calculated to be α = 54.1 (SE 15.31), and β= 1.237 (SE 0.051). The β coefficient can be interpreted as a unit change in HAQ on average leads to a 24% increase in expenditure.

These SEs for *alpha* and *beta* are based on the variability of unit costs between providers, and do not properly reflect the uncertainty in mean costs conditional on HAQ. This should include uncertainty in the mean number of inpatient days and joint replacement procedures conditional on HAQ, which is not given in the data on which this regression is based.

Pugner 2000[37]

Pugner et al reviewed cost studies undertaken between 1978 and 1998 in patients with RA in 8 countries (European, US and Canada). They found that costs tended to increase more than proportionately to changes in HAQ, consistent with the exponential cost function used by Abbott. However, the data they present appear to be charges rather than costs and so are not suitable to use unadjusted in the UK setting.

Michaud et al 2003[43]

This is a longitudinal study of 7527 patients completing a total of 25000 semi-annual (six-monthly) questionnaires from Jan 1999 to December 2001 in the US. The study design and analysis have several features that suggest a high internal validity though it is difficult to establish the degree of generalisability to the UK.

- Patients were recruited from the practices of US rheumatologists. Patients enrolled in the database as part of pharmaceutical company sponsored registers were excluded from this study
- The study is prospective, that is, HAQ was measured first and subsequently health service use
- The data were collected during the era when biologics were licensed and entering clinical practice. About 25% of patients used biologic drugs
- Direct costs are given in three categories: “outpatient”, including health worker visits, medications, diagnostic tests and procedures, “hospital costs” and “drugs” including DMARDs, biologics, NSAIDS, GI medications and non RA drugs.
- The price year is given (2001)
- All direct medical costs are included, regardless of the payer. This is important because almost all medical expenditures are covered by the NHS in the UK. The paper presents data stratified by health insurer and for uninsured patients to allow the effect of financing on expenditures to be assessed.
- The study reports costs not charges
- The analysis is based on primary data, allowing accurate estimation of uncertainty of the mean coefficients
- The analysis uses generalized estimating equations, which accounts for the panel structure of the data and repeated measurements on the same individuals

- The analysis uses multiple regression allowing control for other factors
- Both log-linear and linear models of the effect of HAQ on costs were undertaken.

The results are shown in Table 10.15.3 for the mean direct costs, and the effect of HAQ on direct costs estimated in the multiple regression.

Table 10.15.3 Mean (SE) semiannual drug, hospital and procedure costs in RA (US$, 2001)[43]

	Drug costs		Hospital costs		Outpatient costs	
Beta coefficient from multivariable analysis(*)						
	Mean	SE	Mean	SE	Mean	SE
HAQ	434	43	325	46	112	14
2001 direct medical costs for 7,527 RA patients, by cost type (per 6 months)						
	Mean	SE	Mean	SE	Mean	SE
6 month cost	3162	38	786	31	770	10

(*) Beta coefficients represent the expected difference in costs for a 1-unit difference in the predictor variable. Clinical variables are "lagged" and therefore represent costs that occur in the 6 months following the clinical assessment.

The currency conversion index (purchasing power parity, 2008) is US$ = 0.6542 GBP (OECD 2009)[233], and the UK health sector pay and prices inflation factor from 2001 to 2008 is 1.31[234]. Given these conversion indices, hospital and outpatient costs as a function of HAQ are

- Change in 3 month hospital cost for a 1 unit change in HAQ = £139 (SE £20)
- Change in 3 month outpatient cost for a 1 unit change in HAQ = £48 (SE 6)

There are limitations to the generalisability of these data to the UK.

Resource use is influenced by the type of insurance held by the patient and is thought to be greater in fully insured individuals in the US than the average in the UK. Michaud found that for a given HAQ score, semi-annual costs were $590 lower for drugs, $328 lower for hospital services and $235 lower for outpatient services for those having no insurance compared with similar individuals with private insurance, independently of HAQ. Income also influenced expenditure on outpatient procedures in the US independently of HAQ.

Michard found health indicators such as fatigue and depression, and other clinical indicators such as the RADAI score influenced expenditure on outpatient procedures, independently of HAQ. These are not measured in the current decision model. Relative unit costs may differ in the US from the UK. If so, deflating or inflating by a constant conversion rate might not reflect expenditure patterns in the UK. Michaud lists the unit costs in 2001 as $49.50 for a

physician visit, $688 for a gall bladder procedure and $4083 for hospitalisation for conditions involving major joints of the lower extremity. In the UK, a specialist visit costs £253 (TCLFUSFF 313), a gall bladder day case procedure costs £1389 (TDC GA10B) and major foot procedures £2963 (TEI HB31Z). Although it is difficult to match US DRGs with UK HRGs, these data suggest that unit costs of outpatient and day-case procedures may be more expensive relative to inpatient procedures in the UK than in the US

The data do not include use of community nursing and nursing home services which could be relevant to those with very severe disability.

Conclusion

This paper has reviewed published literature on the relationship between HAQ and costs of non-drug health care services. Table 10.15.4 compares the studies and their key strengths and weaknesses with respect to the decision model in the current appraisal.

Table 10.15.4 Cost studies and their key strengths and weaknesses

Study, Years undertaken	Country, sample size, patient group	Resources covered	Strengths	Weaknesses
Kobelt 2002 [42]Years 1987 – 1996	UK, 917?, RA	Inpatient, outpatient (?), community (?)	UK data	Dated, few patients in severe HAQ state, includes RA drug costs, analysis poorly reported, no SE.
Abbott[235], Years unknown	UK, Sample size unknown, IP	Inpatient	UK data	Analysis poorly reported, incorrectly calculated SE
Bansback 2006[171], Years unknown	UK, 917?, RA	Inpatient, outpatient (?), community (?)	UK data	As Kobelt, incorrectly calculated SE
Michaud 2002[43], Years 1999-2001	US, 7527, RA	Inpatient, outpatient, diagnostic tests	Analysis based on IPD and clearly described, drugs separately reported	US data

IPD. Individual patients data. RA Rheumatic arthritis. IP Inflamatory polyarthritis

The study by Michaud has the highest internal validity, and appears to be the only study to correctly estimate standard errors from the primary data, taking account of repeated measures on the same individuals. Michaud estimated (in 2008 UK currency)

- Mean change in 3 month hospital cost for a 1 unit change in HAQ = £139 (SE £20)
- Mean change in 3 month outpatient cost for a 1 unit change in HAQ = £48 (SE 6)
- Mean change in 3 month total cost for a 1 unit change in HAQ = £187 (SE 21)

The main limitation of these data for the decision model is that differences between the US and UK health care systems limit the generalisabilty of these data to the UK.

The UK studies are poorly reported, and therefore it is difficult to be assured of their validity and precision. Based on the data in Kobelt 2002[42], Bansback estimated (in 2008 UK currency)

- Mean change in 3 month total cost for a 1 unit change in HAQ = £103 (SE 67)

The mean costs per unit change in HAQ estimated by Michaud et al are greater than those estimated by Bansback et al 2006, and the standard errors considerably smaller. However, given the limitations of the Bansback analysis, these data are not easily comparable. It is unclear whether the Kobelt 2002 data include outpatient costs or not, whether the adjustment to the Kobelt data for DMARD costs is correct, whether the Kobelt data includes costs for the most severe patients, the price year of the Bansback regression is not stated and the standard errors have not been calculated from the individual patient data in the Bansback regression.

Despite these limitations, the mean coefficient represents a useful approximate linear relationship between HAQ and health service costs that is generalisable to the current decision model. The base-case decision model will use a linear relationship between HAQ and direct hospital and outpatient costs estimated from Bansback. Drug costs will be estimated separately in the decision model. The intercept is not important to the decision model because it applies to all health states and all treatments in all cycles of the model. The Michaud estimate and the Abbott estimate will be used in a sensitivity analysis.

10.16 Impact of psoriasis on costs

Introduction

This paper describes the impact of psoriasis on health service and social care costs. These estimates will be used in the decision model to predict health service costs over the patients' lifetimes.

Psoriasis is a chronic skin disease that can seriously impair patients' quality of life. Treatment often leads to a period of remission after which further treatment is necessary. Therefore the costs of psoriasis treatments can be substantial. A wide range of treatments are available including topical treatments, systemic drugs and photo(chemo)therapy.

Methods of literature search

A rapid literature search was carried out of the following sources:

- evidence presented to previous NICE appraisals of psoriatic arthritis and psoriasis treatments,
- the manufacturers' submissions to the current appraisal,
- Pubmed in October 2009 with the search string: "costs psoriasis"

To be used in the decision model, estimates were needed of NHS health and/or social care costs according to the severity of psoriasis, for example, by PASI score, or expected costs of controlled and uncontrolled psoriasis according to some response criterion such as PASI 75. Ideally the estimates of costs would be based on prospectively collected data on resource use in individual patients, rather than expert opinion. Data should be from the UK or a country with a similar universal, publicly-financed health care system.

Results of literature search

Most estimates of costs or resource use in the literature were based on expert opinion. A previous model of psoriasis treatments (Woolacott et al 2006)[169] assumed one inpatient stay per year for patients with non-response of biologic therapy based on expert opinion. The manufacturers' submissions from Abbott and Schering-Plough in the current appraisal of biologic therapies for PsA also estimated the costs of managing psoriasis, based on expert opinion. Abbott [174] estimated that costs of managing psoriasis varied from £153 per 6 months for a PASI score of about 1.5, £934 for a PASI score of 9, £859 for a PASI score of 15, and £1003 per 6 months for a PASI score of 40. Schering-Plough[175] estimated 3-monthly costs of

managing psoriasis as £167 per PASI point if phototherapy was used and £53 per PASI point if phototherapy was not used (See section 6.1). Two other economic evaluations of psoriasis treatments [236, 237] made similar assumptions to Woolacott et al 2006 based on expert opinion. Colombo et al[238] found the mean cost for patients with moderate plaque psoriasis (PASI $\leq$ 20) was €5,226.04, while the mean cost for patients with more severe disease (PASI > 20) was €11,434.40 per year in Italy in 2004. Marchetti estimated a year of fluocinonide therapy for mild-to-moderate plaque psoriasis (<20% of body surface area) would cost an average of $3394 in the US at 1998 prices, corresponding to £788 per 3 months at 2008 UK prices[239].

Two studies were found that estimated costs in controlled and uncontrolled patients with moderate to severe psoriasis based on prospectively collected individual patient data. Hartman et al [191]conducted a RCT in the Netherlands comparing day-case dithranol treatment, UVB therapy and inpatient dithranol treatment for 219 patients with a mean PASI at baseline of 15.3 (SD 6.9) and a mean body surface area of 21% (SD 13.8%). Patients did not receive biologic therapy in the RCT. Resource use data were collected on drugs, UVB sessions, consultations, nursing time, inpatient days, outpatient visits, primary health care and time lost from normal activity. Hartman et al defined 'treatment success' as a reduction of the baseline area of at least 90% during the treatment period, and 'relapse' as a return of 50% or more of the baseline area of psoriasis. Hartman et al report the numbers of patients who fail initial treatment, the number with initial success but relapse during the year, and the number who have 1 year remission.

The results of Hartman et al are shown in Tables 10.16.1 and 10.16.2

Table 10.16.1. Direct health-care costs estimated by Hartman et al [191] (Euros, 1998 prices)

	Initial treatment Mean; median (IQR) €	*Per month without relapse Mean (€)*	*Per month after relapse Mean(€)*
Day-case	765; 723,(554-988)	19	264
UVB	600; 585,(458-744)	5	219
Inpatient	6823; 6380,(5200-8519)	25	220

Table 10.16.2 Outcomes at 1 year estimated by Hartman et al, [191] excluding patients lost to follow up

	N	*Pr (treat fails)*	*Pr(initial success then relapse within 1 yr)*	*Pr (1 year remission)*
Daycase	94	0.37	0.24	0.39
UVB	70	0.41	0.35	0.25
Inpatient	52	0.09	0.65	0.26

Poyner et al [190] recorded private expenditures and NHS costs (GP consultations and treatments) for 272 patients with mild-to-moderate psoriasis after a 12-week course of either calcipotriol or dithranol. Mean healthcare expenditure by the NHS over 6 months was £55.61 at 1999 prices (£79 at 2008 prices). The cost of treating psoriasis (excluding the initial course of treatment) was greater to the patient than to the NHS.

The mean NHS cost of an outpatient session of phototherapy is £116 [189]. Guidelines suggest patients typically undergo 4-10 sessions (National Psoriasis Foundation, accessed 22 November 2009. http://www.psoriasis.org). 6 sessions would cost £636.

Estimate of costs of psoriasis in the decision model

The decision model requires the health service costs of patients who do not use biologic therapies, or those whose psoriasis does not respond to biologic therapy, according to severity of psoriasis at baseline. Many of the studies in the literature review concluded that costs vary by baseline severity, though there does not appear to be a uniform classification of mild, moderate and severe psoriasis across the different studies, with some using PASI, some DLQI and others the percentage of body surface area. Reich (2007) defines PASI>10 or BSA > 10% as 'at least moderate', and PASI≤10 as 'mild-to-moderate'[194].

For 'moderate-to-severe' patients, we assume that 'treatment responders' to biologic therapy, as measured by PASI 75, incur the monthly costs of patients in remission estimated by Hartman et al[191]. The initial treatment cost of UVB therapy estimated by Hartman is very similar to NHS Reference Costs for England, indicating these data are likely to be generalisable to the UK. Patients who are not using biologic therapy, or not responding to biologic therapy, will undergo one course of UVB treatment per year. Of these, those that fail UVB treatment incur subsequent monthly costs estimated by Hartman for patients after relapse. Those that initially succeed but relapse during the year are assumed to be in remission for 6months.

We choose UVB because it is a widely used therapy for moderate-to-severe psoriasis in the UK. Evaluating the most effective and cost-effective psoriasis treatment for patients who are not using biologic therapy or in whom biologic therapy is ineffective is beyond the scope of this study. We use the costs of inpatient dithranol as a sensitivity analysis.

The currency conversion rate in purchasing power parity is $= €0.883 and $=£0.654(OECD 2009[233]), and the inflation index from 1998 to 2008 is 1.42(PSSRU[234]).

The mean cost of UVB in 2008 UK prices is

- Initial treatment = 600 * 1.42 / 0.883 *0.654= £632
- Per month without relapse = 5 * 1.42 / 0.883 *0.654= £5
- Per month after relapse = 219 * 1.42 / 0.883 *0.654= £231

Given these data, we estimate the annual cost for each health state following UVB as follows:

- Annual cost if treatment succeeds=632 + 12*5= 696
- Annual cost if treatment relapse at 6months =632 +6*5+6*231=2099
- Annual cost if treatment fails=632+ 12 *231= 3402

The weighted mean annual cost if UVB treatment is given is therefore

- Mean annual cost = 3402* 0.41 + 2099* 0.35 + 696* 0.25 = £2262

The annual cost if the psoriasis were controlled by biologic drugs and no UVB treatment were given would be 12 *5 = £63

The mean costs of moderate-to-severe psoriasis used in the decision model per 3 month period are

- For patients using biologics and achieving PASI 75 response: £63/4 = 16(SE 1)
- For patients not achieving PASI 75 response from using biologics:£2262/4=566 (SE 25)
- For patients not using biologic therapy: £2262/4=£566 (SE 25)

The standard errors are calculated from the inter-quartile ranges given in Hartman assuming normal distributions for costs. The costs of biologic therapies and the costs of treating disability are estimated separately in the decision model. If it is assumed that patients without biologics or without response of biologics will undergo one course of inpatient therapy per year instead of UVB, the cost increases to £8532 per year or £2133(SE 93) per 3 month period.

For 'mild-to-moderate' patients, the treatment cost estimated by Marchetti [239](£788 per 3 months) is US data and likely to overestimate the cost in the UK. We assume patients with mild-to-moderate psoriasis who are not using biologic therapy or are uncontrolled by biologic therapy undergo one course of UVB therapy per year, costing £636[189]. The mean cost after treatment (averaged over responders and non-responders) is estimated from Poyner et al[190]. The total cost over the year is 636+2*79 = £794

The mean costs of mild-to-moderate psoriasis used in the decision model per 3 month period are

- For patients using biologics and achieving PASI 75 response: £16 (SE 1)
- For patients not achieving PASI 75 response from using biologics:£794/4=£198(SE 9)
- For patients not using biologic therapy: £198 (SE 9)

Conclusion

This paper describes the impact of psoriasis on health service costs for patients using biologic therapy and not using biologic therapy. The estimates used in the base-case decision model for mild-to-moderate patients are based on UK resource use and cost data. Costs are based on the results of a Dutch RCT for moderate-to-severe patients. The health system in the Netherlands is a social insurance system, but results are likely to be generalisable to the UK. This analysis does not account for adverse effects of repeated psoriasis treatments such as skin cancers.

10.17 Estimation of the effect of HAQ and PASI on utility in the decision model

Introduction

Clinical benefit is captured in the decision model by estimating expected HAQ and PASI at each time point at each state in the model (on and off biologic drugs). This appendix describes the relationship between HAQ, PASI and utility (a preference-based measure of health related quality of life).

Methods

Section 6.1 describes the Assessment Groups critical review of the manufacturers' submissions to the current appraisal. Each company analysed the relationship between HAQ, PASI and utility in a different way. It was difficult to assess whether differences in these results arose from differences in the primary data or from the chosen method of analysis. Consequently, the AG requested that each company estimate a similar regression analysis on their data, to assess whether results were comparable (Appendix 10.6). The AG requested that the analysis should be an ordinary least squares regression of utility versus HAQ, PASI and an interaction term HAQ*PASI.

Results

All three manufacturers re-analysed their data and the results are shown in Table 10.17.1

Table 10.17.1. Results of linear regressions of utility versus HAQ, PASI and HAQ x PASI

	Coefficients					Variance-covariance matrices				
Wyeth										
	Mean	SE	z	P>z			Intercept	HAQ	PASI	HAQ x PASI
Intercept	0.895	0.007	128.652	0.000		Intercept	0.000048430			
HAQ	-0.295	0.008	-37.157	0.000		HAQ	-0.000030080	0.000062880		
PASI	-0.004	0.000	-9.039	0.000		PASI	-0.000001640	0.000000947	0.000000207	
HAQ x PASI	0.000	0.000	-0.669	0.504		HAQ x PASI	0.000001311	-0.000002207	-0.000000136	0.000000183
Schering-Plough										
	Mean	SE	z	P>z			Intercept	HAQ	PASI	HAQ x PASI
Intercept	0.871	0.001	1126.782	0.000		Intercept	0.000000598			
HAQ	-0.249	0.001	-348.431	0.000		HAQ	-0.000000422	0.000000511		
PASI	-0.002	0.000	-25.447	0.000		PASI	-0.000000037	0.000000027	0.000000010	
HAQ x PASI	0.000	0.000	0.741	0.459		HAQ x PASI	0.000000026	-0.000000030	-0.000000007	0.000000006
Abbott										
	Mean	SE	z	P>z			Intercept	HAQ	PASI	HAQ*PASI
Intercept	0.886	0.018	48.692	0.000		Intercept	0.000329500			
HAQ	-0.232	0.025	-9.343	0.000		HAQ	-0.000292000	0.000614600		
PASI	-0.003	0.002	-1.667	0.096		PASI	-0.000014000	0.000012900	0.000002195	
HAQ x PASI	-0.004	0.002	-1.950	0.051		HAQ*PASI	0.000012600	-0.000033000	-0.000001607	0.000004094

Conclusion

The results of these regressions are similar in all datasets. This indicates that the relationship between HAQ, PASI and utility is stable across independent clinical trials, and gives us confidence that the results are generalisable to the general population.

The interaction between HAQ and PASI does not reach statistical significance at the 5% level in any dataset but is very close to the 5% level in the Abbott data.

The selection of one of these regressions to use as the basecase in the York decision model is rather arbitrary. We use the Wyeth results as the basecase and other functions as sensitivity analyses.

10.18 Estimation of PASI score for treatment responders in the decision model

Introduction

The Psoriasis Area and Severity Index (PASI) is a scoring system to evaluate baseline and response of therapy in psoriasis. The British Association of Dermatologists [168] recommend PASI 75 for measuring primary response of psoriasis in patients with psoriatic arthritis. PASI 75 is a binary outcome that indicates a 75% or greater improvement in PASI from baseline. RCTs commonly report this and other measures of response such as PASI 50 and PASI 90. Section 5.2 estimates the mean probability across all trials of achieving PASI 50, PASI 75 and PASI 90 for each biologic therapy and placebo using summary data from the RCTs.

These multivariate response indicators (PASI 50, 75 and 90) indicate the probability of achieving a *minimum* percentage improvement in PASI compared with baseline. However, the decision model requires the *mean* absolute or percentage change in PASI as an input parameter, given each type of biologic therapy and no therapy.

This appendix describes how the mean absolute change in PASI is calculated in the decision model.

Methods

We calculate the marginal probabilities of each mutually exclusive outcome:

$Pr(\%\Delta PASI<49) = 1\text{-}Pr(PASI\ 50)$
$Pr(50<\%\Delta PASI<74) = Pr(PASI\ 50)\text{-}\ Pr(PASI\ 75)$
$Pr(75<\%\Delta PASI<89) = Pr(PASI\ 75)\text{-}\ Pr(PASI\ 90)$
$Pr(90<\%\Delta PASI) = Pr(PASI\ 90)$

Figure 10.18.1 shows a segment of the decision tree for the psoriasis response and for psoriasis non-response for a given drug. $Pr(<PASI\ 50 | < PASI\ 75)$ indicates the probability of a change in PASI between 0 and 49%, given improvement of less than PASI 75, and is calculated as

$$Pr(<PASI\ 50 | < PASI\ 75) = Pr(\%\Delta PASI<49)/(1\text{-}Pr(PASI\ 75))$$

We know the improvement for this group is within the range zero to 50%, and in the base-case we (conservatively) assume that the relative improvement in PASI for this group is zero. For change in PASI between 50% and 74%, we assume the change is 50%. For a change between 75% and 89%, we assume the change is 75%, and between 90% and 100%, we assume the change is 90%.

Consequently, if baseline absolute PASI is P_0, the mean absolute change in PASI for those achieving a PASI 75 response (while on therapy) is

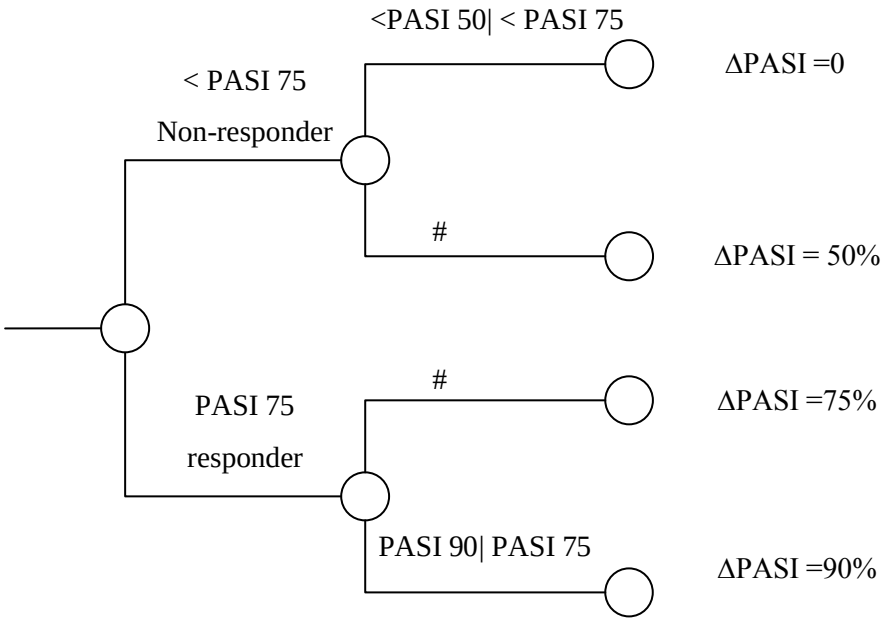
$$E(\Delta PASI \mid PASI\ 75) = P_0*\{0.75*Pr(75<\%\Delta PASI<89)+0.9*Pr(PASI\ 90)\}/Pr(PASI\ 75)$$

The mean absolute change in PASI for those not achieving a PASI 75 response (while on biologic therapy) is

$$E(\Delta PASI \mid< PASI\ 75) = P_0*\{0*Pr(\%\Delta PASI<49)+ 0.5*Pr(50<\%\Delta PASI<74)\}/(1-Pr(PASI\ 75))$$

Conditioning the change in PASI on PASI 75 allows the consequences to be explored of using different decision rules about whether to withdraw biologic therapy or not if a PASI 75 response is not achieved, or to withdraw if a PASI 75 response is achieved but a PsARC response is not achieved

Figure 10.18.1. Segment of decision tree showing the mean change in PASI for psoriasis response and psoriasis non-response



Sensitivity analysis

Simple sensitivity analyses will assume different values of the thresholds for the change in PASI, such as using the upper end of the range, or the mid-point. For example, for PASI response between 50% and 74%, we could assume that the change is 74%, or 57% (the mid point). Note that, a-priori, we have no reason to expect the distribution of percentage changes in PASI within a given range to be uniformly distributed within that range, and so we have no reason to expect the mid-point to better estimate the mean change than other values.

An alternative sensitivity analysis is suggested by data from the Abbott submission [174]. Abbott used regression to estimate the relationship between PASI response and the mean absolute change in PASI. Their results are reproduced in Table 10.18.1

Table 10.18.1 (Table A2.3 in Abbott[174]): PASI at 12 weeks dependent on patient demographics and type of response

Description	Covariate	Parameter estimate	Standard error	t Value	Pr > |t|
Intercept	α	0.36879	0.28977	1.27	0.212
Baseline PASI_t	β_1	1.01496	0.08344	12.16	<.0001
Baseline Age	β_2	-0.00461	0.00541	-0.85	0.3997
Gender (1= Male)	β_3	0.08901	0.10511	0.85	0.4032
Baseline PsA Duration	β_4	0.00075643	0.00666	0.11	0.9103
Whether on MTX (1=yes)	β_5	0.00433	0.10234	0.04	0.9665
Whether a PASI 50-75 responder	β_6	-0.85124	0.16655	-5.11	<.0001
Whether a PASI 75-90 responder	β_7	-1.13011	0.15625	-7.23	<.0001
Whether a PASI 90+ responder	β_8	-1.89522	0.18899	-10.03	<.0001
Treatment=biologic	β_9	-0.50235	0.1288	-3.9	0.0004

PASI_t = Transformed PASI = Log(PASI+0.5)

$PASI_{12} = \alpha + \beta_1 PASI_0 + \beta_2 Age_0 + \beta_3 Gender + \beta_4 Duration_0 + \beta_5 MTX + \beta_6 PASI\ 50\text{-}75_{12} + \beta_7 PASI\ 75\text{-}90_{12} + \beta_8 PASI\ 90+_{12} + \beta_9 Treatment$ (ii)

Results

Table 10.18.1 illustrates the calculation of the change in PASI for responders and non-responders using the probabilities of psoriasis response given in Section 5.2 and the assumptions in the methods section above. For convenience, these probabilities are shown again in Table 10.18.2.

Table 10.18.2. Predicted probabilities of psoriasis response and proportionate change in PASI for responders and non-responders

	Etanercept	Infliximab	Adalimumab	Placebo
Pr(PASI 50)	0.40	0.91	0.74	0.13
Pr(PASI 75)	0.18	0.77	0.48	0.04
Pr(PASI 90)	0.07	0.56	0.26	0.02
Percentage change in PASI for PASI 75 non-responders	13.7%	31.1%	24.0%	NA
Percentage change in PASI for PASI 75 responders	81.2%	85.9%	83.1%	80.6%

NA : the change in PASI for non-responders on placebo is not used in the decision model

Conclusion

On average, infliximab is predicted to give the greatest probability of a psoriasis response and the greatest change in PASI in both responders and non-responders. Adalimumab is second-most effective and etanercept is predicted to be the least effective in terms of psoriasis.

10.19 All cause mortality

Introduction

All cause mortality rates for a given age are higher in people with PsA than the general population. Wong et al found men attending a PsA clinic have a 65% greater mortality rate than the general population in Canada, and women 59% greater mortality[30]. A UK population-based study using the General Practice Research Database found 50% greater mortality in patients with severe psoriasis than the general population, and no change in this SMR after excluding patients with psoriatic arthritis, indicating that patients with psoriatic arthritis have similar mortality risk to those with severe psoriasis[240]. However, there is no clear evidence that biologic therapies change these mortality risks.

Published life tables give mortality risks in the general population for a given age and gender. However, it has been shown that in developed countries, all-cause mortality hazards increase at an exponential rate after the age of 40 years, and a Gompertz function closely approximates these hazards [241]. Using a parametric function instead of looking up the hazards directly from life tables requires fewer parameters in the decision model and arguably saves computation time. Furthermore a parametric hazard function might allow more accurate interpolation of the hazards between years if the cycle length of the model is less than one year.

This paper describes the estimation of the Gompertz function to predict all cause mortality hazards.

Methods

In the Gompertz function, mortality hazards $h(x)$ at age x (where $x \geq 40$) are:

$h(x) = R \exp(a\,x)$, where R and a are parameters.

Taking logs,

$\log(h(x)) = \log(R) + a\,x$

This linear relationship is straightforward to estimate from life-table hazards using ordinary least squares regression of log-hazards vs age. These hazards can be adjusted for the PsA population by multiplying by the standardised mortality ratio for the disease.

Results

The results of the regression of log life table hazards versus age in years are shown in Table 10.19.1 for the general population in men and women for the years 2006-2008.

Table 10.19.1. Results of regression of log(life table hazards) versus age in years in the general population aged 40 years or over

Men	*Mean coefficient*	*SE*	*95% CI*
Age	0.0946	0.00067	0.0932 to 0.0959
Constant (log R)	-10.257	0.046	-10.349 to -10.165
Adj R-squared	0.9965		
Women	*Mean coefficient*	*SE*	*95% CI*
Age	0.101	0.00067	0.0999 to 0.1027
Constant (log R)	-11.109	0.046	-11.203 to -11.017
Adj R-squared	0.9969		

Conclusion

The Gompertz function can estimate general population life table all cause hazards with a high degree of precision.

10.20 Sequential use of biologic therapy

Introduction

The base-case decision model assumes that patients who enter the model are 'biologic naïve', and that those who fail therapy have no further options and, consequently, receive palliative care only. In practice, it many patients who withdraw from their first biologic agent will switch to another[242]. It is potentially important that the decision model takes account of this option. Hence the model was extended to consider, as far as available evidence allows, the cost-effectiveness of sequential use biologics in patients who have failed on earlier biologic therapy.

This appendix describes the literature search and methods used to obtain the response and withdrawal parameters to undertake this modelling. The results of the cost-effectiveness analysis in the sub-group of patients who switch to another biologic drug are presented in Section 6.2.

Methods

The approach taken here is to consider the effectiveness and cost-effectiveness of alternative strategies for a sub-group of patients who have failed a first course of biologic therapy. For example, if etanercept had been tried and failed, the choice would be between a second trial with adalimumab or infliximab, or no further 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: (i) patients who has failed etanercept because of adverse events; and (ii) those who failed because of lack of efficacy. We do not make a distinction here between those who had complete lack of response (measured by PsARC at 3 months) and those who had secondary loss of treatment efficacy.

We search the clinical literature and publications from UK and other registers to find response and/or withdrawal rates from a second drug for patients in PsA or RA who failed a first drug because of lack of efficacy or adverse events.

The base-case decision model has two measures of initial response (PASI 75 for psoriasis and PsARC for arthritis) and an estimated rate of withdrawal after the first 3 months. Some of the

clinical literature report relative risks (such as hazard ratios) of failing a second biologic drug, compared to failing a first drug. We assume the odds of PsARC for a drug used as second line therapy are equal to the odds as first therapy (estimated by the evidence synthesis in Chapter 5), multiplied by the relative risk for failing second therapy vs first therapy. We make a similar assumption to estimate the hazards of withdrawal after 3 months for a second course of biologic therapy. Given that in the base-case model patients are not withdrawn for failing to obtain PASI 75, we assume the probabilities of PASI 75 in the second course of therapy are the same as in the first course. All other parameters of the model are the same as in the base-case.

Results of the literature search

A review the literature did not find any randomised controlled trials that had studied these subgroups. However, the review of publications from biologics registers described in Appendix 10. found 4 papers that included some relevant information about 2nd course biologic therapies.

Table 10.20.1 shows the results of 3 papers that estimated the probabilities of remaining on therapy ('persistence') in PsA patients for first and second courses of biologic drugs. In all the studies, the probability of persistence up to one year is lower for second biologic than first biologic. These papers did not report withdrawal for second biologic conditional on the reason for withdrawal from the first biologic. Gomez-Reino also estimated the rates of withdrawal for adverse events and inefficacy for each biologic. These data show that in all the biologic therapies at first course, patients tended to be more likely to withdraw for adverse events than inefficacy. Rates of withdrawal from infliximab when used as second line therapy tend to be higher than other drugs used as second line therapy. However, standard errors are not reported so this may be due to chance. Perhaps more importantly, these are not randomised data and patients cohorts are unlikely to be similar between the drugs.

Table 10.20.1. Probabilities of persistence up to one year or rates of withdrawal with first biologic drug and second biologic drug. The reason for withdrawal is shown if given in the paper

Course of treatment	*N starting*	*Number failed*	*% failed*	*Reason failed*	*Pr Survival 1 yr*
Coates 2007, UK, PsA patients					
First	60	14	23%	All reasons	NA
Second	12	7	58%	All reasons	NA
Saad 2009, UK, PsA patients					
First	566	NA		All reasons	0.82(0.79 to 0.85)
Second	178	NA		All reasons	0.74(0.71 to 0.78)
First	566	NA		Inefficacy	0.92(0.89 to 0.94)
Second	178	NA		Inefficacy	0.70(0.63 to 0.75)
First	566	NA		Adverse events	0.96(0.94 to 0.97)
Second	178	NA		Adverse events	0.76(0.69 to 0.81)
Gomez – Reino 2006, Spain, PsA patients					
First	289	55	19%	All reasons	0.87(0.83 to 0.9)
Second	15	8	53%	All reasons	0.81(0.65 to 0.9)
Gomez – Reino 2006, Spain, All chronic arthritis patients					
Course of treatment				*Reason failed*	*Rate of failure- per 100 patient years treated*
First, infliximab				Adverse events	6.5
First, infliximab				Inefficacy	4.7
Second, infliximab				Adverse events	32.7
Second, infliximab				Inefficacy	38.5
First, etanercept				Adverse events	3.8
First, etanercept				Inefficacy	3.6
Second, etanercept				Adverse events	6.1
Second, etanercept				Inefficacy	9.3
First, adalimumab				Adverse events	7.2
First, adalimumab				Inefficacy	3.2
Second, adalimumab				Adverse events	12.5
Second, adalimumab				Inefficacy	12.5

NA Not reported

Table 10.20.2 shows the result of one paper that reported hazard ratios for withdrawal from second course of therapy compared with the first course of therapy[195]. The paper distinguishes between outcomes for patients who start a second course of biologics after adverse events in the first course, and patients who start a second course of biologics following lack of efficacy in the first course. The data is for RA patients, rather than PsA, and is from patients in the UK BSR register who had at least 6 months follow up by the end of April 2005.

Table 10.20.2. Hazard ratios for withdrawal from second course of therapy compared with the first course of therapy. Source: Hyrich 2007[195]

Course of treatment	*N starting*	*number failed*	*% failed*	*Reason failed*	*HR for discontinuation of 2nd therapy, compared with rate for 1st therapy(*)*
First	6739	2360	35%	All reasons	
First	6739	841	12%	Inefficacy	
First	6739	1023	15%	Adverse events	
First	6739	496	7%	Other reason	
Second | inefficacy in 1st	503	78	16%	Inefficacy	2.7 (2.1-3.4)
Second | AE in 1st	353	33	9%	Inefficacy	1.2 (0.8-1.6)
Second | inefficacy in 1st	503	50	10%	Adverse events	1.1 (0.9-1.5)
Second | AE in 1st	353	71	20%	Adverse events	2.3 (1.9-2.9)

(*) Mean (95% CI)

Parameters in the decision model

There are 4 sets of parameters to estimate to implement the model for switching biologic therapy (Table 10.20.3). We assume the hazard ratios for failing a second biologic compared to failing the first biologic are the same for all biologics.

Table 10.20.3. Parameters to estimate in the decision model for switching biologics

		Reason for discontinuation of first course of biologic therapy	
		Inefficacy	Adverse event
Reason for discontinuation of second course of biologic therapy	Initial PsARC response (at 3 months), by drug *j*	$p.psarc_{j2}(1^{st}$ *inefficacy)*	$p.psarc_{j2}(1^{st}$ *AE)*
	Rate of secondary non-response or adverse event after 3 months	$p.long_2(1^{st}$ *inefficacy)*	$p.long_2(1^{st}$ *AE)*

Initial PsARC response given patient discontinued first course because of lack of efficacy

Based on the data in Table 10.20.2, we assume that if the first biologic agent was discontinued due to inefficacy, the odds of achieving a PsARC response in the first 3 months on the second agent was reduced on average 2.7 –fold (95% CI 2.1-3.4). Therefore if the odds of a PsARC response at 3 months in drug *j* used as first biologic are $o.psarc_{j1}=p.psarc_{j1}/(1-p.psarc_{j1})$ then the odds of a PsARC response at 3 months in drug *j* used as second biologic given the first was discontinued for lack of efficacy are :

$o.psarc_{j2}(1^{st}$ *inefficacy)* $= o.psarc_{j1}/2.7$

Initial PsARC response given patient discontinued first course because of adverse event

The probability of an initial PsARC response for the second agent, given the first was discontinued for an adverse event is unchanged, so :

$o.psarc_{j2}(1^{st}\ AE) = o.psarc_{j1}$

Withdrawal after first 3 month trial period given patient discontinued first course because of lack of efficacy

Based on the data in Table 10.20.2, we assume that if the first biologic agent was discontinued due to inefficacy, the risk of withdrawal after 3 months due to inefficacy was increased 2.7-fold. However, the odds of withdrawal due to adverse events was unchanged, given the 95% CI includes 1.

In Table 10.20.2, 6739 patients started a first biologic. Of these, 2360 patients withdrew, 841 (36%) for inefficacy and 1023 (43%) for adverse events. If the rate of withdrawal after 3 months from the first biologic agent for any reason is $p.long_1$, then the rate of withdrawal from the first biologic agent for inefficacy is $p.long_1$*0.36. We assume that the rate of withdrawal after 3 months for the second agent, given the first was discontinued for lack of efficacy, is:

$p.long_2(1^{st}\ inefficacy) = p.long_1$*0.36*2.7 + $p.long_1$*0.43+ $p.long_1$*0.21

Withdrawal after first 3 month trial period given patient discontinued first course because of adverse event

Given the data in Table 10.20.2, we assume that if the first biologic agent was discontinued due to adverse events, the risk of withdrawal from the second biologic due to adverse events was increased by 2.3 (95% CI 1.9-2.9). The overall expected rate of withdrawal after 3 months for the second agent, given the first was discontinued for an adverse event is:

$p.long_2(1^{st}\ AE) = p.long_1$*0.36+ $p.long_1$*0.43*2.3+ $p.long_1$*0.21

The hazard ratios in Table 10.20.2 will be entered into the model as probability distributions. The hazard ratio on a log-scale for continuing lack of efficacy has mean 0.993 (SE 0.120), and the hazard ratio on a log-scale for continuing adverse events has mean 0.832 (SE 0.106).

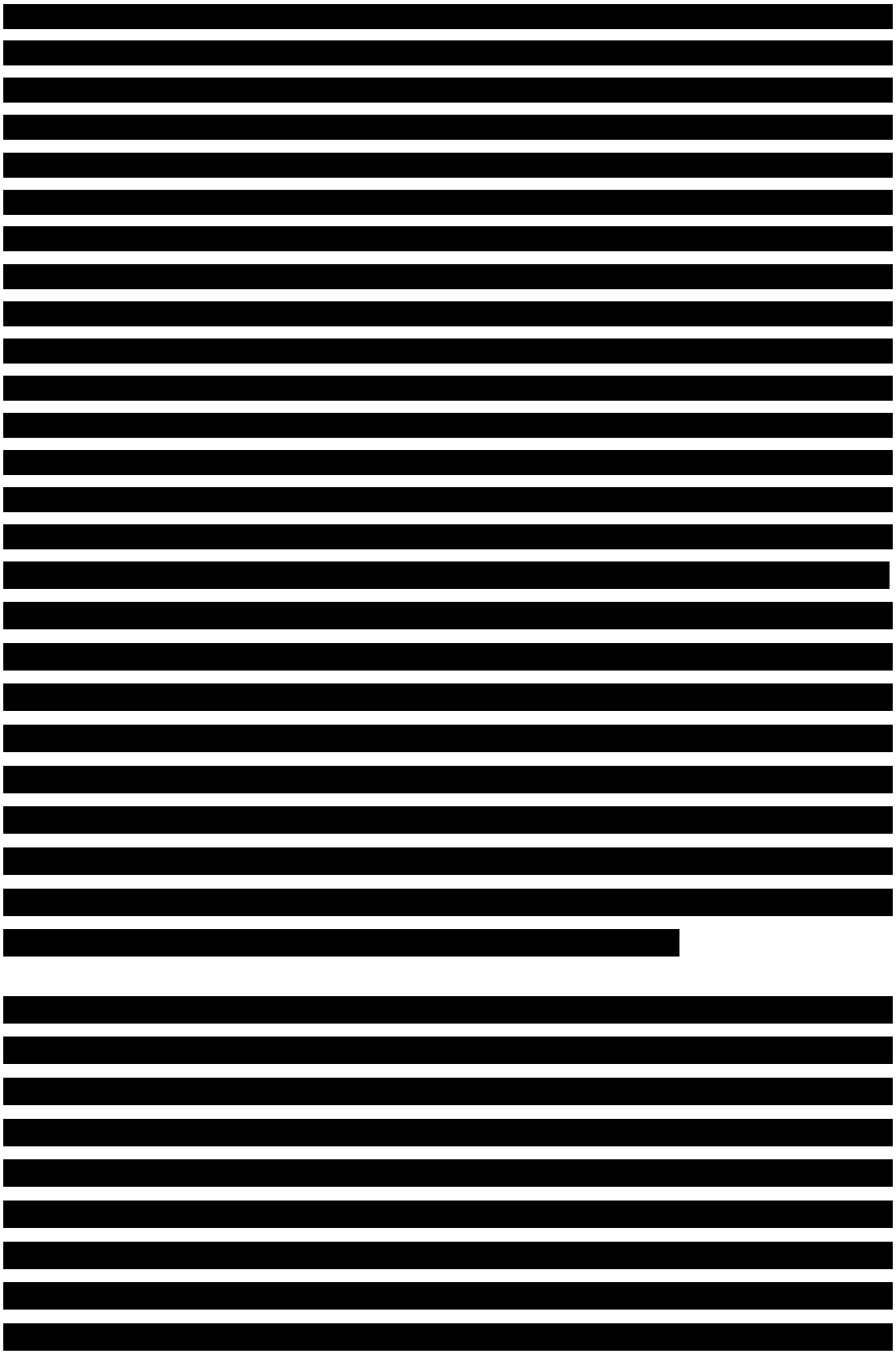
Conclusions

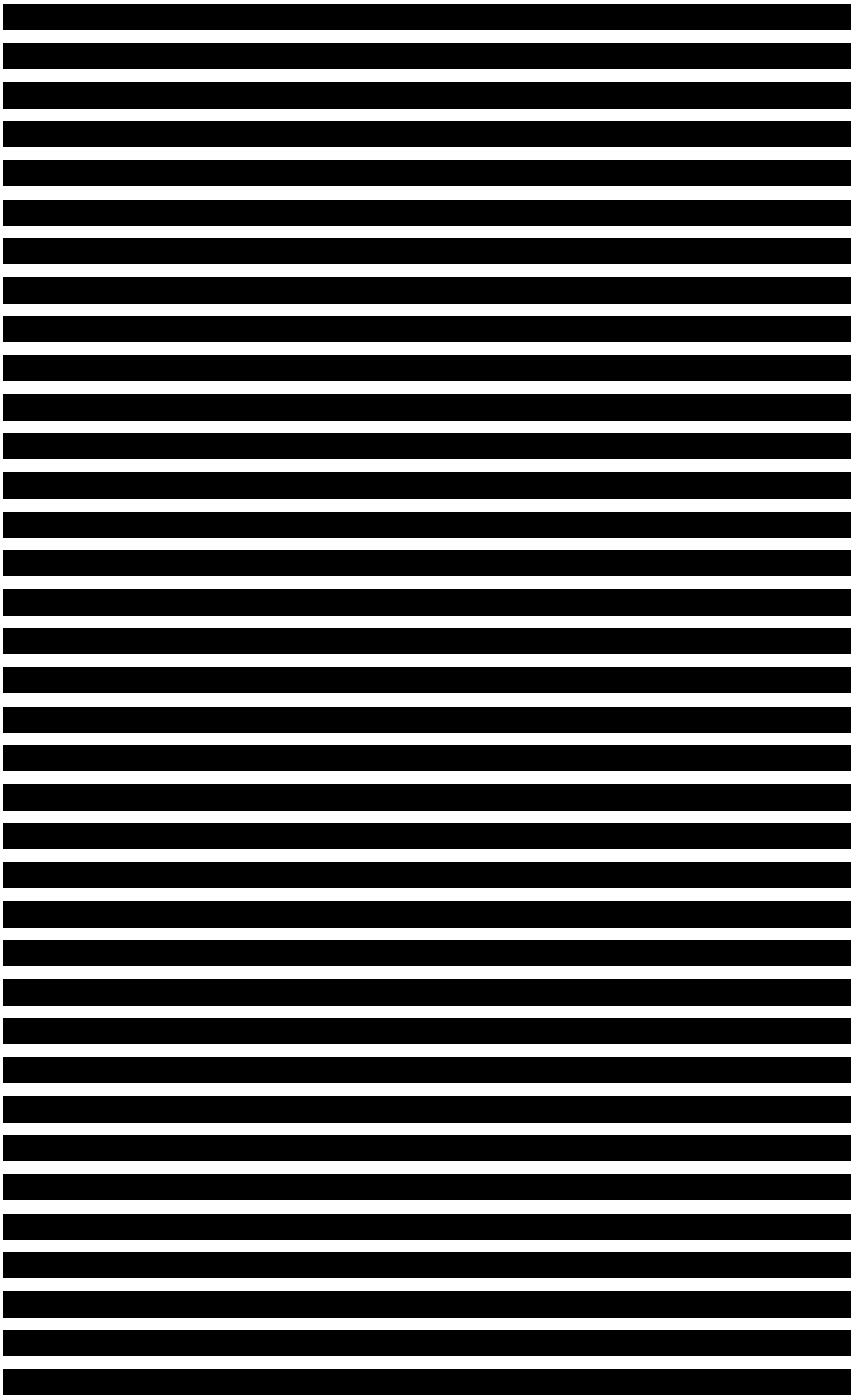
This subgroup analysis is necessarily exploratory, given the limitations of the data for outcomes after switching biologic therapies. These limitations include:

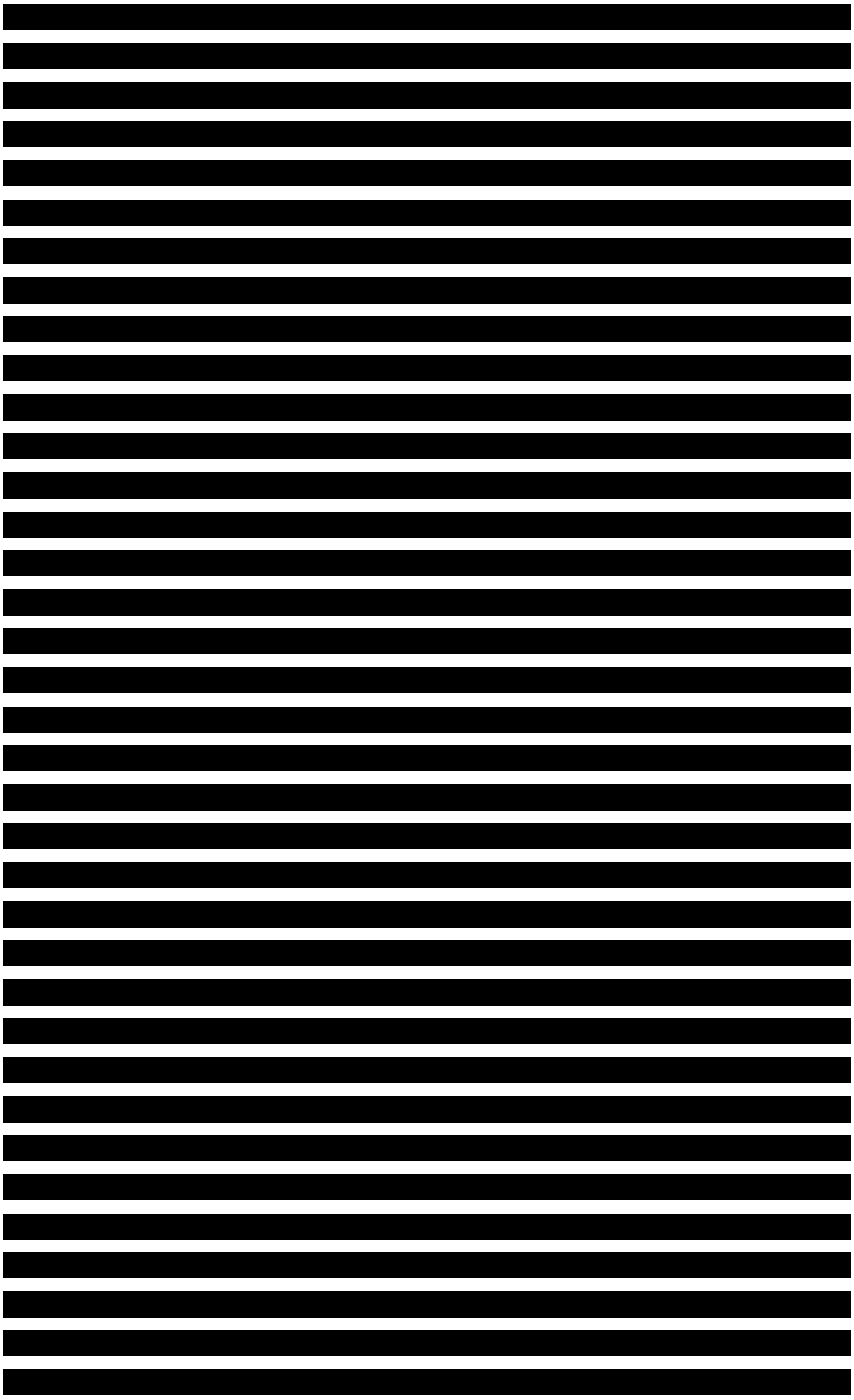
- The data on outcomes after switching comes from RA patients not PsA. Data of withdrawal by type of disease suggests there may be differences in withdrawal rates between RA and PsA [229, 243]. However, the data on outcomes after switching from PsA patients was not reported in sufficient detail for the decision model. We assume in the decision model that even if there are differences in absolute withdrawal rates between RA and PsA, the hazard ratios comparing withdrawal from first-line therapy with second-line therapy do not differ by disease.
- The data are from observational studies. Therefore there is the possibility of selection bias and other confounding factors. However, Hyrich [195] cautions that designing a randomised experiment for patients to receive a second agent on the basis of their outcome (inefficacy or toxicity) would present considerable practical and ethical difficulties. Therefore observational studies may be the best data that can be obtained.

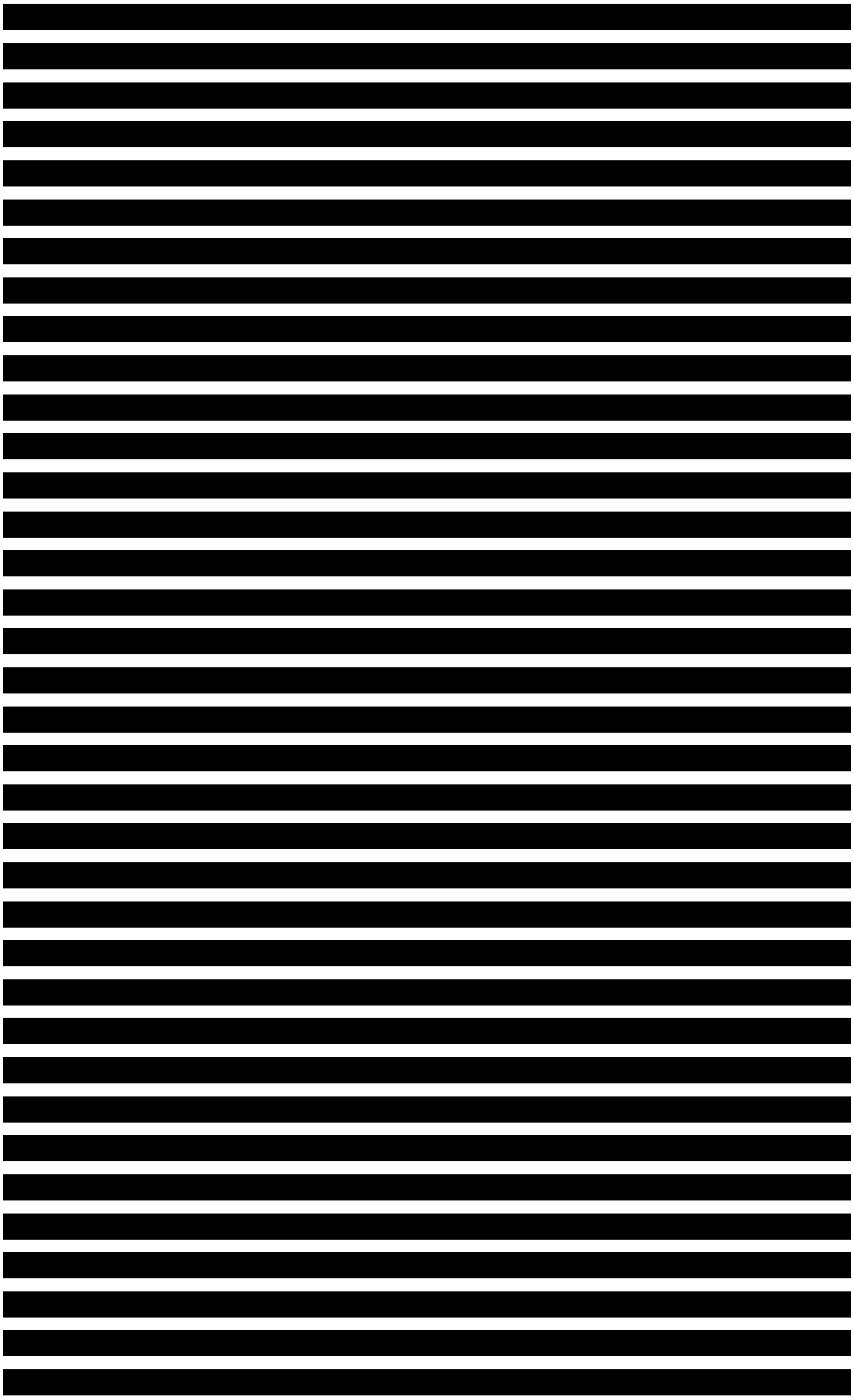
The data cannot differentiate between those who had complete lack of response (such as PsARC at 3 months) and those who had secondary loss of treatment efficacy. The decision model has therefore assumed the hazard ratios apply equally to both types of response.

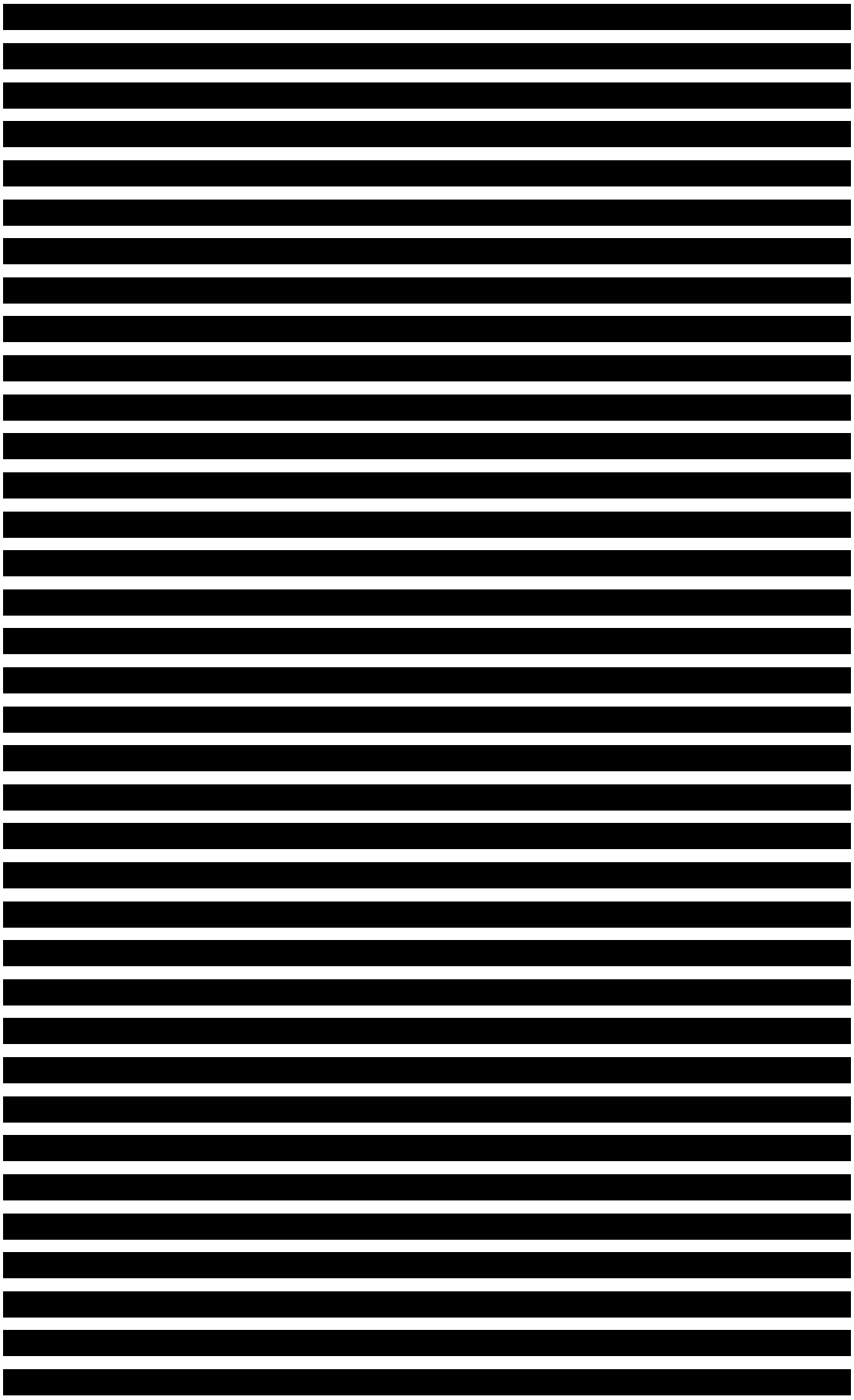
10.21 R programme for the York economic analysis

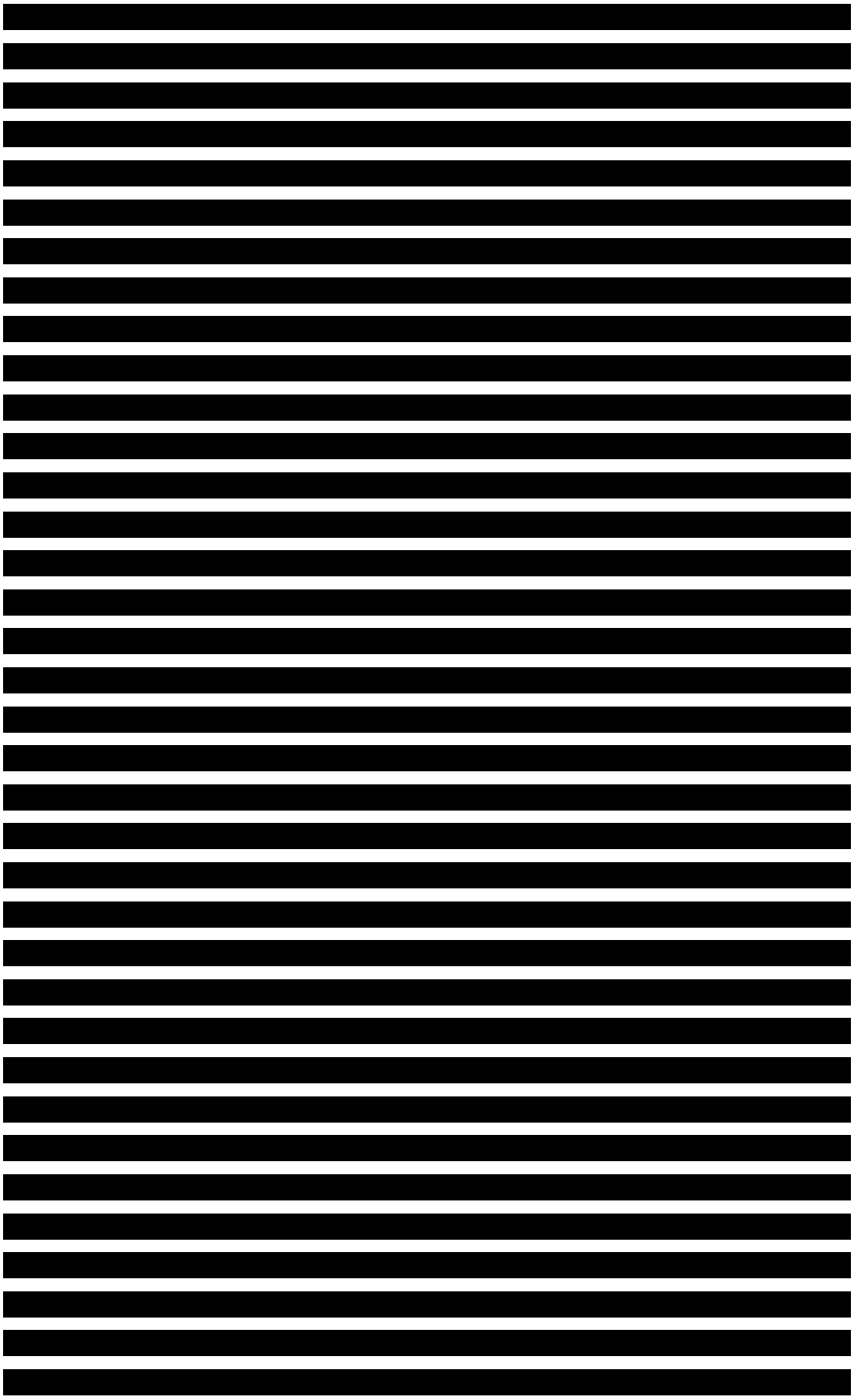


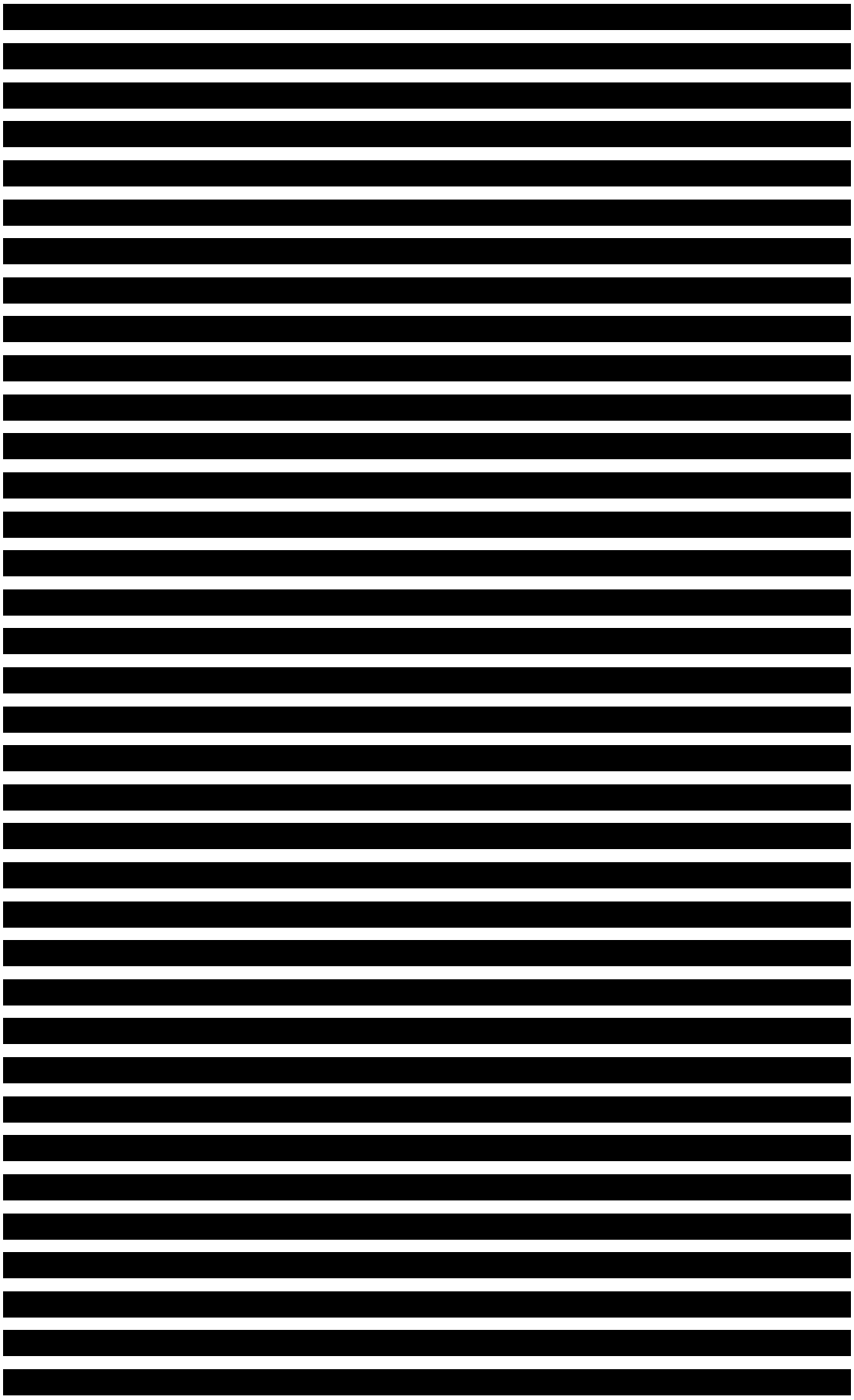


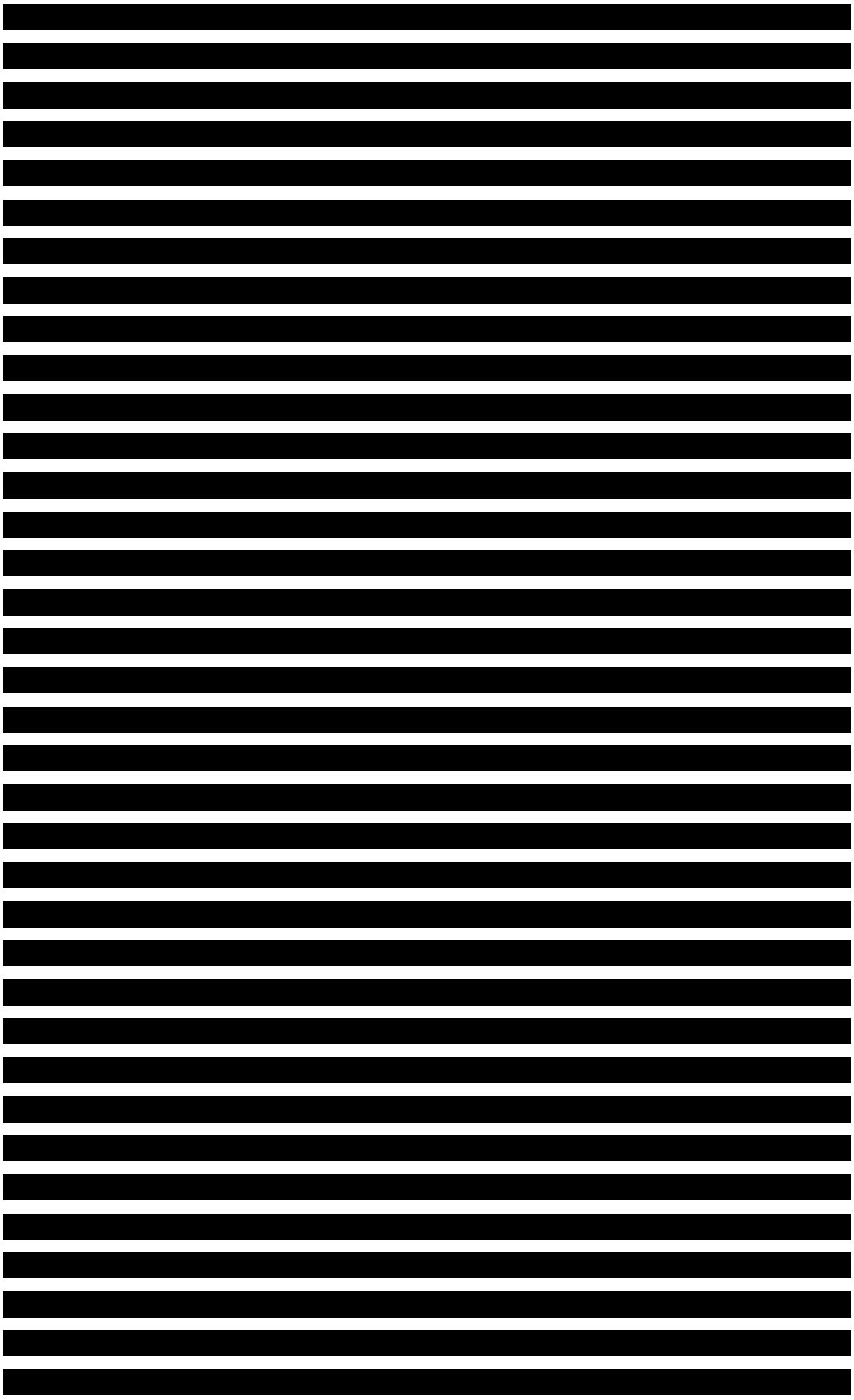


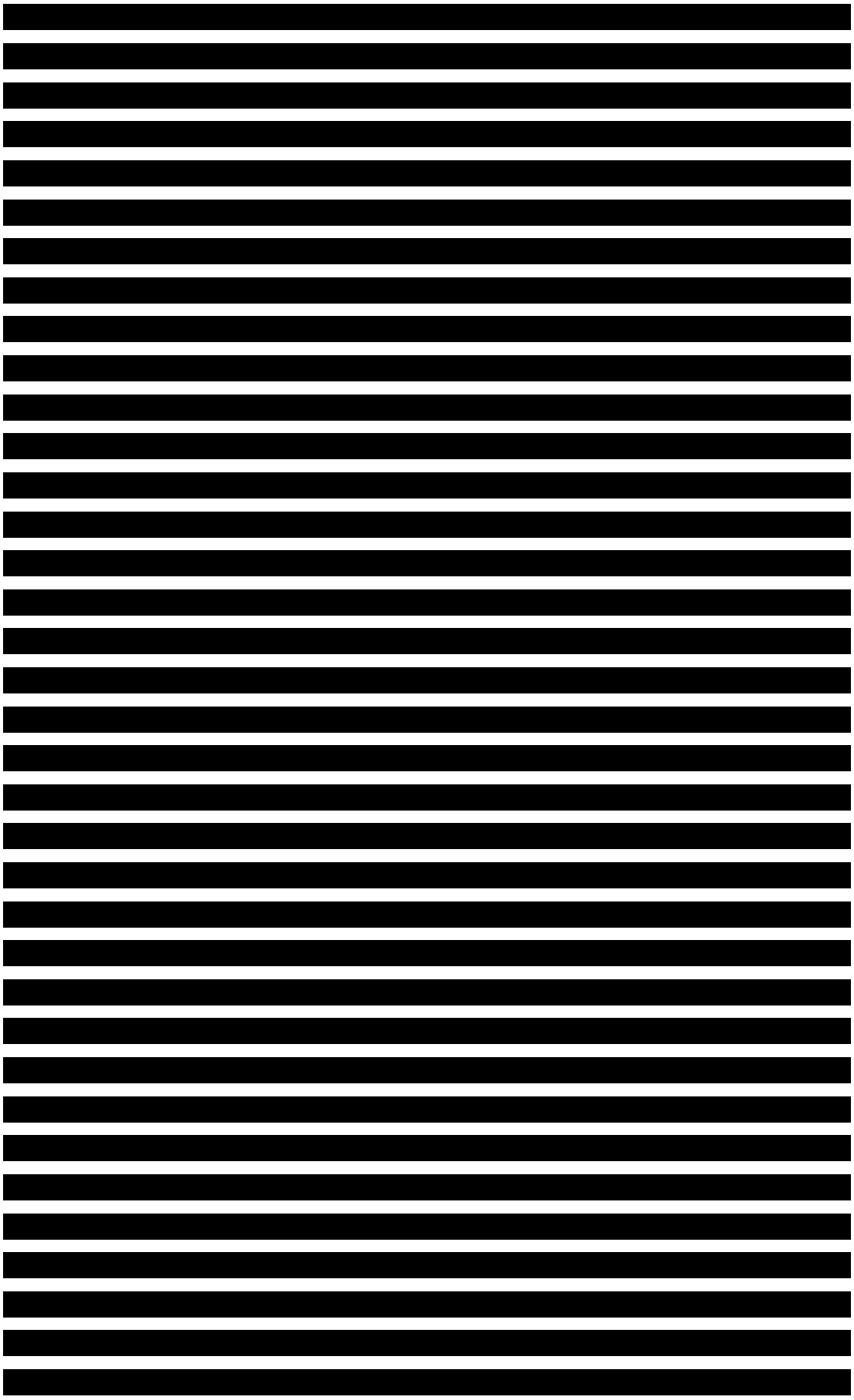


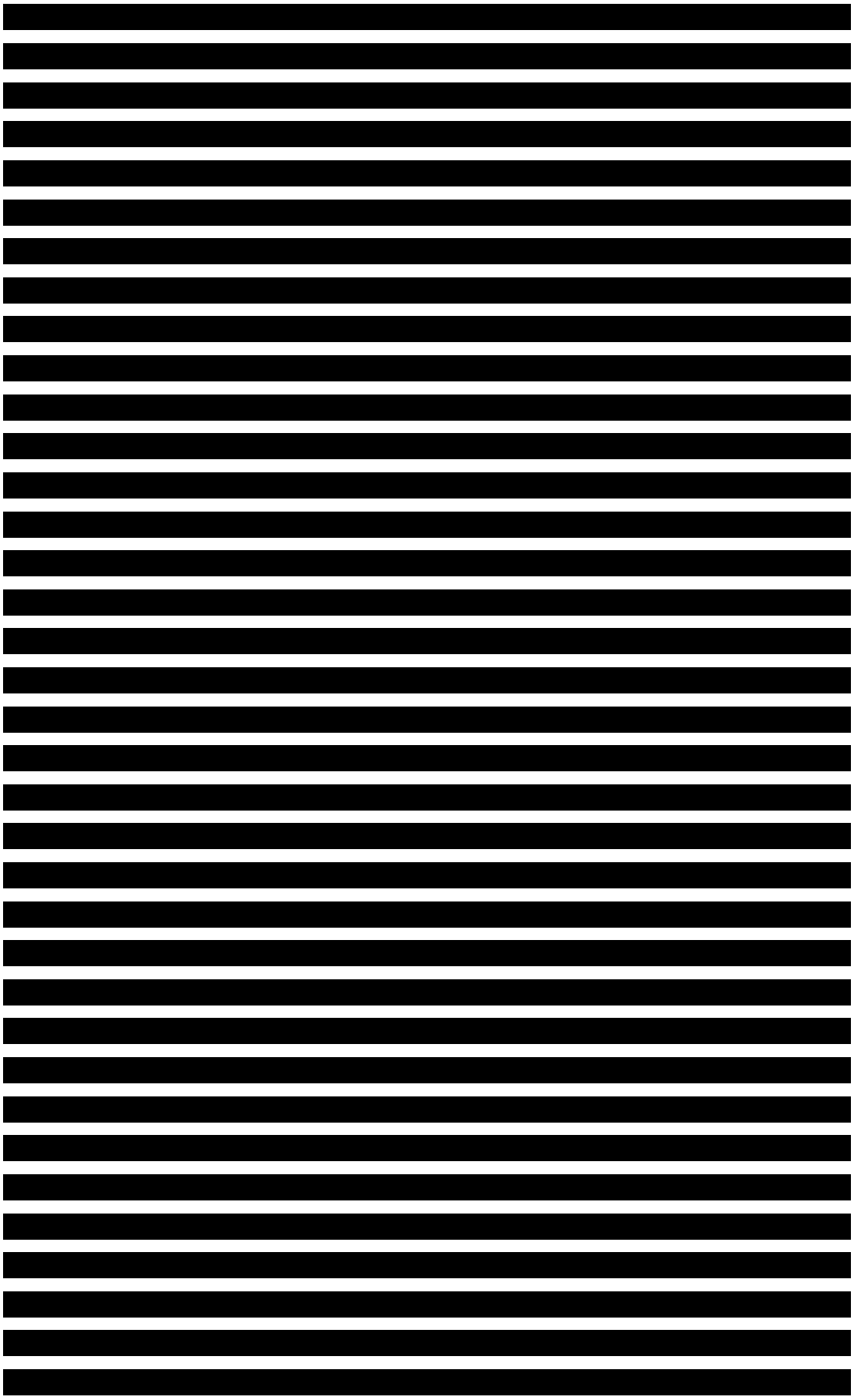


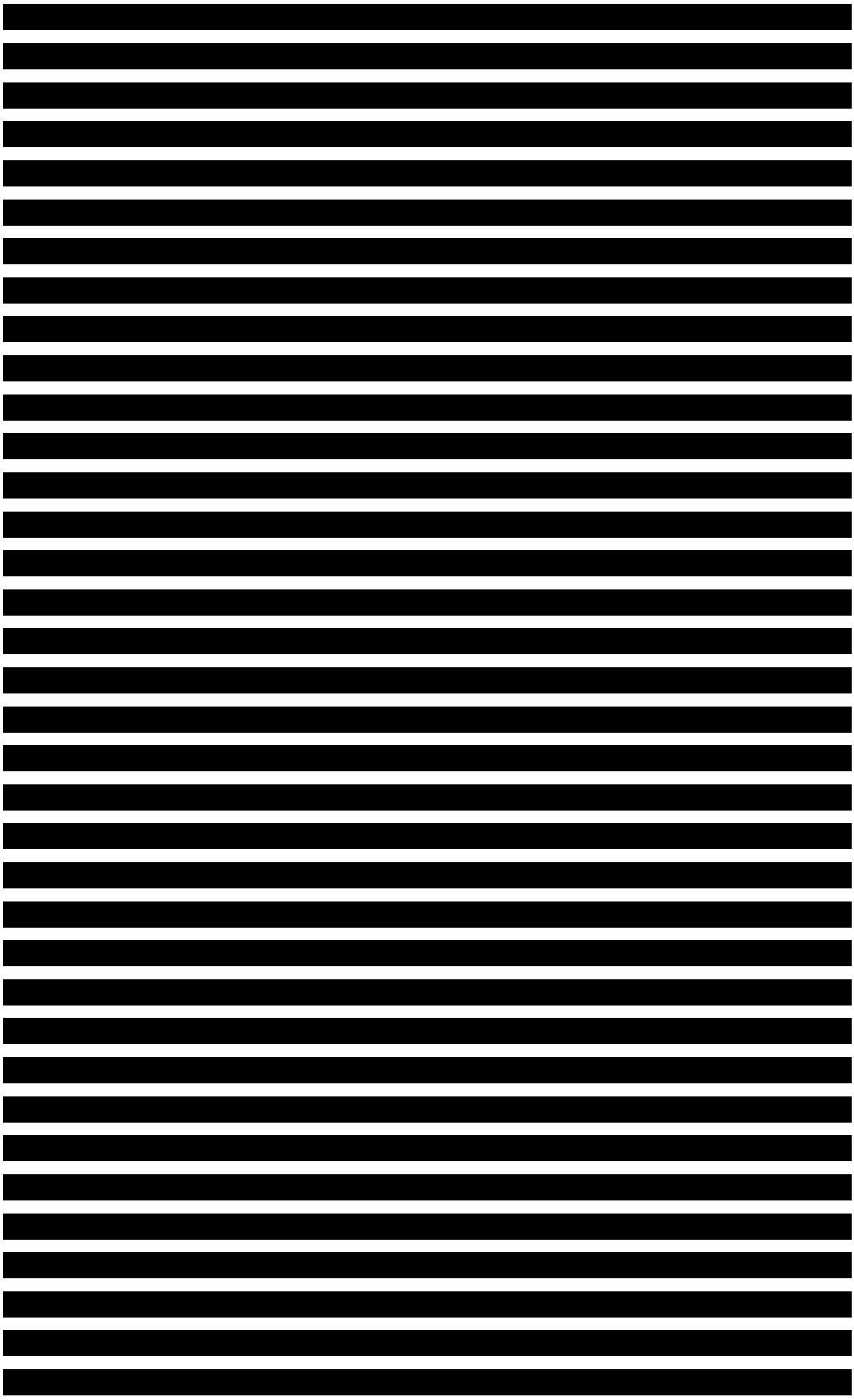


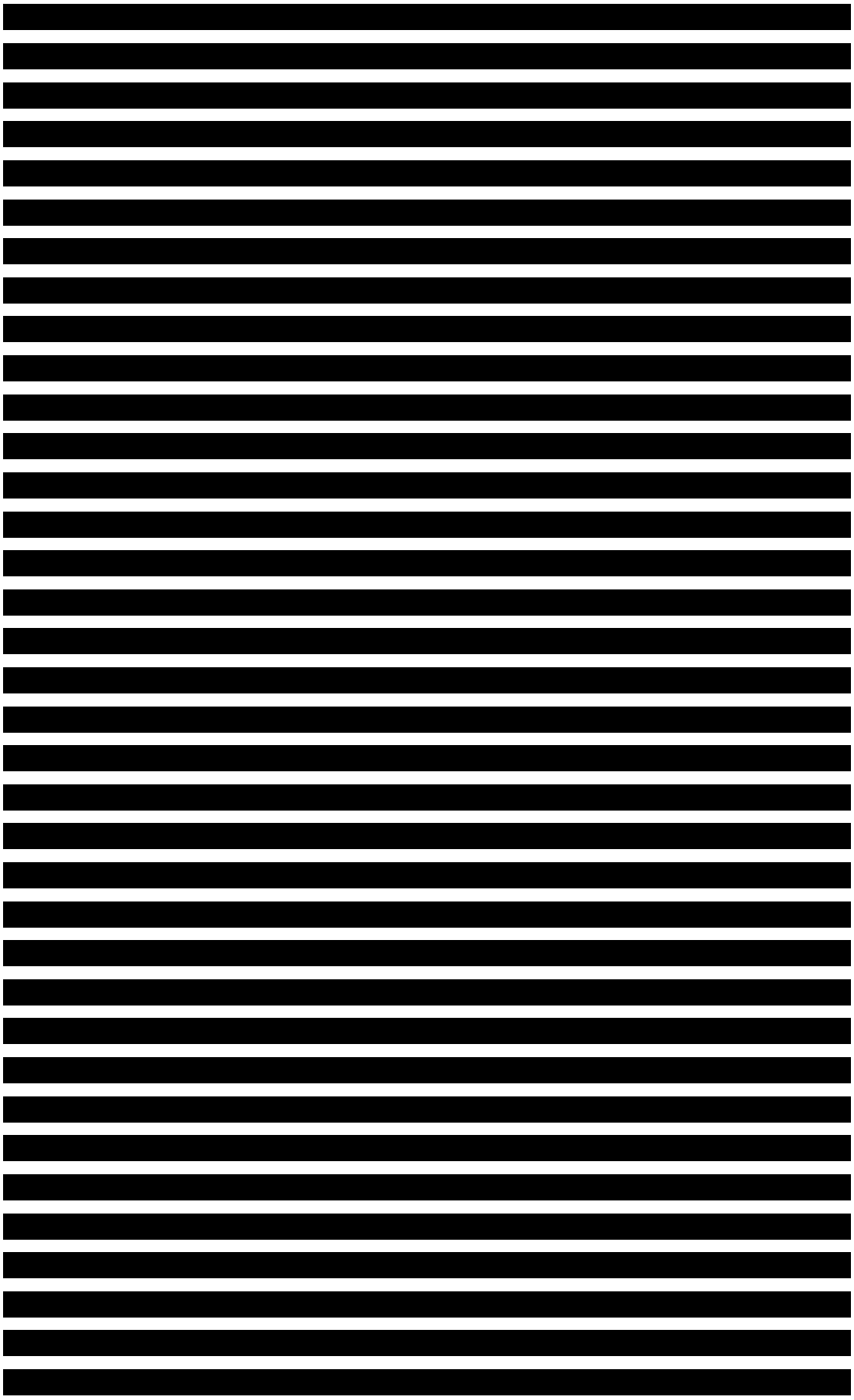


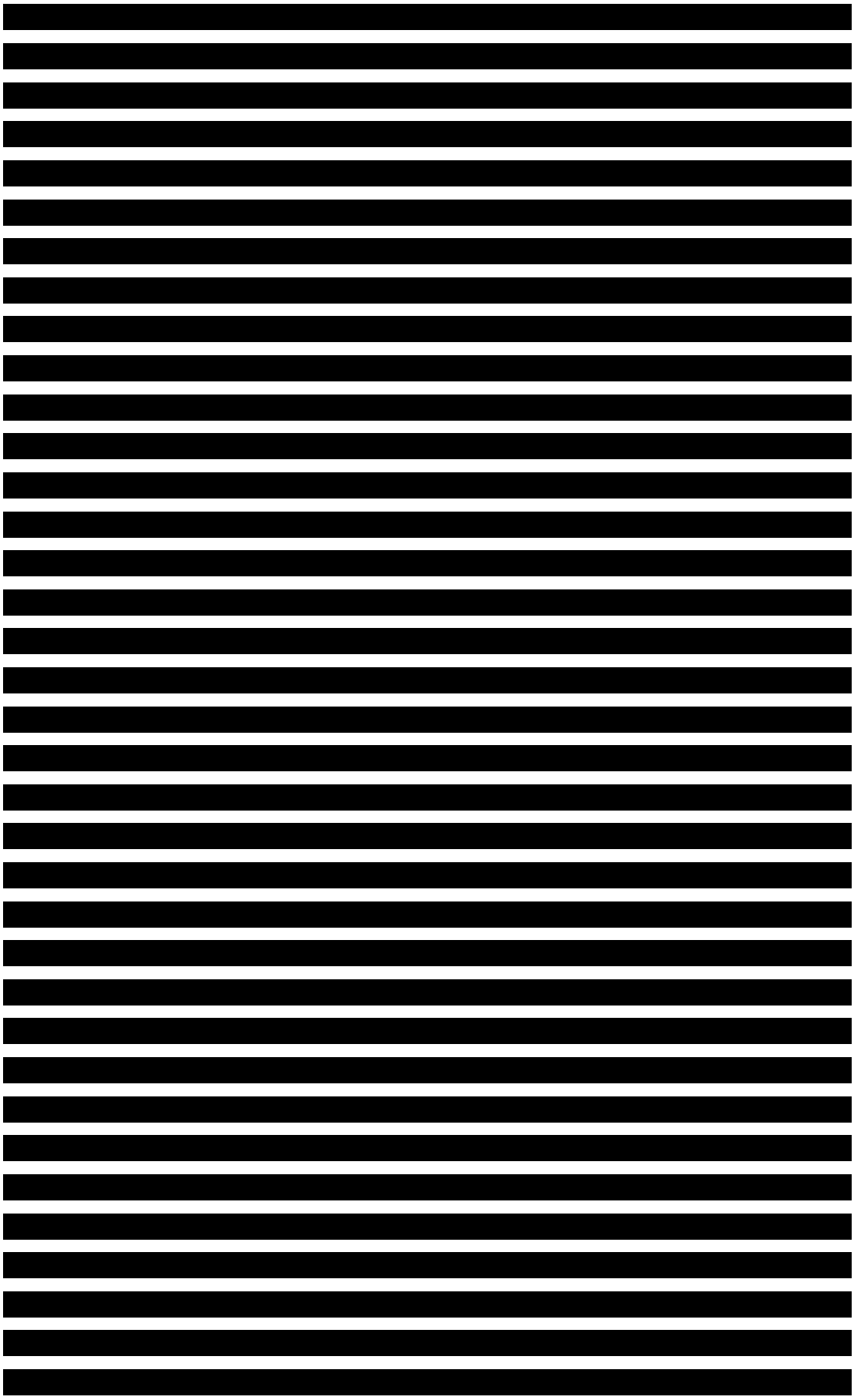


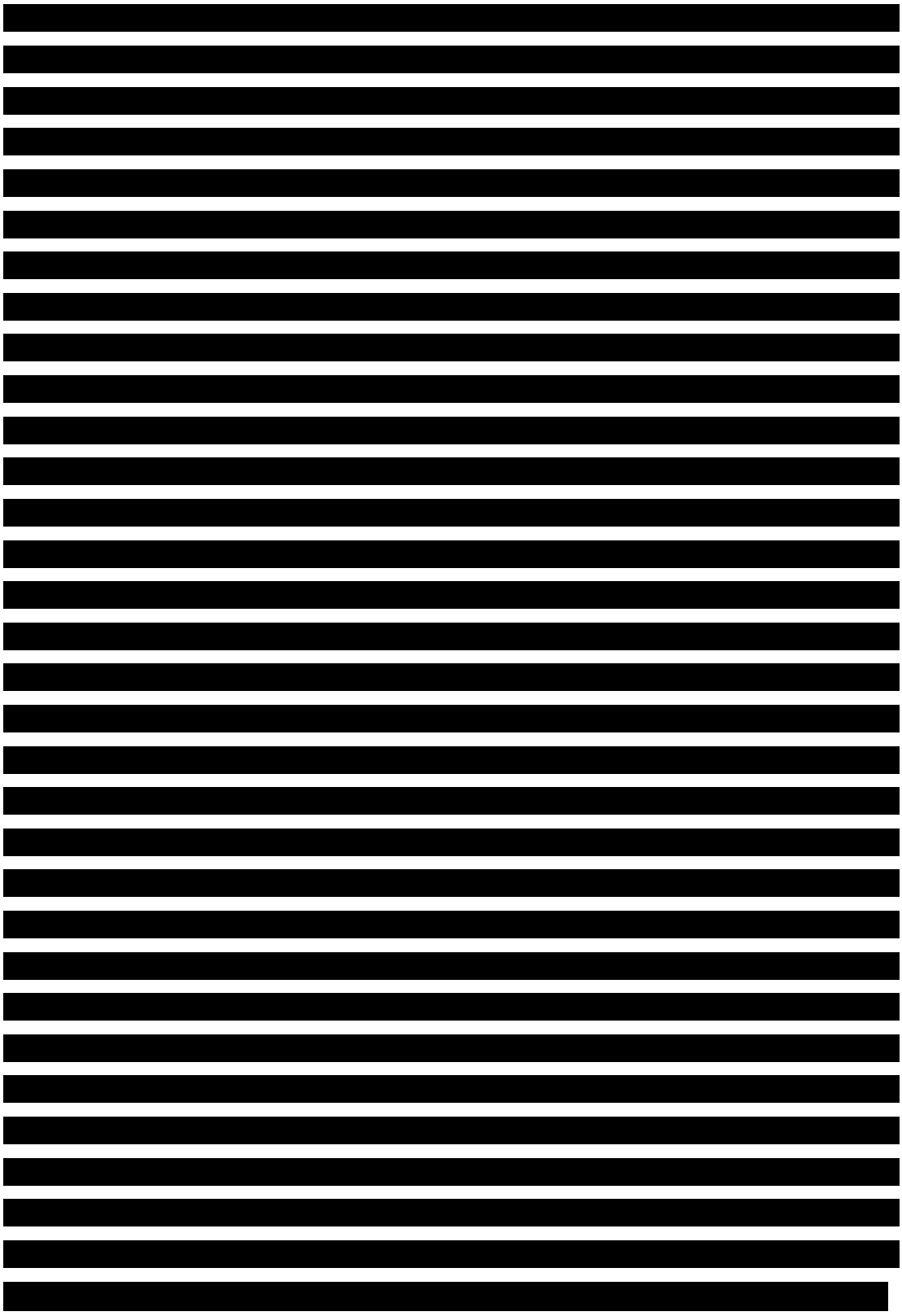












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