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Abstract

Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation

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Objectives: To assess the comparative clinical effectiveness and cost-effectiveness of adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis (AS).

Data sources: Major electronic databases were searched up to November 2005. Unpublished evidence such as conference abstracts, reviews of published economic evaluations, and company submissions to the National Institute for Health and Clinical Excellence (NICE) were also reviewed.

Review methods: The assessment was conducted according to accepted procedures for conducting and reporting systematic reviews and economic evaluations. Full economic evaluations that compared two or more options for treatment and considered both costs and consequences were eligible for inclusion in the economic literature review.

Results: Nine placebo controlled randomised controlled trials (RCTs) were included in the review of clinical effects. These included two studies of adalimumab, five of etanercept and two of infliximab in comparison with placebo (along with conventional management). No RCTs directly comparing anti-tumour necrosis factor-α (TNF-α) agents were identified. Meta-analyses were conducted for data on Assessment in Ankylosing Spondylitis (ASAS) (20, 50 and 70% improvement), mean change in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and mean change in Bath Ankylosing Spondylitis Functional Index (BASFI) at 12 weeks following initiation of anti-TNF-α therapy or placebo for all three drugs. Meta-analyses were also conducted at 24 weeks for etanercept and infliximab. Each meta-analysis of anti-TNF-α therapy demonstrated statistically significant advantages over placebo, although there was no significant difference between individual anti-TNF-α agents. At 12 weeks, ASAS 50% responses were 3.6-fold more likely with anti-TNF-α treatment than placebo. Compared with baseline, BASDAI scores were reduced by close to 2 points at 12 weeks. Functional scores (BASFI) were reduced at 12 weeks. Six full economic evaluations (two peer-reviewed published papers, four abstracts) were included in the review. The conclusions among economic evaluations were mixed, although the balance of evidence indicates that over short time-frames anti-TNF-α therapies are unlikely to be considered cost-effective. The limitations of the clinical outcome data impose restrictions on the economic assessment of cost-effectiveness. Direct unbiased RCT evidence is only available in the short term. Current assessment tools are limited and at present BASDAI and BASFI are the best available, although not designed for, or ideal for, use in economic evaluations. The review of the three models submitted to NICE identified a number of inherent flaws and errors. The incremental cost-effectiveness ratios (ICERs) of etanercept and adalimumab were roughly similar, falling below an assumed willingness-to-pay threshold of £30,000. The ICER for infliximab was in the range of £40,000–50,000 per quality-adjusted life-year (QALY). The short-term (12-month) model developed by this report's authors confirmed the large front-loading of costs with a result that none of the three anti-TNF-α agents appears cost-effective at the current acceptable threshold, with infliximab yielding much poorer economic results (£57,000–120,000 per QALY). The

assumptions of the short-term model were used to explore the cost-effectiveness of the use of anti-TNF-α agents in the long term. This model is far more speculative than the first since trends and parameter values must be projected far beyond the available evidence. Sensitivity analyses reveal wide variations in estimates of cost over the long term although it is considered unlikely that costs will decrease over time.
Conclusions: The review of clinical data related to the three drugs (including conventional treatment) compared with conventional treatment plus placebo indicates that in the short term (12–24 weeks), the three treatments are clinically effective in relation to assessment of ASAS, BASDAI and BASFI. Indirect comparisons of treatments were limited and did not show a significant difference in effectiveness between the three agents. The short-term economic assessment indicates that none of the three anti-TNF-α agents is likely to be considered cost-effective at current acceptability thresholds, with infliximab consistently the least favourable option. There is an absence of evidence concerning a number of limiting factors related to patients suffering from AS, the disease itself and its treatment. In order to obtain robust estimates of the longer term clinical effectiveness and cost-effectiveness of anti-TNF-α agents for AS, clinical trials that aim to address these limiting factors need to be conducted.

Contents

Glossary and list of abbreviations

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

Glossary

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 vertebrae together; this stiffening is called ankylosis.

Anti-TNF-α Anti-tumour necrosis factor-α therapies or agents (restricted to adalimumab, etanercept and/or infliximab for the purposes of this assessment).

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.

Biological therapies (biologicals) Medical preparations derived from living organisms. Include anti-tumour necrosis factor drug and other new drugs that target the pathologically active T cells involved in psoriasis and psoriatic arthritis.

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

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

Disease-modifying antirheumatic drugs (DMARDs) DMARDs are drugs capable of modifying the progression of rheumatic disease. The term is, however, applied to what are now considered to be traditional disease-modifying drugs, in particular sulfasalazine and methotrexate. The biologicals such as adalimumab, etanercept and infliximab are not generally referred to as DMARDs.

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

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

Non-steroidal anti-inflammatory drugs A large range of drugs of the aspirin family, which reduce inflammation and control pain, swelling and stiffness.

T cell (T lymphocyte) A type of white blood cell that is part of the immune system that normally helps to protect the body against infection and disease. T cells produce a number of substances (cytokines) that regulate the immune response.

Tumour necrosis factor One of the cytokines, or messengers, thought to be fundamental to the disease process that underlies ankylosing spondylitis.

List of abbreviations

AE	adverse event
AS	ankylosing spondylitis
ASAS	Assessment in Ankylosing Spondylitis
ASQoL	Ankylosing Spondylitis Quality of Life
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BASRI	Bath Ankylosing Spondylitis Radiology Index
BNF	British National Formulary
BSR	British Society for Rheumatology
BSRBR	British Society for Rheumatology Biologics Register
CEA	cost-effectiveness analysis
CI	confidence interval
CIC	commercial in confidence
CMA	cost-minimisation analysis
CPI	consumer price index
CRD	Centre for Reviews and Dissemination
CUA	cost–utility analysis
DCART	disease-controlling antirheumatic treatment
DMARD	disease-modifying antirheumatic drug
EQ-5D	EuroQol 5 Dimensions
ESR	erythrocyte sedimentation rate
FBC	full blood count
HCQ	hydroxychloroquine
HLA	human leucocyte antigen
HUI	health utility index
ICER	incremental cost-effectiveness ratio
IPD	individual patient data
IQR	interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	intention-to-treat
LFT	liver function test
LMA	longitudinal meta-analysis
LRiG	Liverpool Reviews and Implementation Group
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MFI	Multidimensional Fatigue Inventory
mSASSS	modified Stoke Ankylosing Spondylitis Spinal Score
MTX	methotrexate
NA	not applicable
NICE	National Institute for Health and Clinical Excellence
NR	not reported
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OLS	ordinary least squares
OR	odds ratio
p.a.	per annum
PPP	purchasing power parity
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QoL	quality of life
RA	rheumatoid arthritis
RCT	randomised controlled trial
RR	relative risk
SA	sensitivity analysis
SD	standard deviation
SEM	standard error of the mean
SF-36	Short Form 36
SMR	standardised mortality ratio
SSZ	sulfasalazine
TB	tuberculosis
TNF	tumour necrosis factor
U&E	urea and electrolytes
VAS	visual analogue scale
WMD	weighted mean difference

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

Executive summary

Background

Ankylosing spondylitis (AS) is a chronic inflammatory condition (a member of the spondyloarthropathies) affecting the spine, sacroiliac joints and peripheral joints, causing pain, stiffness and disability. Diagnosis is problematic and current UK incidence and prevalence data are uncertain. Currently, there is no standard or effective therapy for AS. Conventional management is composed of physiotherapy, non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs). None of these agents has been shown to alter the progression of the disease, but they may offer palliation of pain and symptoms. Adalimumab, etanercept and infliximab target the activation of tumour necrosis factor-α (TNF-α) and its subsequent activation of downstream inflammatory processes, and as such have the potential to offer symptom palliation as well as altering disease progression.

Objectives

The objectives of this review were to assess the comparative clinical effectiveness and cost-effectiveness of adalimumab, etanercept and infliximab for the treatment of AS. The following comparisons are made:

- adalimumab and conventional management versus conventional management
- etanercept and conventional management versus conventional management
- infliximab and conventional management versus conventional management
- between adalimumab, etanercept and infliximab, where data are available.

Methods

The assessment was conducted according to accepted procedures for conducting and reporting systematic reviews and economic evaluations. Evidence on clinical effects and cost-effectiveness of anti-TNF-α therapy was identified using a comprehensive search strategy (for the period up to November 2005) of bibliographic databases (including the Cochrane Library, EMBASE and MEDLINE) as well as handsearching activities. Unpublished evidence such as conference abstracts was considered for inclusion in the assessment.

The assessment of health economics evidence included a review of published economic evaluations and a critique of company submissions to the National Institute for Health and Clinical Excellence.

Inclusion criteria

The assessment was restricted to adults diagnosed with active AS. Randomised controlled trials (RCTs) comparing an anti-TNF-α agent (adalimumab, etanercept or infliximab) with conventional management or another anti-TNF-α agent were considered for inclusion.

Clinical outcomes had to include at least either a response to treatment based on Assessment in Ankylosing Spondylitis (ASAS) criteria, disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)], function [Bath Ankylosing Spondylitis Functional Index (BASFI)] or their component measurements. Studies reporting quality of life or adverse events were also eligible for inclusion.

Full economic evaluations that compared two or more options for treatment and considered both costs and consequences were eligible for inclusion in the economic literature review.

Results

Clinical findings

Nine placebo controlled RCTs were included in the review of clinical effects. These included two studies of adalimumab, five of etanercept and two of infliximab in comparison with placebo (along with conventional management). No RCTs directly comparing anti-TNF-α agents were identified.

Data from the nine RCTs were included for at least one outcome in the meta-analysis. Meta-analyses were conducted for data on ASAS (20, 50 and 70% improvement), mean change in

BASDAI and mean change in BASFI at 12 weeks following initiation of anti-TNF-α therapy or placebo preparation for all three drugs. Meta-analyses were also conducted at 24 weeks for etanercept and infliximab only. Each meta-analysis of anti-TNF-α therapy, as a group or as individual anti-TNF-α agents, demonstrated statistically significant advantages over placebo.

At 12 weeks ASAS 50% responses were 3.6-fold more likely to be achieved with anti-TNF-α treatment than with placebo [relative risk 3.58, 95% confidence interval (CI) 2.72 to 4.71].

Compared with baseline, disease activity scores were reduced by close to 2 BASDAI points at 12 weeks (random-effects weighted mean difference –1.89, 95% CI –2.23 to –1.55). Functional scores (BASFI) were reduced at 12 weeks (weighted mean difference –1.46, 95% CI –1.69 to –1.24).

Meta-analyses for each anti-TNF-α drug were also conducted. Statistical indirect comparisons, based on available anti-TNF-α versus placebo comparisons, were unable to distinguish a statistically significant difference between individual anti-TNF-α agents.

Economic evaluation

Six full economic evaluations (two peer-reviewed published papers, four abstracts) were included in the review. The conclusions among economic evaluations were mixed, although the balance of evidence indicated that over short time-frames anti-TNF-α therapies were unlikely to be considered cost-effective.

The limitations of the clinical outcome data impose restrictions on the economic assessment of cost-effectiveness. The only period for which direct unbiased RCT evidence was available was in the short term. The current assessment tools are limited and at present BASDAI and BASFI are the best tools available, although not designed for, or ideal for, use in economic evaluations.

The review of the three submitted models identified a number of inherent flaws and errors. Once the serious errors had been corrected, the incremental cost-effectiveness ratios (ICERs) of etanercept and adalimumab were roughly similar, falling below an assumed willingness-to-pay threshold of £30,000. However, once the Schering-Plough model had been corrected, the ICER for infliximab was in the range of £40,000–50,000 per quality-adjusted life-year (QALY).

The short-term (12-month) model developed by the assessment group confirmed the large front-loading of costs with a result that none of the three anti-TNF-α agents appears cost-effective at the current acceptable threshold, with infliximab yielding much poorer economic results (£57,000–120,000 per QALY).

The assumptions of the short-term model were used to explore the cost-effectiveness of the use of anti-TNF-α agents in the long term. It is acknowledged that this model is far more speculative than the first since trends and parameter values must be projected far beyond the available evidence, with consequent loss of precision. Sensitivity analyses reveal wide variations in estimates of cost over the long term; however, the analyses challenge the assumptions made in the company submissions that costs will decrease over time.

It is not possible to make a definitive assessment of economic performance in the face of the wide-ranging uncertainties; however, three clear conclusions can be drawn:

- Assuming clinical equivalence, the higher costs associated with infliximab (even if given less frequently) make it a much less favourable option than either adalimumab or etanercept.
- It is unlikely that extending the period of continuous treatment over decades will automatically improve cost-effectiveness.
- Without proven criteria by which to identify those patients most likely to benefit, the sequential trial and error approach to finding an effective agent for a patient will lead to less attractive economic results than those provided in the current single treatment model.

Implications for the NHS

In terms of budget impact, uncertainties in the basic epidemiology of AS and the eligibility of patients to be offered anti-TNF-α agents lead to an extremely wide range of potential additional costs to the NHS. However, the present analyses indicate that the approval of anti-TNF-α agents for the general treatment of active AS is likely to lead to considerable financial consequences as well as large additional service demands.

Conclusions

The review of clinical data related to the three drugs (including conventional treatment) compared with conventional treatment plus

placebo indicates that in the short term (12–24 weeks) the three treatments demonstrate clinical and statistical effectiveness in relation to assessment of ASAS, BASDAI and BASFI. Indirect comparisons of treatments were limited and were not able to determine a significant difference in effectiveness between the three agents.

The short-term economic assessment indicates that none of the three anti-TNF-α agents is likely to be considered cost-effective at current acceptability thresholds, with infliximab consistently the least favourable option. Analyses carried out by the assessment group over the longer term challenge the assumptions made in the company submissions that costs will decrease over time. Owing to these large and sustained costs, the impact on the NHS budget is likely to be considerable.

Recommendations for further research

There is an absence of evidence concerning a number of limiting factors related to patients suffering from AS, the disease itself and its treatment.

Patient factors

- What are the current incidence and prevalence rates for AS?
- What patient variables are appropriate to predict disease progression?
- If a patient does not respond to one anti-TNF-α agent will they respond to another?
- What criteria should be used in the decision to discontinue treatment?
- Should the same criteria be applied to patients restarting treatment after previous treatment failure?

Disease factors

- What is standard disease progression?
- Could alternative disease measurements be developed to inform economic modelling more adequately?

Treatment factors

- Is disease progression halted/slowed in patients treated with anti-TNF-α agents?
- Do patients require treatment with anti-TNF-α agents continuously?
- Can anti-TNF-α treatment be titrated down or withdrawn over time?
- Can anti-TNF-α treatments be of use to manage disease flares rather than continuously?
- Is there dose creep that requires drug dosages to increase over time?
- What are the issues related to sequencing of treatments?
  - Which treatment should be considered first line?
  - If one treatment fails should a second/third be tried?
  - If one treatment works initially and then fails should a second/third be tried?
  - If the second/third treatment fails should the first be tried again?
- What role does conventional treatment (NSAIDs) play when an anti-TNF-α agent is prescribed?

In order to obtain robust estimates of the longer term clinical effectiveness and cost-effectiveness of anti-TNF-α agents for AS, clinical trials that aim to address these limiting factors need to be conducted.

Chapter 1

Review aims

The aim of this review was to assess the comparative clinical effectiveness and cost-effectiveness of adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis (AS). The following comparisons are made:

- adalimumab and conventional management versus conventional management
- etanercept and conventional management versus conventional management
- infliximab and conventional management versus conventional management
- between adalimumab, etanercept and infliximab, where data are available.

Chapter 2
Background

Description of underlying health problem

Disease

AS is a chronic inflammatory condition that primarily affects the spine and sacroiliac joints, causing pain and stiffness in and around the spine. AS is a member of the spondyloarthropathies, which include psoriatic arthritis, reactive arthritis and enteropathic arthritis.[1]

Over time chronic spinal inflammation (spondylitis) can lead to fusion of the spinal vertebrae (ankylosis), which is debilitating and irreversible.

The disease is not only limited to the spine; many AS patients also suffer from periodic inflammation of peripheral joints (particularly of the hip and knee), as well as periodic eye inflammation (uveitis). Up to 60% of patients (upon dissection) have an inflammatory bowel disease similar to Crohn's disease with symptoms of variable intensity. Patients with AS may suffer from symptoms throughout their life, but periods of remission of active disease and lessening of symptoms are not uncommon.

Epidemiology

Prevalence and incidence of AS

Evidence from the USA suggests that there is an annual incidence rate of 7.3 per 100,000 person-years.[2] This suggests that in the UK there are approximately 3800 new cases of AS every year. However, this figure should be treated with caution, as it is not based on incidence rates for the UK, but extrapolated from US data.

The prevalence of AS in the UK is unknown. However, in Caucasians, the prevalence of AS has been estimated to range between 0.05% and 0.23%, as quoted in the British Society for Rheumatology (BSR) guidelines.[3] These values are originally taken from two studies, a Hungarian study from 1977[4] and a UK study from 1949,[5] both of which are of dubious quality and relevance. The Hungarian population, although Caucasian, is likely to differ from that of England and Wales, as will the diagnosis criteria used for AS. The UK study is very much outdated, hence it is likely that both the population demography and our understanding of AS will have changed substantially since then.

Risk factors and age of onset of disease

AS is three to four times more common in men than women.[1] Disease patterns also vary according to gender, with women reported to have milder disease than men.[6] Indeed, many reports show that women have a later age of onset, less severe disease and more extraspinal involvement.[7]

AS often presents in the third decade of life. In many cases, symptoms present in the mid-teens[6] and the average delay between the onset of symptoms and diagnosis is reported to be approximately 8–9 years.[8,9]

There is evidence that AS may be inherited.[7] However, owing to the anticipated underdiagnosis of AS in past decades, the extent to which a family history of AS predisposes an individual to the disease is unclear.

Aetiology

The pathogenesis of AS is not well understood. Interactions between the class I major histocompatibility complex (MHC) molecule human leucocyte antigen B27 (HLA-B27) and the T-cell response, including the release of tumour necrosis factor-α (TNF-α), have been proposed as initiating the impulse for the inflammatory process in AS. Pathogenic theories are numerous in AS and several of them imply HLA-B27. In the arthritogenic peptide theory, an antigen would be presented by HLA-B27 to $CD8^{+}$[10] or $CD4^{+}$ T lymphocytes.[11] The triggering antigen could be derived from fibrocartilage or cartilage or be a foreign antigen from a bacteria.[10,12]

The presence or absence of the HLA-B27 gene does not automatically confirm or refute the diagnosis of AS. Most people with HLA-B27 do not have the disease.[6] To illustrate, in the USA 7% of the population carry the gene, but only 1% actually exhibit AS.[13] However, there is a strong link between AS and the HLA-B27 gene, with approximately 90–95% of AS patients carrying the HLA-B27 gene.

Enthesitis, inflammation of the enthesis (the site of insertion of ligaments, tendons and other tissues into bone), has been described as the most characteristic histopathological finding in AS. However, the importance of enthesitis relative to synovitis, subchondral marrow inflammation and osteitis in AS is debatable.[14] Recent research has shown that the entheseal fibrocartilage is the major target of the immune response and the primary site of the immunopathology. Immunocompetent cells could obtain access to fibrocartilage-derived antigen from bone marrow-derived blood vessels.[15] This hypothesis has been sustained by quantitative cellular analysis of immunostained sacroiliac biopsy specimens that have shown activated T cells and macrophages in early and active sacroiliitis in AS.[16]

Diagnosis

Early diagnosis of AS is critical if patients are to delay the occurrence of irreversible damage.[7] Unfortunately, early clinical symptoms of AS can be very deceptive, as stiffness and pain in the lower back are frequently seen in many other conditions, and this may also be confounded by a low awareness of AS among non-rheumatologists.[17] Hence, often many years can pass before a diagnosis of AS is confirmed, especially in women, in whom the index of suspicion is much less.

The diagnosis of AS is based on the modified New York criteria, which measures the patient's symptoms using both radiological and clinical criteria.[18] This radiological requirement for radiographic sacroilitis grade II bilaterally or grade III or IV unilaterally, which may not appear for up to several years after first symptoms, could further delay the diagnosis of AS.[17] However, in clinical practice diagnosis may often be based on less specific features.

Assessment

There is a variety of outcome measures for the assessment of patients with AS. First, there are three distinct elements of the AS disease process that can be measured: disease activity, physical function and structural damage.[19]

The most common instrument used to measure the disease activity of AS is the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).[20] The BASDAI is a validated, composite index which assesses the five major symptoms of AS: fatigue, axial and peripheral pain, stiffness and enthesopathy. It is quick and easy to use and is often routinely administered in clinical trials and in daily practice.[19]

The Bath Ankylosing Spondylitis Functional Index (BASFI) is the most widely used tool to assess physical function in AS.[21] The BASFI is a validated, composite index made up of ten questions which address function and the patient's ability to cope with AS. The BASFI is quick and easy to complete, reliable and sensitive to change across the whole spectrum of disease.[22] The Dougados Functional Index (DFI) is also often used to assess functional ability in AS.[23]

The evaluation of structural damage and progression in AS is primarily based on radiography. Two instruments used to assess structural damage are the Bath Ankylosing Spondylitis Radiology Index (BASRI)[24] and the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS).[25]

Secondly, it is important to assess the specific symptoms of AS. A variety of symptom specific assessment tools is available for use, including the Multidimensional Fatigue Inventory (MFI) and the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES). Quality of life issues must also be addressed and there are both disease-specific and general health-related quality of life measures suitable for use in AS patients.[19]

Assessment of response to therapy

Response to treatment in AS is typically measured by the BASDAI. The Assessment in Ankylosing Spondylitis Working Group (ASAS) has recommended that response to therapy be assessed by a 50% reduction or fall of two or more units in BASDAI, and the spinal pain visual analogue scale (VAS) to reduce by two or more units (*Box 1*). This assessment is carried out between 6 and 12 weeks after commencement of therapy, and subsequently reviewed quarterly. Other measures that may be used for assessing response include the BASFI and expert opinion.

Withdrawal or change of selected therapy [e.g. change from non-steroidal anti-inflammatory drug (NSAID) to disease-modifying antirheumatic drug (DMARD) therapy or dose changes] is considered if the BASDAI does not fall by two or more units or decrease by 50%, and/or if the spinal pain VAS does not decrease by two or more units, within 3 months of commencement therapy or if the initial response is not maintained. Treatment is also ceased or changed if serious adverse events occur.

The ASAS group also recommend that clinical benefit is indicated by improvements in pain,

BOX 1 *Efficacy end-points*

Assessments in Ankylosing Spondylitis (ASASs) response criteria: improvements of at least 20%, 50% and 70% in at least three of four domains:

A. Spinal inflammation: composite of two items from BASDAI (items 5 and 6, below)
B. Total back pain and nocturnal back pain: combined
C. Patient global assessment of health
D. Functional impairment: composite score of ten items on BASFI (see below).

ASAS: a binary outcome, expressed as number or proportion of patients achieving threshold level of response.

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
Scores on six separate items:

1. Fatigue
2. AS pain in neck, back or hips
3. Pain in joints other than neck, back or hips
4. Discomfort in areas tender to touch or pressure
5. Intensity of morning stiffness
6. Duration of morning stiffness.

Scoring: For items 1–5 VAS ranging 'none' to 'very severe', 0–10 for each item; for item 6 VAS '0' to '2 or more' hours. Total of items 1–4 added to mean of items 5 and 6 and then divided by 5 to give BASDI. BASDAI: a continuous scale outcome, reported in studies as score at follow-up or change in score from baseline (or previous follow-up).

Bath Ankylosing Spondylitis Functional Index (BASFI)

1. Putting on socks without aids
2. Picking up pen from floor
3. Reaching high shelf without aids
4. Getting up from an armless chair
5. Getting off floor from back
6. Standing unsupported for at least 10 minutes
7. Climbing 12–15 steps without aids
8. Looking over shoulder
9. Performing a demanding activity
10. Doing a full day's activity.

Scoring: VAS ranging 'easy' to 'impossible', 0–10 for each item, total for across all ten items divided by 10 to give BASFI. BASFI: a continuous scale outcome, reported in studies as score at follow-up or change in score from baseline (or previous follow-up).

Adapted from tables in Calin *et al*.[26] and ASAS Working Group.[27]

inflammation, well-being and function. By taking these core four sets and their respective measurement instruments, the ASAS group has constructed specific response criteria to be used in the measurement of treatment response in AS trials.[19] The number of improvements made constitutes different ASAS responses.[1] For example, the following ASAS outcome measures exist: ASAS20, ASAS40, ASAS50 and ASAS70.

Criteria for treatment

Treatment with anti-TNF-α agents may be appropriate if:

- the patient's disease satisfies the modified New York criteria (*Box 2*)
- all reasonable measures have been taken to ensure that symptoms are due predominantly to AS and that alternative causes, including spinal fracture, disc disease and fibromyalgia, have been excluded
- AS is active; active spinal disease should be defined as:
  - BASDAI at least 4 units
  - and spinal pain VAS (last week) at least 4 cm
  - both on two occasions at least 4 weeks apart without any change in treatment
- failure of conventional treatment with two or more NSAIDs, each taken sequentially at maximum tolerated/recommended dosage for 4 weeks.

Exclusions as for rheumatoid arthritis (RA) apply. Reference should be made to the individual drug data sheets, but important exclusions include:

- women who are pregnant or breast-feeding
- active significant infection

BOX 2 *Modified New York criteria for AS and BSR criteria for active AS*

Modified New York criteria for AS

Patients normally fulfilling modified New York criteria (1984) for definitive AS.

Radiological criterion: sacroiliitis, grade II bilaterally or grade III or IV unilaterally.

Clinical criteria (two of the following three): low back pain and stiffness for more than 3 months which improves with exercise but is not relieved by rest; limitation of motion of the lumbar spine in both the sagittal and frontal planes; limitation of chest expansion relative to normal values correlated for age and gender.

BSR criteria for active AS

BSR guidelines for eligibility for treatment with anti-TNF-α agents require demonstration of active AS, where:

- active spinal disease should be defined as BASDAI at least 4 cm and spinal pain VAS (within last week) at least 4 cm. Both recorded on two occasions at least 4 weeks apart, without any change in treatment
- failure of conventional treatment with two or more NSAIDs, each taken sequentially at maximum tolerated/recommended dosage for 4 weeks.

Adapted from ASAS Working Group[27] and BSR Guidelines.[1]

- septic arthritis of a native joint within the past 12 months
- sepsis of a prosthetic joint within the past 12 months or indefinitely if the joint remains *in situ*
- New York Heart Association (NYHA) grade 3 or 4 congestive cardiac failure
- clear history of demyelinating disease.

Prognosis

AS is a chronic disease which does not have a single defined natural history. The course of the disease is unpredictable, with periods of remission and relapse occurring at any stage. With treatment, symptoms can usually be relieved or controlled so that the patient can lead a normal, productive life. However, even with treatment, the patient may develop permanent posture and movement problems. Posture problems may include the destruction of the lumbar lordosis, buttock atrophy and increased thoracic kyphosis, and the patient's neck may stoop forward. Movement problems may include loss of spinal mobility, with restrictions of flexion, extension of the lumbar spine and expansion of the chest. In addition, peripheral joint mobility is affected; frequently, this involves hip joints (which may warrant total hip replacement).

The clinical signs of the disease can range from mild stiffness to a totally fused spine, with any combination of severe bilateral hip involvement, peripheral arthritis or extra-articular manifestations.[7]

Although many outcomes are possible, findings from an early prospective study suggest that a predictable pattern of AS emerges within the first 10 years of disease.[28] In a cohort of 51 AS patients with a mean disease duration of 28 years, the natural course of the disease was examined over a 23-year period. It was found that 74% of the patients who had mild spinal restriction after 10 years did not progress to severe spinal involvement. In contrast, 81% of the patients who had severe spinal restriction were severely restricted within the first 10 years.

Another study showed that seven variables (which present within 2 years of onset of the disease) were correlated with disease severity [odds ratio (OR), 95% confidence interval (CI)]:

- hip arthritis (OR 22.85, 4.43 to 118)
- erythrocyte sedimentation rate (ESR) greater than 30 mm/hour (OR 7, 4.84 to 9.50)
- poor efficacy of NSAIDs (OR 8.33, 2.56 to 27.10)
- limitation of lumbar spine (OR 7, 2 to 25)
- sausage-like finger or toe (dactylitis) (OR 8.45, 1.48 to 9)
- oligoarthritis (OR 4.25, 1.38 to 13.10)
- onset at 16 years or younger (OR 3.47, 1.06 to 12.75).[29]

Burden of disease

Mortality and morbidity

In terms of mortality, evidence from a number of hospital centre studies indicates that patients with AS have a standardised mortality ratio (SMR) of 1.5 or greater.[30–33] As with RA, the increased risk of death is usually related to increased rates of cardiovascular events, potentially reflecting the influence of ongoing inflammation on the progression of atherosclerosis. AS is a complex and debilitating disease and for some can be associated with considerable morbidity. However, 90% of individuals suffering from AS remain fully independent or minimally disabled in the long term.[6]

Socio-economic impact

AS generally occurs in the third decade of life, at which age individuals are generally productive members of society. The progressive nature of the ongoing damage together with disease activity and loss of functional ability leads to increasing work disability and loss of employment, particularly in individuals who undertake manual work. In a cross-sectional UK study, 31% of participants were unable to work as a result of their AS.[34] This means that the socio-economic impact of the disease is significant for both the patient and society.[17]

Current service provision

Currently, there is no standard therapy for AS. Conventional management of AS involves regular physiotherapy and NSAIDs, together with DMARDs.

Physiotherapy and exercise are often recommended as first-line/baseline therapies. The objective is to enable patients to remain mobile for longer. Physiotherapy and exercise are not expected to affect the natural history of the disease. In addition, NSAIDs are often prescribed. NSAIDs offer a quick palliation of symptoms for the majority of patients, although their long-term effects on disease progression are unclear.[35] The aim of this type of drug treatment is to allow the patient with AS to exercise regularly.[6]

Second line therapies include DMARDs such as sulfasalazine (SSZ) and methotrexate (MTX). These can be used, together with systemic or intra-articular corticosteroids, for the relief of extreme symptoms of pain and stiffness. Unfortunately, the use of DMARDs for the treatment of AS patients has been somewhat disappointing. The conclusions of the Cochrane review on the use of sulfasalazine in patients with AS are as follows: "across all AS patients, SSZ demonstrated some benefit in reducing ESR and easing morning stiffness, but no evidence of benefit in physical function, pain, spinal mobility, enthesitis, patient and physician global assessment. Patients at early disease stage, with higher level of ESR (or active disease) and peripheral arthritis might benefit from SSZ".[36]

Methotrexate has also been reviewed by a Cochrane group. The reviewers found that "there was no statistically significant benefit of MTX in the examined outcomes for AS patients".[37]

Other and more experimental therapies have also been used in AS. These include pamidronate, amitriptyline, penicillamine, tetracycline and ciprofloxacin. However, none of these drugs has been able to demonstrate significant benefits in terms of pain control for patients with AS and have only yielded modest or no BASDAI response.[35,38]

Description of new interventions

Anti-TNF-α agents

As described early in this chapter, TNF-α may be implicated in the disease processes of AS. It is intended that therapies aimed at inhibiting TNF-α may thus limit disease symptoms and/or progression.

Currently, there are three TNF-α agents licensed for use in active AS in the UK: adalimumab, etanercept and infliximab.

Adalimumab (Abbott)

Adalimumab (Humira®) is a recombinant monoclonal antibody which binds to TNF-α and blocks its interaction with the TNF receptor, thereby preventing the downstream activation of proinflammatory cytokines. It is not currently licensed for AS, although studies have been conducted in patients with active AS. The anticipated dose is 40 mg every 2 weeks by subcutaneous injection.[39]

Etanercept (Wyeth)

Etanercept (Enbrel®) is a recombinant dimeric fusion protein that competitively antagonises the action of TNF-α upon its receptor. It is licensed for the treatment of active AS in adults who have had an inadequate response to conventional therapy. The recommended dose is 25 mg twice a week by subcutaneous injection.[39] However, in practice it is increasingly being given as 50 mg weekly.

Infliximab (Schering-Plough)

Infliximab (Remicade®) is a chimeric monoclonal antibody which, as with adalimumab, binds to TNF-α and prevents its receptor-mediated inflammatory response. It is licensed for the treatment of active AS in adults with severe axial symptoms who have not responded adequately to conventional therapy. The recommended dose is 5 mg/kg by intravenous injection at 0, 2 and 6 weeks, followed by a maintenance dose of 5 mg/kg every 6–8 weeks.[39]

Drug-related adverse events

Adalimumab, etanercept and infliximab have been associated with several side-effects, notably infections which can be severe, including upper

respiratory infections, reactivation of latent tuberculosis (TB) and septicaemia. A recent study by Bongartz and colleagues[40] estimated that for RA patients treated with adalimumab or infliximab the number needed to harm was 59 (95% CI 39 to 125) for one additional serious infection within a treatment period of 3–12 months. This study[40] also showed an increase in malignancies (dose dependent), with the number needed to harm estimated as 154 (95% CI 91 to 500) within a treatment period of 6–12 months. However, as noted in a commentary[41] on the Bongartz study, until data from large national registries become available these results should be treated cautiously.

Other side-effects of anti-TNF-α therapy include nausea, abdominal pain, worsening heart failure, hypersensitivity reactions, fever, headache, depression, lupus erythematosus-like syndrome, pruritus, injection-site reactions and blood disorders (including anaemia, leucopenia, thrombocytopenia, pancytopenia and aplastic anaemia).[39]

Chapter 3
Methods

Identification of evidence: clinical effectiveness

Search strategy
The search incorporated a number of strategies. Search terms for electronic databases included a combination of index terms for AS and free text words for the technologies involved (generic and trade names of the drugs).

The following electronic databases were searched by one reviewer (YD) for relevant published literature for the period up to November 2005: Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effectiveness (DARE), EMBASE, Health Technology Assessment (HTA) database, ISI Web of Science – Proceedings (Index to Scientific & Technical Proceedings), ISI Web of Science – Science Citation Index Expanded, MEDLINE and NHS Economic Evaluation Database (NHS EED).

Details of the search strategies and the number of records retrieved for each search are provided in Appendix 1.

Reference lists of included studies and company submissions were searched to identify other relevant studies of clinical effectiveness, costs or cost-effectiveness.

Handsearching of three rheumatology conference abstracts (up to 31 January 2005) was conducted for BSR 2003, 2004, 2005, European League Against Rheumatism (EULAR; Annual European Congress of Rheumatology) 2003, 2004, 2005, and American College of Rheumatology 2003, 2004, 2005.

All the references were initially exported to an EndNote bibliographic database (Thomson ISI ResearchSoft, CA, USA). From this EndNote library, references were then uploaded to TrialStat! SRS 3.0 web-based systematic review system (TrialStat! Corporation, Ontario, Canada) for deduplication and application of inclusion/exclusion criteria (see below).

Selection of evidence: clinical effectiveness

The records identified in the electronic searches were assessed for inclusion in two stages.

Initial screening – electronic (SRS)
Using the SRS web-based systematic reviewing system each record (title and, if available, abstract in electronic form) was screened for inclusion in the clinical review by two reviewers operating independently (any pairing of ABol, RD, YD, RH and CM).

Full-text versions of all records passing (i.e. not excluded) the initial screening process were obtained to permit more detailed assessment. A table summarising the initial screening of search results is given in Appendix 1.

Study selection and categorisation – full text
Full-text reports of the selected records were obtained and assessed independently by at least two reviewers for inclusion (YD, RH, CM). The inclusion/exclusion assessment of each reviewer was recorded on a pretested, standardised (paper) form.

The level of agreement between pairs of reviewers varied according to reviewer pairing, but was generally high. Results of study selection are presented in Chapters 4 and 5. A table summarising the selection and inclusion of studies is provided in Appendix 1 (*Table 43*).

Methods for reviewing clinical effectiveness

Inclusion criteria
The following inclusion criteria were applied to evidence sources identified in the search.

- study design(s):
  - randomised controlled trials (RCTs)
  - non-RCTs (such as non-randomised Phase I trials) in the absence of sufficient RCT-based data

- patient population:
  - etanercept and infliximab: adults with active AS whose disease has responded inadequately to conventional therapy
  - adalimumab: adults with active AS
- interventions:
  - adalimumab, etanercept or infliximab plus conventional management
- comparators:
  - conventional management (such as NSAIDs, physiotherapy, DMARDs and corticosteroids) without anti-TNF-α therapy
- outcomes:
  - pain and other symptoms
  - functional capacity (e.g. BASFI)
  - disease activity (e.g. BASDAI)
  - adverse effects of treatment
  - disease progression (e.g. BASDAI)
  - health-related quality of life [e.g. Short Form 36 (SF-36) or Ankylosing Spondylitis Quality of Life (ASQoL)].

Exclusion criteria

Randomised studies were excluded if they:

- provided only unplanned, interim findings
- provided data on only a subgroup of the enrolled patients
- were continuing to recruit patients
- were trials in which patient numbers treated with a specific intervention (i.e. adalimumab, etanercept or infliximab) or disease status (i.e. active AS) could not be determined.

Data abstraction: clinical effectiveness

Data extraction for the review of clinical effectiveness was carried out by three reviewers (RD, RH, AJ). Data were abstracted by one reviewer into pretested data extraction forms created within the Access database application (Microsoft Corporation), and then checked for accuracy by a second reviewer.

Data presented from multiple reports of single trials were extracted onto a single data extraction record.

Quality assessment: clinical effectiveness

Two reviewers (YD and RH) independently evaluated the included studies for methodological quality (using forms created in Access) using criteria based on the Centre for Reviews and Dissemination (CRD) Report 4[42] (see Appendix 2). Any discrepancies in quality grading were resolved through discussion.

Data analysis: clinical effectiveness

Abstracted data were presented as tables and, if appropriate, included in the meta-analysis (see below).

Data in the form of relative risks (RRs) and 95% confidence intervals were analysed using the Mantel–Haenszel method, fixed-effect model provided by the RevMan Analyses 1.0 application within RevMan 4.2. For continuous outcomes, weighted mean differences (WMDs) were analysed, using a fixed-effect model and the same analytical software.

Heterogeneity was tested by the χ^2 test and the I^2 statistic was obtained to describe the proportion of the variability using RevMan Analyses 1.0. Where quantitative heterogeneity was indicated, analysis using a random-effects model was conducted for comparison with results of fixed effect-based analysis and is discussed within the appropriate section of the results. Results of the meta-analysis should be considered as being based on fixed-effect model unless stated otherwise.

Identification and selection of evidence: cost-effectiveness

A systematic search of the economic evidence concerning anti-TNF-α therapy for the treatment of AS was conducted. The aim was to identify published cost-effectiveness studies of anti-TNF-α therapy for the treatment of AS versus any other conventional therapy.

Using the search strategy 'ankylosing spondylitis and cost' (*Table 1*), 166 papers were identified. Of these 54 duplicates were discarded, and the remaining 112 were selected.

Selection of evidence: cost-effectiveness

Full-text reports of the selected records were obtained and assessed independently by two reviewers (ABol and CM) for inclusion. The inclusion/exclusion assessment of each reviewer was recorded on a pretested, standardised (paper) form.

Any disagreements for inclusion of cost-effectiveness studies were resolved by discussion.

TABLE 1 *Search strategy for cost-effectiveness studies*

Database	Years	Search strategy	References identified
MEDLINE	1966 to 31 January 2006	Ankylosing spondylitis and cost	56
Science Citation Index/Web of Science	1995 to 31 January 2006	Ankylosing spondylitis and cost	73
Science Citation Index/ISI Proceedings	1995 to 31 January 2006	Ankylosing spondylitis and cost	20
DARE, HTA, NHS EED	1995 to 31 January 2006	Ankylosing spondylitis and cost	14
Handsearching	1995 to 31 January 2006		3
	Total references identified		166
	Duplicates		54
	New total		**112**

Methods for reviewing cost-effectiveness

Inclusion criteria: cost-effectiveness

The following criteria had to be met in order for the evidence source to be considered in the review of cost-effectiveness:

- study design:
  - full economic evaluations that compared two or more options and considered both costs and consequences, including cost-effectiveness analysis (CEA), cost–utility analysis (CUA), cost–benefit analysis and cost-minimisation analysis (CMA)
- population:
  - etanercept and infliximab: adults with active AS whose disease has responded inadequately to conventional therapy
  - adalimumab: adults with active AS
- intervention:
  - adalimumab, etanercept or infliximab plus conventional management
- comparators:
  - conventional management without anti-TNF-α or placebo
  - adalimumab, etanercept or infliximab plus conventional management
- health outcomes in an economic framework:
  - incremental cost per quality-adjusted life-year (QALY) gained
  - disease-specific measures, such as ASAS 20 responder, ASAS partial responder, disease-controlling antirheumatic treatment (DCART) 20 responder, BASDAI scores, BASFI scores.

Exclusion criteria: cost-effectiveness

Reports were excluded from the review of economic evaluations if:

- they were RA studies
- they were not full economic evaluations
- the interventions did not include adalimumab, etanercept or infliximab.

Data abstraction: cost-effectiveness

Data from the included economics studies were abstracted into structured tables by one reviewer (CM) and then checked for accuracy by a second reviewer (ABol).

Quality assessment: cost-effectiveness

Two reviewers (ABol and CM) independently evaluated the included economics studies for methodological quality using criteria based on BMJ 'Guidelines for authors and peer reviewers of economic submissions'[43] (see Appendix 2). Any discrepancies in quality grading were resolved through discussion.

Data synthesis: cost-effectiveness

Data are presented in structured tables and described within the appropriate section of the results.

Chapter 4
Review of clinical effects

Introduction

Scope of clinical review

The scope of this clinical review included assessment of the clinical effects (positive change in status as well as adverse events) of each of the three anti-TNF-α agents: adalimumab (Humira), etanercept (Enbrel) and infliximab (Remicade) compared with conventional management of active AS. In so far as the evidence permitted, comparison between anti-TNF-α agents was explored.

The clinical review focused on identification and analysis of RCT-based evaluations of the three anti-TNF-α agents, but other designs were considered for the review. In particular, open-label extension studies of included RCTs were identified.

Selection of evidence

Evidence identified from bibliographic databases

A total of 728 non-duplicate records was identified in the search of electronic databases (see Chapter 3 and Appendix 1). These records were first screened for further consideration where more detailed inclusion/exclusion criteria were applied (216 records). Of the 216 records considered in detail, 36 records related to RCTs of adalimumab, etanercept or infliximab against placebo. Eight RCTs were identified within these records, all of which were placebo controlled.[26,44–50] Two RCTs studied adalimumab,[44,45] four studied etanercept[26,46–48] and two studied infliximab.[49,50]

Twenty-one records were related to open-label extension studies of five of the identified RCTs.[26,46–48,50]

For resource reasons, other non-RCTs, which could not be linked with an included RCT, were not considered further within the time-frame of the assessment.

Evidence from manufacturers' submissions to NICE

Submissions of evidence were received from each of the three anti-TNF-α manufacturers.[51–53] Each submission included an overview of RCTs of the company's anti-TNF-α product, which appeared comprehensive in terms of the range of RCTs included (compared with the results of the present searches). Only the Wyeth submission included an RCT not already identified in the search (Wyeth: 0881A3-314, referred to as the Wyeth study[53] elsewhere in this chapter), bringing the total number of etanercept RCTs to five. The data on this additional RCT were submitted to the assessment group as commercially in confidence.

To obtain further data on disease and functional measures (particularly change in score data accompanied with appropriate standard deviations), a data request pro forma was designed, which was distributed by the National Institute for Health and Clinical Excellence (NICE) on behalf of the reviewers. All three manufacturers responded.

Evidence from handsearching and unpublished sources

Handsearching of major conference proceedings (including web-based abstract listings) identified a number of abstracts of potential relevance to the review. On closer consideration of the additional benefit of including these abstracts and given the volume of data identified in the search of databases or provided in company submissions, it was determined that additional abstracts were not to be considered further for inclusion in the review. Therefore, all abstracts that are included in the review were indexed on and identified through searching of electronic databases. The authors are confident that no RCTs were missed by not considering the 'handsearched abstracts' further.

Included studies: RCTs

Selection

In all, nine placebo-controlled RCTs (reported among 37 records and representing the Wyeth study:[53] 1611 participants) were selected for inclusion in the clinical review.[26,46–81] Data from eight of the nine RCTs were included in the meta-analysis for at least one outcome. The only study not subject to meta-analysis was Brandt,[47] a relatively small study (n = 33) of etanercept which only followed patients for 6 weeks.

Study characteristics

All studies included a placebo-controlled arm and continued some form of conventional care (such as NSAIDs with or without DMARDs) for patients allocated to either treatment with anti-TNF-α agent or placebo. The Wyeth study[53] included etanercept at two dosing regimens (50 mg once weekly or 25 mg twice weekly) as well as a placebo group.[46] Only the 25-mg regimen is considered in the clinical review. Two RCTs studied adalimumab,[44,45] five studied etanercept[26,46–48,53] and two studied infliximab.[49,50]

Composite binary measures of 'response' to therapy were primary end-points in all nine RCTs. These measures of response were ASAS 20 for seven trials[26,44–46,48,49,53] and BASDAI 50 for the Brandt and Braun studies.[47,50] A range of additional continuous scale outcomes, such as BASDAI, BASFI and the Bath Ankylosing Spondylitis Metrology Index (BASMI), as well as their component measures, was recorded within trials. These are presented in *Table 2*.

Key eligibility criteria were linked to assessment and grading of patients' AS. Demonstration of 'active AS' was a stated prerequisite in seven trials.[26,44–48,53] The inclusion criteria for Calin,[26] Davis[48] and the Wyeth study[53] appeared broader, as patients with lower scores for disease, function or symptoms than the other six trials were eligible for enrolment. These studies accepted patients with '3:10' scores (e.g. scores of ⩾30 on 100-mm VAS or BASDAI ⩾3 on a ten-point scale) for BASDAI and some symptoms (such as back pain), whereas the other trials only accepted patients with '4:10' scores (e.g. VAS ⩾40 on 100-mm VAS, or BASDAI scores from 4 on a ten-point scale). The two trials of adalimumab also required patients to have inadequately responded to, or be intolerant of, at least one NSAID or to have experienced treatment failure with one or more DMARDs.

Complete ankylosis excluded patients from ATLAS, ASSERT, Calin, Davis, Gorman and the Wyeth study[26,44,46,48,49,53] and active TB was stated as an exclusion from ASSERT, Brandt and Braun.[47,49,50] The Davis, Gorman and Wyeth studies[46,48,53] stated that those treated with DMARDs other than sulfasalazine, methotrexate or hydroxychloroquine were ineligible for inclusion.

Three of the etanercept studies[26,46,48] permitted continuation of NSAID, DMARD or corticosteroid therapy. Within the ASSERT and Braun infliximab studies[49,50] and the Brandt etanercept trial,[47] NSAIDs were permitted but DMARDs or corticosteroids were not. Reduction in dose of NSAID was permitted in the Brandt and Braun studies.[47,50] The two adalimumab studies appeared to permit the use of DMARDs or corticosteroids, but limited initiation or change in dose of DMARD therapy before week 36 and restricted reduction in corticosteroid therapy until after week 24 of either study.

Information on co-therapies was not available for the Wyeth study,[53] although according to the entry criteria DMARDs were permitted (at least at the beginning of the study) and quite possibly continued as in other etanercept studies such as Calin and Davis.[26,48]

All of the studies were conducted in multiple centres, although no exact number of study centres was provided for Brandt, Gorman, Braun or the Wyeth study.[46,47,50,53] The Brandt and Braun studies[47,50] were limited to Germany, four studies included patients in Europe,[26,44,48,49] four included patients in the USA;[44,46,48,49] ASSERT, Davis and Canadian AS were conducted in Canada,[45,48,49] but the location of the Wyeth study[53] centres could not be determined from the information provided.

Study characteristics are detailed in *Table 2*. Individual trials are summarised in the section 'Included study summary' (p. 18).

Participant characteristics

The majority of participants were male in all studies. Men made up 70–90% of the patients studied in ASSERT, Brandt, Calin, Davis, ATLAS, Canadian AS and the Wyeth studies.[26,44,45,47–49,53] Only Braun[50] (infliximab 68%, placebo 63%) and the etanercept arm (65%) of Gorman[46] recruited a proportion of men outside this range. Mean age ranged from 32 years (Brandt,[47] placebo arm) to 45.43 years (Calin,[26] etanercept arm). All other trial arms reported a mean (or median) age within the 38–43-year range. Disease duration ranged from 8 years (ASSERT,[49] infliximab arm) to 16 years (Braun,[50] infliximab arm). Details on determination of disease duration were not described. Detection of HLA-B27 genotype, reported in five trials,[46–50] was in the range of 77–95%. Biomarker/acute-phase reactant levels were reported for seven of the nine studies.[26,44,45,48–50,53] Treatment history was reported for six studies.[26,44–46,48,53]

TABLE 2 *Study characteristics: RCTs*

Study	Comparison[a]	End-points (primary; secondary)	Centres, location	Inclusion	Exclusion	Co-therapies	Support
ATLAS[44]	Adalimumab 40 mg (once every 2 weeks, 24 weeks) Placebo Early escape from 12 weeks	ASAS 20 at week 2; [**Commercial-in-confidence information removed**] ASAS 50, ASAS 70, BASDA 150, SF-36 (PCS, MCS), ASQoL	43 sites USA and Europe	Active AS Active AS: 2 of 3 of BASDAI score ⩾40 mm, total back pain (VAS) ⩾40 mm, morning stiffness ⩾1 hour; inadequate response/ intolerant to Rx with ⩾1 NSAID; failed one or more DMARDs Total SA permitted, up to 10% of those enrolled		DMARDs (corticosteroids, MTX, SSZ or HCQ) should not have been initiated or increased before week 36; corticosteroids, could have been decreased, or stopped after week 24 at investigator's discretion. MTX, SSZ or HCQ should not have been decreased before week 36	Abbott
Canadian AS[45]	Adalimumab 40 mg (once every 2 weeks, 24 weeks) Placebo Early escape from 12 weeks	ASAS 20 at 12 weeks; [**Commercial-in-confidence information removed**]	11 sites Canada	Active AS Active AS: 2 of 3 of BASDAI score ⩾40 mm, total back pain (VAS) ⩾40 mm, morning stiffness ⩾1 hour; inadequate response/ intolerant to Rx with ⩾1 NSAID; failed one or more DMARDs	Total SA	DMARDs (corticosteroids, MTX, SSZ or HCQ) should not have been initiated or increased before week 36; corticosteroids, could have been decreased, or stopped after week 24 at investigator's discretion. MTX, SSZ or HCQ should not have been decreased before week 36	Abbott
Wyeth study[53]	Etanercept 25 mg (twice per week, 12 weeks) Placebo	ASAS 20 (at 12 weeks) ASAS 50, ASAS 70, BASDAI, partial remission, BASDAI, APR, global assessment, spinal mobility, peripheral joint counts; APR, safety; components of BASDAI and ASAS	Multiple centres (stated)	Active AS: duration of morning stiffness VAS ⩾30; intensity of morning stiffness VAS ⩾30 and PxGA (VAS 0–100) ⩾30 or average VAS for total and nocturnal pain ⩾30 or BASFI ⩾30; Dx: modified New York criteria	Complete ankylosis; DMARDs (other than SSZ, MTX or HCQ)		Wyeth

continued

TABLE 2 *Study characteristics: RCTs (cont'd)*

Study	Comparison[a]	End-points (primary; secondary)	Centres, location	Inclusion	Exclusion	Co-therapies	Support
Brandt[47]	Etanercept 25 mg (twice per week, 6 weeks) Placebo	BASDAI 50 BASDAI, BASFI, BASMI, pain, QoL, CRP	Multiple (stated) Germany	Active AS (by New York criteria, BASDAI ⩾4, spinal pain of ⩾4 on 0–10 scale	Active TB within 3 years; serious infection within 2 months; malignancies within 5 years; MS or a related disorder, current 'severe disease'	DMARDs, oral corticosteroids withdrawn ⩾4 weeks before screening; NSAIDs continued (without increase over the baseline dose, reduction was allowable)	Wyeth (study drug)/ German Ministry of Research
Calin[26]	Etanercept 25 mg (twice per week, 12 weeks) Placebo	ASAS 20 after 12 weeks ASAS 20 (at 2, 4 and 8 weeks), ASAS 50, ASAS 70, ASAS components, BASDAI, APR, spinal mobility, safety (at 2, 4, 8 and 12 weeks)	14 Europe	Active AS Duration of morning stiffness VAS ⩾30; intensity of morning stiffness VAS ⩾30 and PxGA (VAS 0–100) ⩾30 or average VAS for total and nocturnal pain ⩾30 or BASFI ⩾30	Complete ankylosis; DMARD Rx (other than SSZ, MTX or HCQ)	Physiotherapy (where existing programmes, continued); concomitant use of NSAIDs, DMARDs, corticosteriods permitted (participants stratified by baseline DMARD use and then randomised, changes in or multiple NSAID use exclusion criteria)	Wyeth research
Davis[48]	Etanercept 25 mg (twice per week, 24 weeks) Placebo	ASAS 20 (at 12 and 24 weeks) ASAS 50, ASAS 70, partial remission, BASDAI, APR, global assessment, safety	28 USA, Canada, Europe	Active AS Duration of morning stiffness VAS ⩾30; intensity of morning stiffness VAS ⩾30 and PxGA (VAS 0–100) ⩾30 or average VAS for total and nocturnal pain ⩾30 or BASFI ⩾30	Complete ankylosis; DMARD Rx (other than SSZ, MTX or HCQ)	Px continued stable Rx regimens of HCQ, SSZ, MTX, NSAIDs or prednisone; standard doses of analgesics (paracetamol, codeine, hydrocodone, oxycodone, tramadol) permitted	Immunex Corp. (Wyeth research)
Gorman[46]	Etanercept 25 mg (twice per week, 4 months, 112 days) Placebo	Morning stiffness, pain, nocturnal spinal pain, BASFI, PxGA, SJC 'response' (20% improvement in 3/5 measures	Multiple practices (stated) USA	Active AS (New York) despite accepted Rx (moderate disease activity; 40:100 mm VAS, inflammatory back pain, morning stiffness ⩾45 minutes), standard Rx stable >4 weeks	Other SA; complete ankylosis; history of recurrent infection; cancer; serious renal, liver, haematological or neurological disorder	Px continued previous Rx regimens (of NSAIDs and/or DMARDS: prednisone, SSZ, MTX, azathioprine, gold)	Immunex Corp. (Wyeth research)

continued

TABLE 2 *Study characteristics: RCTs (cont'd)*

Study	Comparison[a]	End-points (primary; secondary)	Centres, location	Inclusion	Exclusion	Co-therapies	Support
ASSERT[49]	Infliximab (5 mg/kg at 0, 2, 6, 12 and 18 weeks) Placebo	ASAS 20 (at 24 weeks), ASAS 40, ASAS partial remission, disease activity, physical functioning, range of motion, musculoskeletal assessment, QoL	33 USA, Canada, Europe	AS for ⩾3 months (New York) BASDAI ⩾4 (0–10); spinal pain ⩾4 (VAS, 0–10 cm); normal chest radiograph; TB negative (by PPD skin test or documented screening)	Complete ankylosis; other RA; fibromyalgia; serious infection (⩽2 months), TB (or TB contact); opportunistic infection ⩽6 months; HBV; HIV; transplanted organ; malignancy; MS; CHF	Permitted: NSAIDs (paracetamol, tramadol) stable doses; not permitted: SSZ, MTX <2 weeks*, DMARDs (other than SSZ or MTX) <6 months*, systemic corticosteroids <1 month, anti-TNF (other than infliximab) <3 months*, cytotoxic drugs <12 months* (*prior to screening)	Centocor, USA
Braun[50]	Infliximab (5 mg/kg, 12 weeks) Placebo	BASDAI 50 (improvement of disease activity by 50% at 12 weeks, measured by BASDAI) VAS for spinal pain, BASFI, BASMI, SF-36, the working group response criteria, concentration of CRP in serum and ESR	Multiple centres (stated) Germany	New York criteria for AS BASDAI of ⩾4; spinal pain of ⩾4 cm (VAS)	Active TB ⩾3 years, specific changes in the chest radiograph at baseline; serious infections ⩾2 years; lymphoproliferative disease or malignancy ⩾5 years; signs or symptoms of severe renal, pulmonary, cardiac, neurological or cerebral disease	DMARDs and oral corticosteroids were withdrawn ⩾4 weeks before screening, patients were allowed to take NSAIDs, but the dose could not be increased over the baseline value (the dose could be reduced and such reductions were recorded)	German Ministry of Research and Essex Pharma

[a] Allocated interventions were given in addition to conventional therapy. Early escape: subjects who did not reach ASAS 20 (based on evaluation by the investigator) at or after week 12 were considered for open-label adalimumab treatment (early escape group) or remained on allocated medication; discontinued participation in trial.

APR, acute phase reactants; CHF, congestive heart failure; Dx, diagnosis; HBV, hepatitis B virus; HCQ, hydroxychloroquine; MCS, mental component score; MS, multiple sclerosis; MTX, methotrexate; PCS, physical component score; PPD, purified protein derivative; Px, patient's; PxGA, patient's global assessment; QoL, quality of life; Rx, treatment; SJC, swollen joint count; SSZ, sulfasalazine.

Details of participant characteristics including accompanying co-morbidity are presented in *Tables 3* and *4*. A brief outline of each trial is provided in the next section.

Comparability of AS patients in the RCT evidence base and those in clinical practice

The BSR criteria[1] for anti-TNF-α therapy require that patients have failed or are intolerant to conventional treatment regimens. The adalimumab studies[44,45] had explicit entry criteria limiting to only patients meeting these conditions. The composition of other trials was less clear. Although the presence of 'active AS' in trial participants would be consistent with existing therapies having been unsuccessful, complete criteria for treatment failure may not necessarily have been satisfied.

Therefore, an additional enquiry was forwarded to the manufacturers of etanercept and infliximab to obtain clarification. The manufacturer of infliximab (Schering-Plough) responded indicating that failure of conventional therapies was [**Commercial-in-confidence information removed**]. The comparability of patients from etanercept and infliximab RCTs to patients satisfying BSR criteria in the healthcare setting and licence requirements is therefore uncertain.

Included study summary

Data are reported as provided in the evidence source (published paper, abstract or company submission). Some sources express BASDAI or BASFI score out of 100, whereas others express scores as a proportion of 10; the original format in the source is retained in this section.

Adalimumab studies

In the large ATLAS study,[44] adalimumab (n = 208) 40 mg (once every 2 weeks for 24 weeks) was compared with 107 people allocated to placebo. The composite binary outcome ASAS 20 at week 12 was the primary outcome. In addition, Abbott: [**Commercial-in-confidence information removed**]. Participants were required to demonstrate active AS to be included. Disease activity (BASDAI) for those randomised at baseline was reported in the company submission as mean 6.25 (SD 1.71) for adalimumab, mean 6.34 (SD 1.67) for placebo. Mean functional scores (BASFI) were 52.40 (SD 22.12) for adalimumab and 56.38 (22.00) for placebo.

The smaller Canadian AS study[45] examined the same regimen of adalimumab as ATLAS, but in 38 people (40 mg, once every 2 weeks for 24 weeks) compared with 44 allocated to placebo. Similarly, ASAS 20 at 12 weeks was the primary outcome; Abbott: [**Commercial-in-confidence information removed**]. Canadian AS required participants to demonstrate active AS, recruiting an adalimumab group with a mean BASDAI of 6.15 (SD 1.72) and placebo group with mean BASDAI 6.46 (SD 1.64). Mean functional scores (BASFI) were 53.3 (SD 20.4) for adalimumab and 55.6 (SD 21.8) for the placebo group.

Participants in both trials[44,45] were offered 'early escape' with open-label treatment with adalimumab if they had not achieved an ASAS 20 response at or following their week 12 assessment. The Abbott submission[51] reported that this feature of the trials was agreed with the food and Drug Administration (FDA) for ethical reasons. Those opting for open-label adalimumab were counted only as non-responders for outcomes in either the treatment or placebo group.

Etanercept studies

Brandt[47] studied etanercept (n = 16 administered at 25 mg twice a week for 6 weeks) versus placebo (n = 17). The primary end-point was BASDAI 50 (improvement of disease activity by 50%). Only people with active AS were included. Mean BASDAI for the etanercept group was 6.5 (SD 1.2) and 6.6 (SD 1.0) for the placebo group. Functional scores ranged from a mean BASFI of 53.33 (SD 20.4) for the etanercept arm to a mean of 55.61 (SD 21.8) for the placebo group.

Calin[26] studied etanercept (n = 45, 25 mg given twice weekly for 12 weeks) versus placebo (n = 39). The primary end-point was ASAS 20 after 12 weeks. Only people with active AS were included. Disease activity (BASDAI) was recorded as mean 61.0 and 58.6 for etanercept and placebo groups, respectively (standard deviations not provided). Mean BASFI in the two groups was 6.2 (SD 1.8) or 5.3 (SD 2.4) for etanercept and placebo, respectively.

Davis[48] was one of the larger studies of etanercept (n = 138, 25 mg given twice per week for 24 weeks) versus placebo (n = 139). The stated primary end-point was ASAS 20 (at 12 and 24 weeks). Active AS was required for inclusion, with mean BASDAI for the etanercept group reported as 58.1 (SD 1.5) and 59.6 (SD 1.4) for the placebo group. Functional status (BASFI) at baseline was 60.2 for etanercept and 57.2 for placebo (standard deviations not identified).

TABLE 3 *Participant characteristics: RCTs*

Study	Numbers included		Gender (% male)	Age, mean (SD) (years)	Disease duration (years)	HLA-B27 (% positive)	Biomarkers/EPR	Treatment history	Other reported co-morbidity
ATLAS[44] M03-607	Adalimumab Placebo	208 107	75 74	41.7 (11.69) 43.4 (11.32)	11.28 (9.999) 10.01 (8.34)		CRP 1.76 (2.203) (n = 204) CRP 2.16 (2.845) (n = 105)	DMARDs 19.2% DMARDs 20.6%	Detail in submission
Canadian AS[45] M03-606	Adalimumab Placebo	38 44	76 81	41.9 (11.14) 40.0 (10.87)	14.52 (9.02) 12.14 (8.65)		CRP 1.77 (1.68) CRP 2.29 (2.64)	NSAIDs 89.5%, corticosteroids 13.2% NSAIDs 90.9%, corticosteroids 15.9%	Detail in submission
Wyeth study[53]	Etanercept Placebo	150 51	76 (25 mg) 78.4	39.83 (25 mg) 40.06	9.97 (25 mg) 8.48		CRP 19.75 mg/l (25 mg) CRP 21.66 mg/l	NSAIDs 84.7%, DMARDs 36.7%, corticosteroids (25 mg) 107% NSAIDs 78.4%, DMARDs 33%, corticosteroids 17.6%	
Brandt[47]	Etanercept Placebo	16 17	71 75	39.8 (9.1) 32.0 (7.5)	14.9 (8.3) 11.4 (8.8)	86 94			Anterior uveitus history 35.7%, peripheral arthritis 35.7% Anterior uveitus history 18.8%, peripheral arthritis 35.7%
Calin[26]	Etanercept Placebo	45 39	80 77	45.3 (9.5) 40.7 (11.4)	15.0 (8.8) 9.7 (8.2)		ESR median 27 mm/hour, CRP 19.3 mg/l ESR median 26 mm/hour, CRP 23.6 mg/l	Concomitant use of NSAIDs 85%, DMARDs 41%, corticosteroids 15% NSAIDs 87%, DMARDs 38%, corticosteroids 15%	

continued

TABLE 3 *Participant characteristics: RCTs (cont'd)*

Study	Numbers included		Gender (% male)	Age, mean (SD) (years)	Disease duration (years)	HLA-B27 (% positive)	Biomarkers/EPR	Treatment history	Other reported co-morbidity
Davis[48]	Etanercept Placebo	138 139	76 76	42.1 (range 24–70) 41.9 (range 18–65)	10.1 (range 0–30.7) 10.5 (range 0–35.3)	84 (108 patients, but data not available for all) 84 (109 patients, but data not available for all)	CRP 1.9 (SEM 0.2) mg/dl, 25.9 (SEM 1.8) mm/hour CRP 2.0 (SEM 0.2) mg/dl, 25.4 (SEM 1.9) mm/hour	NSAIDs 126/138, DMARDs 44/138, corticosteroids 18/138 NSAIDs 128/139, DMARDs 43/139, corticosteroids 20/139	Crohn's/UC, uveitis/iritis, psoriasis
Gorman[46]	Etanercept Placebo	20 20	65 90	38 (10) 39 (10)	15 (10) 12 (9)	95 90		NSAIDs 80%, DMARDs 40%, corticosteroids 25%, combination 45% NSAIDs 95%, DMARDs 35%, corticosteroids 10%, combination 35% NSAIDs 90%, DMARDs 38%, prednisone 18%	Peripheral joint involvement 60%, peripheral joint involvement 60%
ASSERT[49]	Etanercept Placebo	201 78	78 87	40 (IQR 32, 47) 41 (IQR 34, 47)	7.7 (IQR 3.3, 14.9) 13.2 (IQR 3.7, 17.9)	86 88	CRP 1.5 (IQR 0.7, 3.2) mg/dl CRP 1.7 (IQR 0.7, 3.3) mg/dl		Uveitus 72/201, psoriasis 16/201, IBD 13/201 Uveitus 25/78, psoriasis 5/78, IBD 6/78
Braun[50]	Etanercept Placebo	35 35	68 63	40.6 (8) 39 (9.1)	16.4 (8.3) 14.9 (9.3)	91 77	CRP 24 (4–131), ESR 29 (2–90) CRP 18 (1–74), ESR 26 (3–88)		Anterior uveitus 50% Anterior uveitus 43%

CRP, C reactive protein; IBD, inflammatory bowel disease; IQR, interquartile range; UC, ulcerative colitis.

TABLE 4 *Further participant characteristics: RCTs*

	BASDAI: anti-TNF-α, mean (SD)	**BASDAI: placebo, mean (SD)**	**BASFI: anti-TNF-α, mean (SD)**	**BASFI: placebo, mean (SD)**	**BASMI: anti-TNF-α, mean (SD)**	**BASMI: placebo, mean (SD)**
ATLAS[44] (Abbott)	6.25 (1.709) 6.41 (range 1.5–9.7)	6.34 (1.67) 6.45 (range 2.0–9.5)	52.40 (22.118)	56.38 (21.999)		
Canadian AS[45] (Abbott)	6.15 (1.72)	6.46 (1.64)	53.3 (20.4) 56.30 (range 4.8–98.0)	55.6 (21.8) 52.90 (range 4.7–99.8)		
Wyeth study[53]	59.39 (NR)	61.14 (NR)	57.7 (NR)	59.69 (NR)		
Brandt[47]	6.5 [(SEM) 1.2]	6.6 [(SEM) 1.0]	53.33 (20.4)	55.61 (21.8)		
Calin[26]	61.0	58.6	6.2 [(SEM) 1.8]	5.3 [(SEM) 2.4]	4.1 (NR)	3.8 (2.1)
Davis[48]	58.1 (SEM 1.5)	59.6 (SEM 1.4)	60.2	57.2		
Gorman[46]	3.0 (0.7)	3.0 (0.7)	4.5 (2.1)	3.2 (2.5)		
ASSERT[49]	6.6 (IQR 5.3, 7.6)	6.5 (IQR 5.2, 7.1)	5.7 (IQR 4.5, 7.1)	6.0 (IQR 4.1, 7.2)	4.0 (IQR 2.0, 5.0)	4.0 (IQR 2.0, 6.0)
Braun[50]	6.5 (1.2)	6.3 (1.4)	5.4 (1.8)	5.1 (2.2)	3.7 (2.0)	3.7 (2.2)

(SEM), assumed to be SEM.

Gorman[46] compared etanercept (n = 20 administered twice per week at 25 mg for 16 weeks, 112 days) with placebo (n = 20). Response based on 20% improvement in ASAS criteria was the primary outcome. Active AS had to be demonstrated to permit inclusion. Mean BASDAI scores were 3.0 (SD 0.7) for both the etanercept and placebo groups. Mean BASFI scores were 4.5 (SD 2.1) for etanercept and 3.2 (SD 2.5) for placebo. Although different by over 1 BASFI score (means differed by 1.3 in score, indicating more severe disease in the etanercept group), it may also be worth noting that Gorman was a relatively small study and therefore susceptible to such imbalances between invention groupings.

Another large trial was presented in the Wyeth submission. The Wyeth study: the three-arm trial, 0881A3-314,[53] compared etanercept at 50 mg given once per week for 12 weeks (n = 155), 25 mg etanercept given twice per week (n = 150) and placebo (n = 51). Its primary outcome was ASAS 20 at 12 weeks. The study required that participants demonstrated active AS. Disease activity (mean BASDAI) scores were 59.39 and 61.14 for etanercept (25 mg) and placebo, respectively. Functional scores (mean BASFI) were 57.7 and 59.7 for etanercept (25 mg) and placebo, respectively (standard deviations not provided in submission).

Infliximab studies

ASSERT[49] was a relatively large study of infliximab (n = 201, administered at 5 mg/kg at 0, 2, 6, 12 and 18 weeks) versus placebo (n = 78) with a primary end-point of ASAS 20 at 24 weeks. The study reported inclusion criteria as AS "for at least 3 months prior to screening"[49] with comparable disease, functional and symptoms scores to other studies. Median BASDAI scores were 6.6 (IQR 5.3 to 7.36) for infliximab and 6.5 (IQR 5.2 to 7.31) for placebo. Median BASFI were 5.7 (IQR 4.5 to 7.1) or 6.0 (IQR 4.1 to 7.2) for infliximab or placebo groups.

Braun[50] compared infliximab (n = 35 given at 5 mg/kg) with placebo (n = 35). The primary end-point was BASDAI 50 (improvement of disease activity by 50%) at 12 weeks. The available reports of the Braun study did not use the term 'active AS' specifically, but the inclusion criteria for AS status appeared comparable to other studies. Mean BASDAI was reported as 6.5 (SD 1.2) for infliximab and 6.3 (SD 1.4) for placebo. Functional measures (BASFI) were 5.4 (SD 1.8) for infliximab and 5.1 (SD 2.2) for placebo.

Quality assessment

Details of the quality assessment of the RCTs are presented in *Table 5*.

Data analysis: RCTs

Approach to analysis

The effects of TNF-α inhibition were explored by combining binary or continuous data in a meta-analysis across all available trials and the three anti-TNF-α drugs (see the section 'Anti-TNF-α agents as a class versus placebo', p. 26). This approach was considered clinically acceptable by the expert advisors, although the three drugs were also examined individually, as subgroups within the meta-analysis (see the section 'Individual anti-TNF-α agents versus placebo', p. 27). Where data have been measured longitudinally, independent time-point analyses have been carried out at 12 and 24 weeks. The assumption that is made, based on these analyses, is that there is no correlation between the results at the various time-points, which may not be true. Data at 16 weeks' follow-up reported for the Groman study is included with the meta-analysis at 12 weeks. The meta-analysis was conducted, as appropriate for the data type, as described in the section 'Data analysis: clinical effectiveness', p. 10.

Although reported,[51] data for adalimumab at 24 weeks (from the ATLAS and Canadian AS studies[44,45]) were not included in the meta-analysis. The principal reason for excluding these data is due to the early escape open-label treatment options programmed into these studies.

From 12 weeks after beginning the trial, non-responders (defined for this trial as those not achieving ASAS 20) in either adalimumab or placebo were offered the option to receive open-label adalimumab for the remainder of the trial. Half or more of placebo-allocated patients took up this option at 12 weeks (55/107 in ATLAS,[44] 28/44 in Canadian AS[45]), rising to around 70% (74/107 in ATLAS[44]) and 80% (36/44 in Canadian AS[45]) of these patients by 24 weeks. Those opting for early escape were recorded as non-responders for ASAS outcomes and presumably rescored as 'no change' for disease and functional score (although there is uncertainty as to the management of data for these outcomes).

Given distinct study protocol from 12 weeks and the massive carry-forward of observations within outcomes reported at 24 weeks, the assessment

TABLE 5 *Quality assessment: included RCTs*

Checklist item	Randomisation			Comparability				Blinding				Withdrawals		
	1. Truly random	2. Allocation concealment	3. Number stated	4. Presented	5. Achieved	6. Eligibility criteria specified	7. Co-interventions identified	8. Assessors	9. Administration	10. Participants	11. Procedure assessed	12. >80% randomised in final analysis	13. Reasons stated	14. Intention to treat
ASSERT[49]	NS	NS	Yes	Yes	Part	Yes	Yes	NS	Yes	Yes	No	Yes	Yes	Part
ATLAS[a 44]	NS	NS	Yes	No	Yes	Part	Yes	NS	Yes	Yes	No	Yes	NS	No
Brandt[47]	NS	Yes	Yes	Yes	Part	Yes	Yes	NS	Yes	Yes	No	Yes	Yes	Yes
Braun[50]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NS	Yes	Yes	No	Yes	Yes	Yes
Calin[26]	NS	NS	Yes	Yes	Part	Yes	Yes	NS	Yes	Yes	No	Yes	Yes	Yes
Can AS[a 45]	NS	NS	Yes	No	Yes	Part	Yes	NS	Stat[b]	Stat[b]	No	Yes	NS	NS
Davis[48]	NS	NS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Ucl	Yes
Gorman[46]	Yes	Yes	Yes	Yes	Part	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Wyeth[a 53]	Stat[b]	NS	NS	Yes	Yes	Yes	NS	NS	Stat[b]	Stat[b]	NS	NS	NS	Yes

Part, partially fulfilled; NS, not stated; Ucl, unclear.
[a] Quality assessment on abstract/submission.
[b] Stated in source 'double-blind' RCT.

group felt that it was inappropriate to include data for ATLAS[44] or Canadian AS[45] in any meta-analysis at 24 weeks.

Methods for the meta-analysis of continuous longitudinal data have been developed by Jones and colleagues[82] and these methods were applied to the change and correlation data provided by companies (see the section 'Longitudinal meta-analysis', p. 31). Correlations were between 12 and 24 weeks, for outcomes in treatment and control groups. Currently there are no methods for the meta-analysis of longitudinal binary data, so only an independent time-point analysis was performed at each of the two time-points.

All the trials that were included in the review looked at the intervention of interest versus placebo; there were no direct comparisons of head-to-head treatment with different anti-TNF-α agents. Using the methods described by Song and colleagues,[83] statistical indirect comparisons of the drugs were considered, using the direct evidence that was available (see the section 'Indirect comparison of anti-TNF-α agents', p. 30). These results should be interpreted with caution owing to there being no direct evidence to which they can be compared. Regrettably, the limits of the trial data at 24 weeks also limited the extent of indirect comparison possible at this time-point.

Data presentation

Pooled effect estimates incorporating available data for all anti-TNF-α therapies analysed for a particular outcome and follow-up are presented within the meta-analysis forest plots (*Figures 1–8*). Within these same plots, studies are grouped according to anti-TNF-α type (i.e. adalimumab, etanercept or infliximab) in the meta-analysis. Pooled estimates (RR, 95% CI; or WMD, 95% CI) are provided for each of these anti-TNF-α subgroups. Study weighting within subgroups can be assessed by apportioning the pooled analysis weighting among the subgroup studies.

Where quantitative (statistical) heterogeneity was indicated, analysis using a random effects model

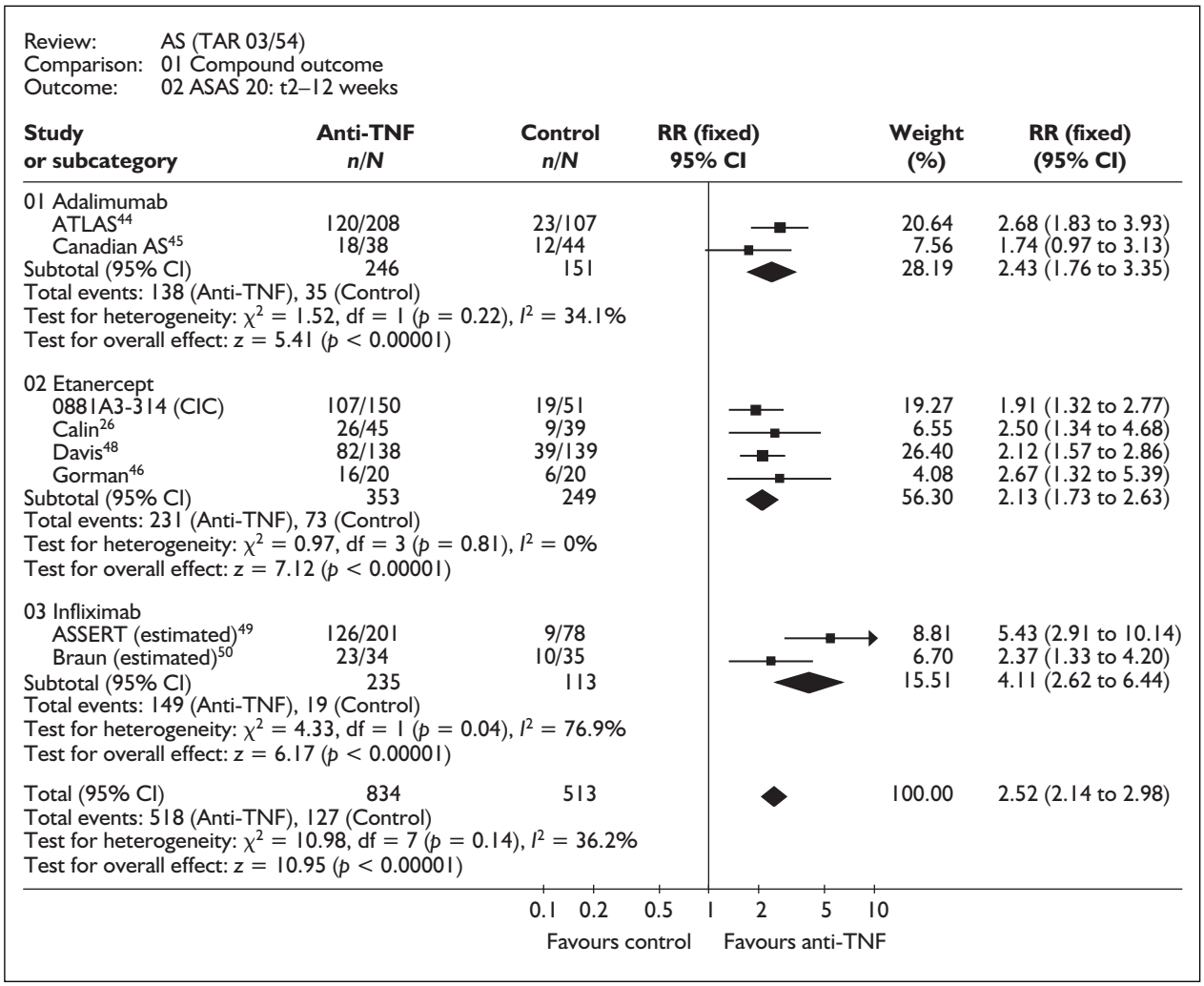

FIGURE 1 *Meta-analysis: composite binary outcomes ASAS 20 at 12 weeks*

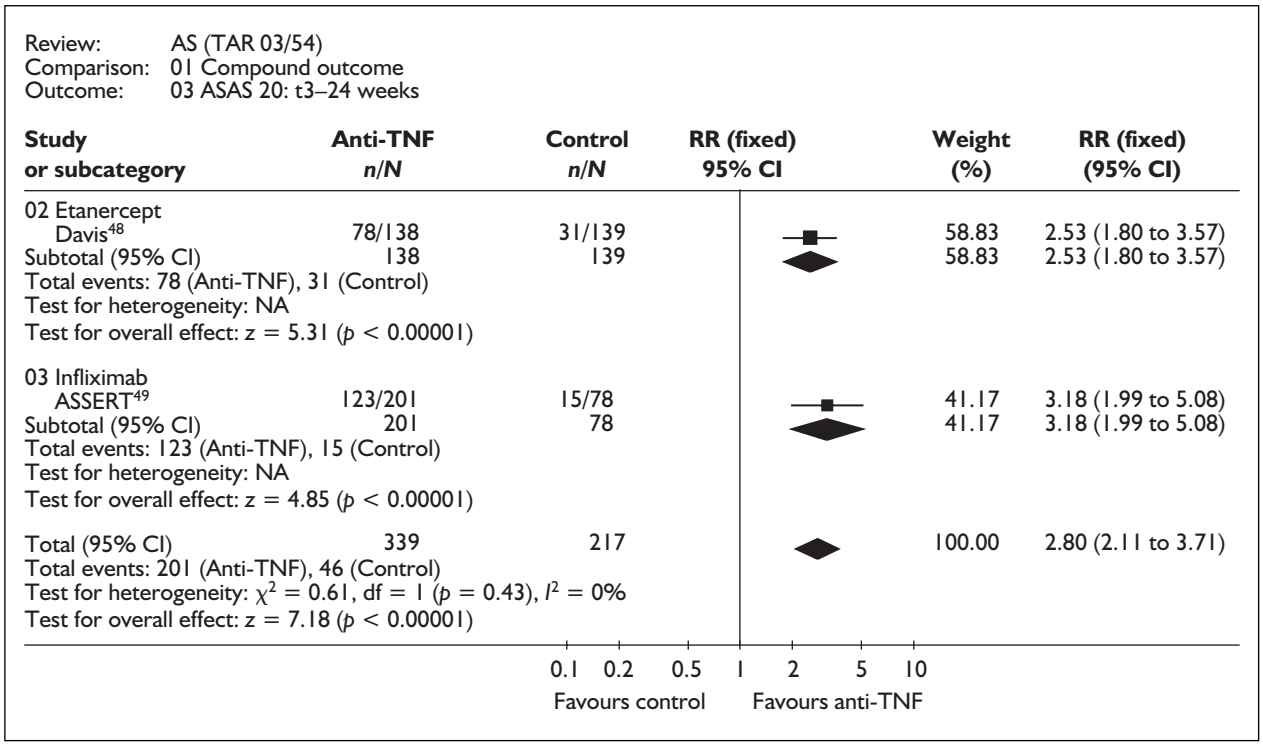

FIGURE 2 *Meta-analysis: composite binary outcomes ASAS 20 at 24 weeks. NA, not applicable.*

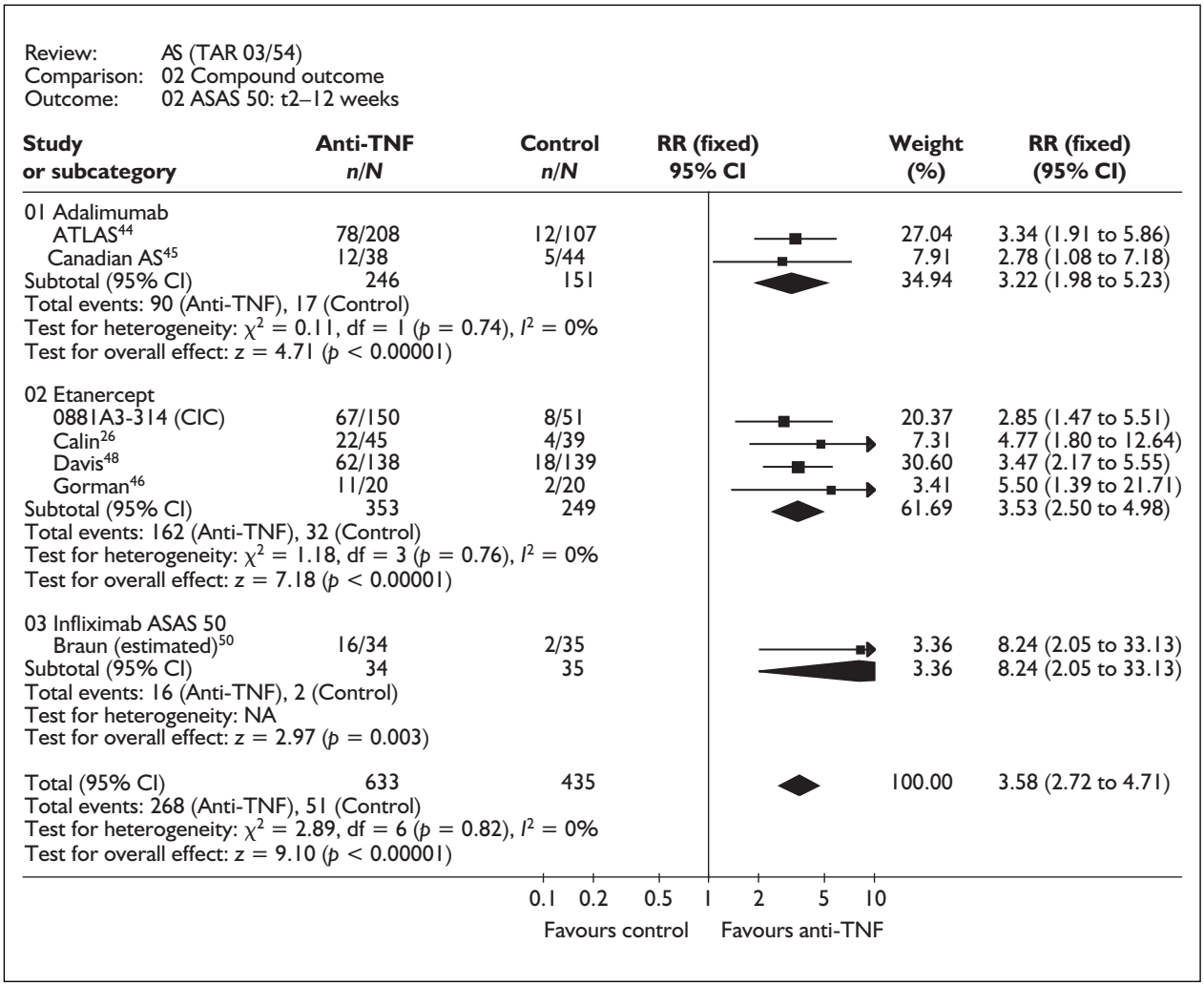

FIGURE 3 *Meta-analysis: composite binary outcomes ASAS 50 at 12 weeks*

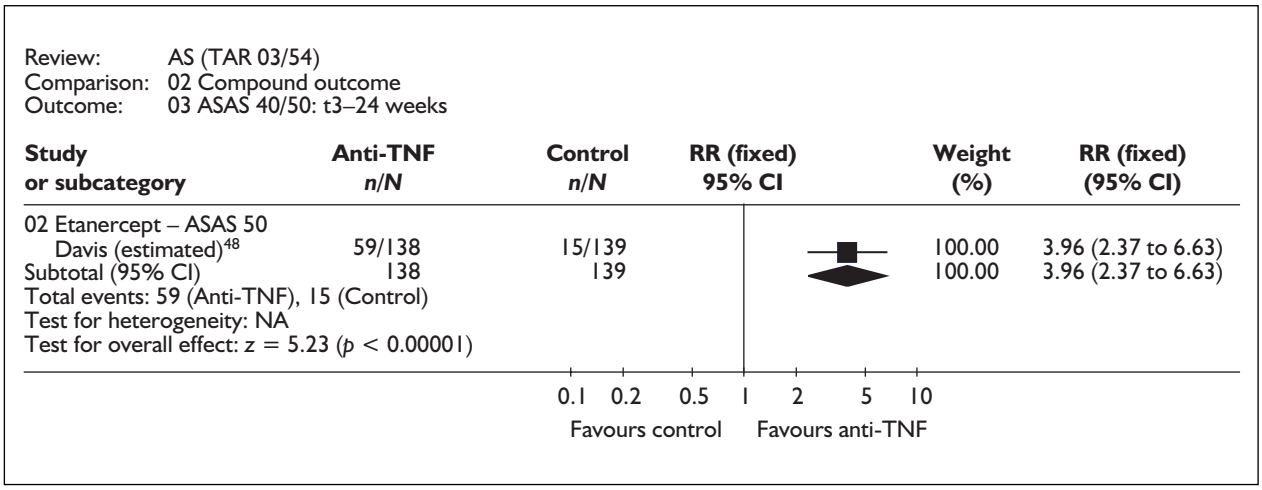

FIGURE 4 *Meta-analysis: composite binary outcomes ASAS 50 at 24 weeks. Estimated: rates of ASAS response interpreted from graphs.*

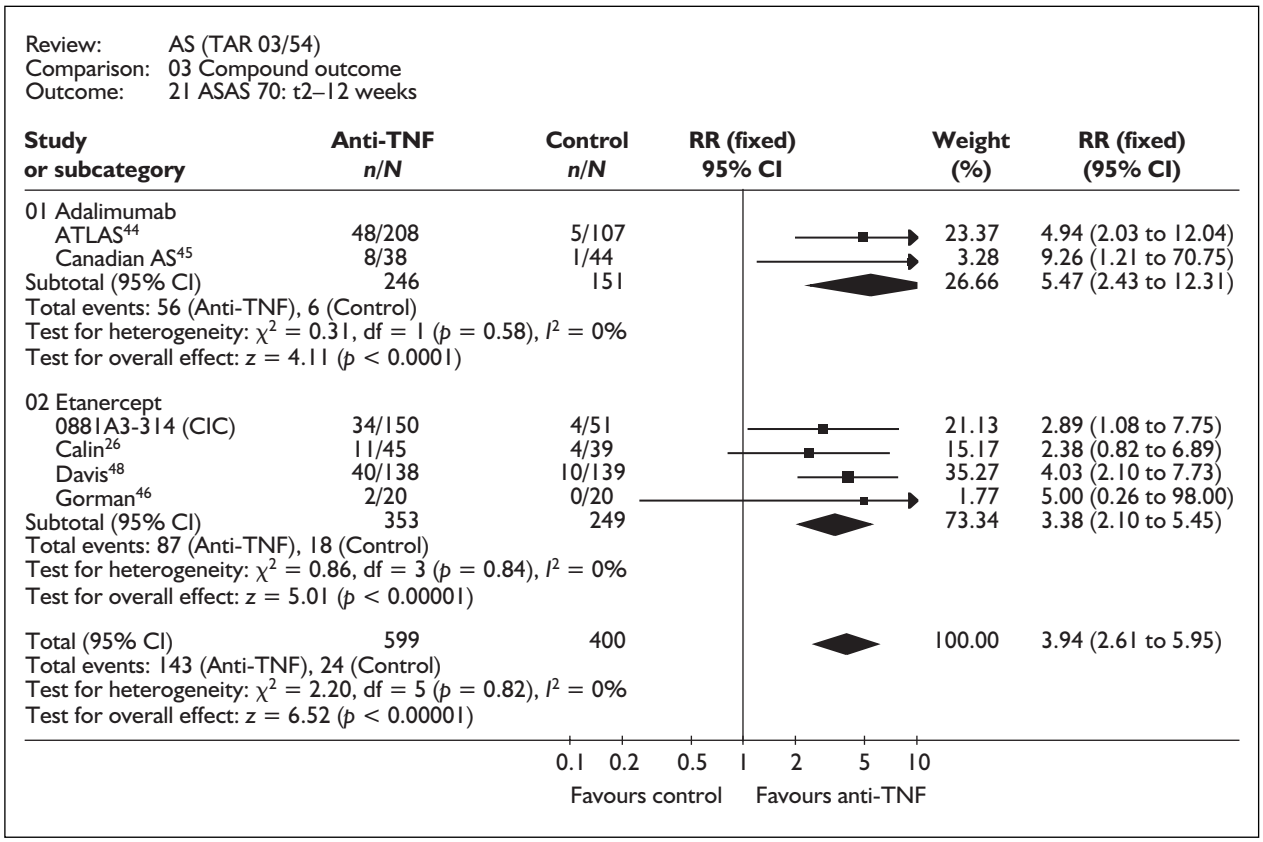

FIGURE 5 *Meta-analysis: composite binary outcomes ASAS 70 at 12 weeks*

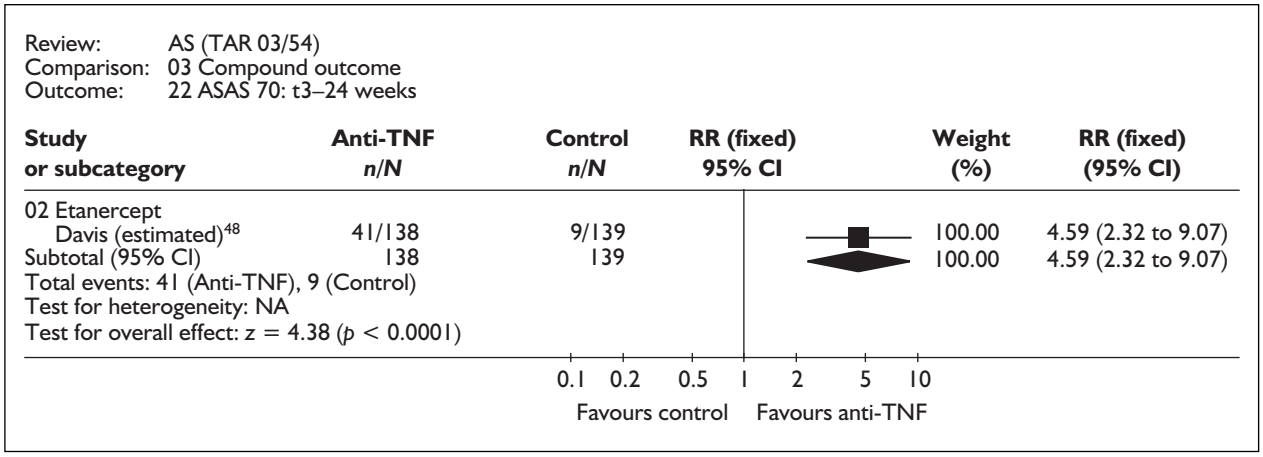

FIGURE 6 *Meta-analysis: composite binary outcomes ASAS 70 at 24 weeks. Estimated: rates of ASAS response interpreted from graphs.*

was conducted for comparison with the results of fixed effect-based analyses. In such cases, the results of random effects analysis are detailed in the text, while fixed effect summaries will be retained in the meta-analysis plots.

Anti-TNF-α agents as a class versus placebo

Composite binary outcomes

A composite binary outcome based on improvement in ASAS criteria was reported for most trials. Data on ASAS 20, ASAS 50 and ASAS 70 are available from at least one study for each of the three anti-TNF-α drugs.

Twenty per cent improvement in ASAS (ASAS 20) data indicates a significant advantage of anti-TNF-α therapy over placebo at 12 weeks and 24 weeks (RR 2.52, 95% CI 2.14 to 2.98; RR 2.80, 95% CI 2.11 to 3.71, respectively) (*Figures 1* and *2*). Studies contributing to the pooled effect estimate consistently and significantly favoured anti-TNF-α

treatment over placebo, with the exception of the small Canadian AS study,[45] which failed to demonstrate a statistically significant difference between treatment and control at 12 weeks. Moderate statistical heterogeneity was detected at 12 weeks (I^2 statistic = 36%, random effects RR 2.41, 95% CI 1.95 to 2.98, analysis not shown), but none was identified at 24 weeks.

A greater and more clinically significant threshold measure of improvement (ASAS 50) also demonstrated significantly greater rates of improvement with anti-TNF-α treatment (RR 3.58, 95% CI 2.72 to 4.71; RR 3.96, 95% confidence interval 2.37 to 6.63, respectively, at 12 and 24 weeks) (*Figures 3* and *4*). Minimal quantitative heterogeneity was observed for the pooled analysis.

When extending the threshold for improvement in ASAS criteria to 70% anti-TNF-α agents are still clearly more efficacious than placebo (RR 3.94, 95% CI 2.61 to 5.95 at 12 weeks only) (*Figures 5* and *6*). Infliximab data did not contribute to the pooled effect as ASAS 70 was not reported by the infliximab studies. Within those studies analysed, the small Gorman study,[46] with few events, and the Calin study[26] did not show a statistically significant difference. Minimal quantitative heterogeneity was observed for the pooled analysis.

Disease activity

Although change in BASDAI score was recorded in many studies, the expression of change in score and detail of reporting varied among studies, thereby limiting and complicating analysis. Mean changes in BASDAI score data, with related standard deviation, were obtained from the respective manufacturers of adalimumab, infliximab and etanercept. Mean percentage changes in BASDAI scores were only available for adalimumab and etanercept studies up to 12 weeks, but not reported from infliximab trials. Analysis of mean change will be followed by mean percentage change in BASDAI in the description below. All changes in score are relative to measurement of mean score at baseline.

The anti-TNF-α drugs were favoured over placebo at both 12 and 24 weeks for either measure of change in score; however, moderate (I^2 statistic = 34% and 22%) or moderate to medium (I^2 = 43%) heterogeneity is indicated for each of the pooled analyses. Using a random effects model, the results of meta-analysis estimate an additional mean reduction in 1.89 points of BASDAI at 12 weeks (random effects WMD –1.89, 95% CI –2.23 to –1.55) and an additional [**Commercial-in-confidence information removed**] points at 24 weeks (WMD [**Commercial-in-confidence information removed**], 95% CI [**Commercial-in-confidence information removed**] to [**Commercial-in-confidence information removed**]), based on pooling of data from Davis[48] (an etanercept study) and ASSERT[49] (infliximab) only (*Figure 7*).

Just over an estimated 20% extra reduction (22.16%) in BASDAI scores was observed for analysis of adalimumab and infliximab data on mean percentage change in BASDAI to 12 weeks (random effects WMD –22.16, 95% CI –28.39 to –15.93).

Function (Figure 8)

As with BASDAI scores, comparison of functional change (mean BASFI) between anti-TNF-α drugs was available as absolute change and percentage changes and calculated relative to baseline values. Moderate to medium levels of heterogeneity (I^2 = 40%) were observed for the pooled analysis of percentage change in BASFI at 12 weeks.

Treatment with anti-TNF-α drugs significantly reduced scores in comparison with placebo in the pooled analysis. An estimated additional 1.46 mean reduction in BASFI score was determined at 12 weeks (WMD –1.46, 95% CI –1.69 to –1.24), which was [**Commercial-in-confidence information removed**] to the added reduction in score up to 24 weeks of [**Commercial-in-confidence information removed**] (random effects WMD [**Commercial-in-confidence information removed**], 95% CI [**Commercial-in-confidence information removed**] to [**Commercial-in-confidence information removed**]). Additional percentage change in BASFI score was estimated to be 23.35% at 12 weeks (random effects WMD –23.35, 95% CI –28.64 to –18.05, using data from available adalimumab and etanercept reports) (*Figure 8*).

Individual anti-TNF-α agents versus placebo

Composite binary outcomes

With reference to each of the subgroupings that made up the meta-analysis in the preceding section, the results of the meta-analysis of ASAS 20, ASAS 50 and ASAS 70 response of individual anti-TNF-α drugs will now be discussed. Each of the three drugs of interest – adalimumab, etanercept and infliximab – will be considered in turn for ASAS 20, ASAS 50 and, if applicable, ASAS 70 for each available period of follow-up.

Analysis of adalimumab performance against placebo indicates that, for pooled effect estimates,

i. BASDAI, mean change from baseline at 12 weeks

[**Contains confidential information**]

ii. BASDAI, mean change from baseline at 24 weeks

[**Contains confidential information**]

iii. BASDAI, mean percentage change from baseline at 12 weeks

[**Contains confidential information**]

FIGURE 7 *Meta-analysis: BASDAI. Adalimumab and etanercept change in score data adjusted from 0–100 to 0–10 scale.*

i. BASFI, mean change from baseline at 12 weeks

[**Contains confidential information**]

ii. BASFI, mean change from baseline at 24 weeks

[**Contains confidential information**]

iii. BASFI, mean percentage change from baseline at 12 weeks

[**Contains confidential information**]

FIGURE 8 *Meta-analysis: BASFI. Adalimumab and etanercept change in score data adjusted from 0–100 to 0–10 scale.*

there are significantly higher rates of improvement with adalimumab for ASAS 20, ASAS 50 and ASAS 70 at 12 and 24 weeks. The likelihood of achieving a set level of improvement, compared with placebo, was 2.43-fold higher for 20% improvement, 3.22-fold higher for 50% improvement and 5.47-fold higher for 70% improvement (12 weeks only); full results presented in *Figures 1–6*.

Of note is that the Canadian AS study[45] is marginally outside statistical significance for ASAS 20 at 12 weeks and presents broad confidence intervals (although still within statistical significance) for other ASAS thresholds. This study lacked statistical power. No quantitative heterogeneity was apparent except for analysis of ASAS 20 at 12 weeks (moderate, $I^2 = 36\%$). The random effects analysis for this outcome and follow-up resulted in a relative risk of 2.29 (95% CI 1.51 to 3.47).

Etanercept analysed at 12 and 24 weeks for performance against ASAS 20, ASAS 50 and ASAS 70 criteria demonstrated significantly higher rates of improvement compared with placebo. Incremental reductions in score were 2.13- and 2.53-fold higher for 20% improvement, 3.53- and 3.96-fold higher for 50% improvement, and 3.38- and 4.59-fold higher for 70% improvement (12 and 24 weeks, respectively; full results presented in *Figures 1–6*). Within individual trials of etanercept, only Gorman[46] and Calin[26] (ASAS 70 assessed at 12 weeks) failed to maintain a statistically significant difference between placebo and treatment.

Infliximab-treated patients assessed for ASAS 20 and ASAS 50 (or ASAS 40) at 12 and 24 weeks showed statistically significant greater rates of improvement than those allocated to placebo. Twenty per cent improvement was 3.56-fold (random effects) and 3.18-fold more likely with infliximab at 12 and 24 weeks. However, the 12-week data should be considered with caution owing to the high levels of heterogeneity indicated (random effects RR 3.56, 95% CI 1.47 to 8.58, $I^2 = 77\%$). The Braun study[50] indicates that, compared with placebo, it is 8.24-fold more likely for a patient treated with infliximab to achieve 50% improvement at 12 weeks. Analysis of 40% improvement from the ASSERT study[49] produces a more conservative estimate of a 2.38-fold increase in the likelihood of achieving this level of

improvement at 12 weeks. At 24 weeks, a 4.01-fold increase in the likelihood of achieving 40% improvement with infliximab in the ASSERT trial[49] is indicated. Full results are presented in *Figures 1–4*. No ASAS 70 data were available.

Disease activity

Assessment of mean change in BASDAI scores between those treated with adalimumab and placebo were [**Commercial-in-confidence information removed**] (95% CI [**Commercial-in-confidence information removed**] to [**Commercial-in-confidence information removed**]) at 12 weeks. No statistical heterogeneity was apparent for meta-analysis across studies of adalimumab.

Etanercept treatment was associated with an incremental reduction in score of 1.67 (WMD –1.67, 95% CI –2.10 to –1.24) at 12 weeks and 2.00 (WMD –2.00, 95% CI –2.61 to –1.39) at 24 weeks (analysis based on the Davis study[48] only).

Treatment with infliximab demonstrated a [**Commercial-in-confidence information removed**] in mean change in BASDAI compared with placebo at 12 and 24 weeks. Results of analysis at 12 weeks were WMD [**Commercial-in-confidence information removed**] (95% CI [**Commercial-in-confidence information removed**] to [**Commercial-in-confidence information removed**]). Although no heterogeneity is indicated for the analysis at 12 weeks, a high degree of statistical heterogeneity is apparent in the analysis at 24 weeks (I^2 = 76%). [**Commercial-in-confidence information removed**].

Mean percentage change in BASDAI was [**Commercial-in-confidence information removed**] with adalimumab treatment. At 12 weeks, around a [**Commercial-in-confidence information removed**] in BASDAI is estimated from meta-analysis of the available data (WMD [**Commercial-in-confidence information removed**], 95% CI [**Commercial-in-confidence information removed**] to [**Commercial-in-confidence information removed**]).

Treatment with etanercept was associated with an 18% extra reduction in BASDAI for meta-analysis at 12 weeks (WMD –17.97, 95% CI –23.37 to –12.58).

Meta-analysis of change in disease activity scores (BASDAI) is presented in *Figure* 7.

Function

[**Commercial-in-confidence information removed**] differences in mean change in functional score (BASFI) were observed for meta-analysis of adalimumab RCTs. The adalimumab-treated group experienced an estimated [**Commercial-in-confidence information removed**] in score of [**Commercial-in-confidence information removed**] at 12 weeks compared with placebo (WMD [**Commercial-in-confidence information removed**], 95% CI [**Commercial-in-confidence information removed**] to [**Commercial-in-confidence information removed**]).

Treatment with etanercept was associated with an additional lowering in score of 1.48 and 1.42, at 12 and 24 weeks, respectively (WMD –1.48, 95% CI –1.83 to –1.13; WMD –1.42, 95% CI –1.89 to –0.95).

An additional mean reduction in score of [**Commercial-in-confidence information removed**] at 12 weeks and [**Commercial-in-confidence information removed**] (random effects) at 24 weeks was estimated for the pooled analysis of available data on infliximab compared with placebo (RR [**Commercial-in-confidence information removed**], 95% CI [**Commercial-in-confidence information removed**] to [**Commercial-in-confidence information removed**]; random effects WMD [**Commercial-in-confidence information removed**], 95% CI [**Commercial-in-confidence information removed**] to [**Commercial-in-confidence information removed**]). Statistical heterogeneity was medium to high (I^2 = 69%) for the analysis at 24 weeks.

Percentage mean change in BASFI score was [**Commercial-in-confidence information removed**] between adalimumab and placebo patient groups. Pooled analysis suggests that there is around [**Commercial-in-confidence information removed**] in functional score with adalimumab at 12 weeks (WMD [**Commercial-in-confidence information removed**], 95% CI [**Commercial-in-confidence information removed**] to [**Commercial-in-confidence information removed**]).

Analysis of mean percentage change in BASFI scorings suggests an additional 21% reduction in score (at 12 weeks) with the use of etanercept (random effects WMD –21.46, 95% CI –28.35 to –14.57); however, statistical heterogeneity was medium to high (I^2 = 57%) for this analysis.

TABLE 6 *Statistical indirect comparison of ASAS*

Indirect comparison	RR	95% CI
ASAS 20: 12 weeks		
Adalimumab versus etanercept	1.08	0.67 to 1.71
Adalimumab versus infliximab	0.64	0.24 to 1.70
Etanercept versus infliximab	0.60	0.24 to 1.48
ASAS 20: 24 weeks[a]		
Etanercept versus infliximab	0.80	0.44 to 1.42
ASAS 40: 12 weeks		
Adalimumab versus etanercept	0.91	0.50 to 1.64
Adalimumab versus infliximab	0.39	0.09 to 1.69
Etanercept versus infliximab	0.43	0.10 to 1.79
ASAS 70: 12 weeks[b]		
Adalimumab versus etanercept	1.62	0.63 to 4.17

[a] Only data on etanercept and infliximab were analysed for this follow-up.
[b] Only data on adalimumab and etanercept available for this outcome/follow-up.

Plots for meta-analysis of change in functional status scores (BASFI) are presented in *Figure 8*.

Indirect comparison of anti-TNF-α agents

Composite binary outcomes

As described in the section above, in the absence of direct, head-to-head evidence on the relative efficacy of anti-TNF-α drugs, a statistical indirect comparison of the three drugs was conducted. Where trial data were available indirect comparisons of pairs of drugs were conducted in a systematic manner so that each drug was compared, in turn, with the other two anti-TNF-α drugs.

The results of the indirect analyses of ASAS response are presented in *Table 6*. Confidence intervals of all the comparisons indicate that the results are not statistically significant. Therefore, little conclusion on the relative efficacy, in terms of composite binary outcome, of one anti-TNF-α drug over another can be offered.

As the results stand, no robust contradiction to the pooling of all drugs has been identified (see the section 'Anti-TNF-α agents as a class versus placebo', p. 26) and no statistically supported assessment of relative efficacy of adalimumab, etanercept or infliximab can be reported.

Disease

An indirect comparison of disease activity (BASDAI) outcomes (*Table 7*) indicates no statistically significant difference between adalimumab and etanercept at 12 weeks, with only a very small difference in means between the drugs indicated by the small value of WMD. Comparison of adalimumab with infliximab indicates (marginal) statistically significant difference between these drugs, favouring infliximab. Comparison of etanercept with infliximab indicates a similar (marginal) statistically significant difference between these drugs, favouring infliximab.

TABLE 7 *Statistical indirect comparison of BASDAI and BASFI*

Outcome	WMD	95% CI
BASDAI: 12 weeks		
Adalimumab versus etanercept	[**Commercial-in-confidence information removed**]	[**Commercial-in-confidence information removed**]
Adalimumab versus infliximab	[**Commercial-in-confidence information removed**]	[**Commercial-in-confidence information removed**]
Etanercept versus infliximab	[**Commercial-in-confidence information removed**]	[**Commercial-in-confidence information removed**]
BASDAI: 24 weeks		
Etanercept versus infliximab	[**Commercial-in-confidence information removed**]	[**Commercial-in-confidence information removed**]
BASFI: 12 weeks		
Adalimumab versus etanercept	[**Commercial-in-confidence information removed**]	[**Commercial-in-confidence information removed**]
Adalimumab versus infliximab	[**Commercial-in-confidence information removed**]	[**Commercial-in-confidence information removed**]
Etanercept versus infliximab	[**Commercial-in-confidence information removed**]	[**Commercial-in-confidence information removed**]
BASFI: 24 weeks		
Etanercept versus infliximab	[**Commercial-in-confidence information removed**]	[**Commercial-in-confidence information removed**]

At 24 weeks, however, differences between etanercept and infliximab within the indirect comparison are no longer apparent.

Therefore, as for the analysis of composite binary outcomes, no contradiction was found to the pooling of all anti-TNF-α agents. Differences observed at 12 weeks are marginal and no statistically supported conclusions can be drawn as to the relative efficacy by 24 weeks of etanercept or infliximab.

Function

Indirect comparison of functional (BASFI) outcomes (*Table 7*) indicated a marginally statistically significant difference between adalimumab and infliximab at 12 weeks, favouring infliximab. No other comparisons at 12 weeks differed statistically significantly. Comparisons between etanercept and infliximab were not statistically significant.

Again, as for ASAS and BASDAI outcomes, no challenge was found to the pooling of all anti-TNF-α agents in terms of efficacy. The advantage of infliximab over adalimumab at 12 weeks was marginal and requires confirmation. No statistically supported conclusions on the relative effect on the functional status of etanercept and infliximab at 24 weeks can be made.

Calculation of the indirect comparisons is outlined in Appendix 3.

Longitudinal meta-analysis

Longitudinal meta-analysis (LMA) conducted for change in BASDAI and BASFI scores using additional data of correlations between change in score from baseline at 12 weeks and 24 weeks was carried out. The correlation data were provided by anti-TNF-α manufacturers. The analysis was considered appropriate for only etanercept and infliximab data at 24 weeks, as the adalimumab studies operated an early escape to open-label treatment from 12 weeks. The outcome of LMA was predicted to produce broadly similar effect estimates as the independent time-point meta-analysis, but potentially narrower confidence intervals. In exploring LMA the intention was to make the best use of available data by taking into account correlations.

Disease activity

LMA calculated [**Commercial-in-confidence information removed**] with the use of anti-TNF-α agents (etanercept and infliximab data only). At 24 weeks additional change in BASDAI from LMA was slightly lower than in the independent time-point meta-analysis and presented narrower confidence intervals.

Function

[**Commercial-in-confidence information removed**]. These results are practically identical to the independent time-point meta-analysis of anti-TNF-α agents at 24 weeks.

Role of LMA

In the example discussed above, independent time-point and longitudinal meta-analysis produced nearly identical results. In this review, anti-TNF-α agents were studied in the context of RCTs of relatively short duration. If studies in this field had recorded outcome measurements over long-term follow-up, LMA may have had the potential to offer more accurate estimates of effect than independent time-point meta-analysis based on such summary data.[82]

Adverse events – recorded in RCTs

Adalimumab

Combined data, provided in confidence by the company,[51] describe the prevalence of adverse events (AEs) in the ATLAS and Canadian AS studies.

Abbott: of 246 patients treated with adalimumab AEs were reported by 177 patients (72%) by 12 weeks and 196 (80%) by 24 weeks. Rates of AE for the placebo groupings (151 patients) were 90 out of 151 (60%) at 12 weeks and 96 out of 151 (64%) at 24 weeks. The Abbott submission reported both 'serious' and 'severe' AEs separately, but the definition or exclusivity of these two AE categories was not stated. Serious AEs for adalimumab occurred in five patients (2%) at 12 weeks, accruing to seven (2.8%) by 24 weeks, compared with two patients (1.3%) and then a further one patient (2%) in the placebo groups. Severe AEs occurred for five (2%), rising to ten (4%) adalimumab-treated patients at 12 and 24 weeks, respectively. In the placebo groupings six (4%) and seven (4.6%) severe AEs were reported. The submission reported that three patients (1.2%), rising to four (1.6%), treated with adalimumab (at 12 and 24 weeks) experienced AEs leading to discontinuation of medication. In placebo groups the equivalent data were two patients (1.3%) at both 12 and 24 weeks.

Abbott: at 12 and then 24 weeks, 72 and 86 out of 246 adalimumab patients (30 and 25%) experienced AEs that were "at least possibly drug-related".[51] Only 31 patients (21%), at both 12 and

24 weeks of the placebo group experienced AEs of this category.

Abbott: specified AEs included infectious AEs in adalimumab-treated patients in 60 patients (24%) and 84 patients (34%), compared with 26 patients (17%) and 32 patients (21%) at 12 and 24 weeks. Only one serious infection was recorded in the treatment groups and one in the control groups at 12 weeks. No further serious infections were observed. One case (in the ATLAS study) of hypersensitivity 'probably related' to the study drug was recorded for adalimumab at 12 weeks. No further AEs of this type were recorded. Injection site reactions were recorded for 24 patients at 12 weeks and 25 at 24 weeks in the adalimumab group (10%), compared with seven patients at 12 weeks and 24 weeks (5%) in the placebo group. The submission determined that no patients experienced malignancies, opportunistic infections (including TB), CHF or demyelinating disease or died during the placebo-controlled trial phase of ATLAS or Canadian AS.

Etanercept

Of the five etanercept RCTs included in this review, trial-specific reporting of AEs could be identified for Calin, Gorman, Brandt and Davis.[26,46–48]

Calin[26] described AE occurring in greater than 5% of patients in either allocation group. Most frequent AEs among both the 45 patients treated with etanercept and the 39 placebo patients were injection-site reactions, which affected twice as many (15 patients, 33%) people in the etanercept group as in the placebo group (six patients, 15%).

An absence of serious AEs or withdrawals due to AEs was reported for the Gorman study.[46] The most common AEs (occurring in over 10% of either group) were again injection-site reactions or infections in the vicinity. Injection-site reactions were reported for five of the etanercept and one member of the placebo group. One patient in the etanercept group developed mild cellulitis around an injection site, requiring, but responding to, antibiotics. Upper respiratory tract infection (URTI) (described as "minor, uncomplicated") occurred in ten etanercept and 12 placebo group patients. Diarrhoea was reported for three patients in the etanercept group and one patient in the placebo group.

No serious AEs or withdrawals took place in the Brandt study.[47] Again, the Brandt study reported that the most common AEs were injection-site reactions in two etanercept, but no placebo group patients, and minor infections (URTI), which occurred at the same rate in both etanercept and placebo groups (six patients in each group).

Within the Davis study,[48] the AEs occurring in over 5% of patients in either the etanercept (138 patients) or placebo (139 patients) group were predominantly related to the injection site or involved URTI. These two categories of AE were more commonly observed in the etanercept group (30% and 21%, respectively) than with placebo (9% and 17%, respectively).

Infliximab

Of the two reports of infliximab RCTs, ASSERT[49] provided a table of AEs whereas Braun[50] only provided an overview of AEs in the main body of the paper. The extent of AEs described here may vary between the trials owing to these differences in reporting as well as the smaller size of Braun (where only 43 patients were treated with infliximab) compared with ASSERT (where 202 patients were treated with infliximab).

Of the 202 patients treated with infliximab in ASSERT, 166 (82%) experienced any AEs compared with 54 (72%) of the 75 participants in the placebo group. Serious AEs were reported for seven (3.5%) of the infliximab-treated individuals and two (2.7%) of the placebo group.

In the Braun study[50] three patients (8.8%) experienced serious AEs resulting in withdrawal from the study. None of the placebo group experienced such serious AEs or withdrew. Of the three patients experiencing serious AEs one person developed TB, one allergic granulomatosis of the lung and the third transient leucopenia. No information on any other AEs was provided in the Braun report.

Open-label extension studies

Published information from open-label studies provides data that are primarily related to subgroups of patients and are therefore of limited value in assessing longer term outcomes for the overall population of AS patients.

Table 8 illustrates that although there are several open-label follow-up studies, patients investigated or the outcomes assessed have little potential to add to this assessment.

TABLE 8 *Open-label extension studies*

Study	Drug Duration Inclusion Primary outcome	Outcomes				Adverse events	Notes
Braun[50]	Infliximab 4 years All those who tolerated infliximab in trial. Trial $n = 70$ 50% improvement in BASDAI at 1 year	1 year. ITT (CI 95%) Two groups: I/I $n = 35$ P/I $n = 34$ 50% improvement in BASDAI: I/I 47% (31–63) P/I 51% (36–67) ASAS partial remission: I/I 18% (8–34) P/I 17% (8–33) Reduction in NSAID use by >50%: I/I 72% P/I 67%	2 years 49/69 completed second year 50% improvement in BASDAI: I/I 41% P/I 49%	3 years 42/69 (62%) completed year 3 50% improvement in BASDAI: I/I 47% P/I 43%	4 years 41/69 50% improvement in 27/41 Talks about withdrawal and readministration	Total discontinued due to adverse events 11/70 (15.7%) Total discontinuation 15/70 Year 2: 90% reported at least one AE Year 3: 96% reported at least one AE	Follow-up every 6 weeks ITT Efficacy analysis on completers Detailed data available only for this group of completers – useful?
Brandt[47]	Etanercept 2 years Patients from original trial who had relapse after drug discontinuation 26/30 restarted treatment Mean time off treatment 27 weeks 50% improvement in BASDAI	54 weeks $n = 23$ 57% reached BASDAI 50% response	102 weeks $n = 21$ 53.8% reached BASDAI 50 response				The numbers seem odd; they say they have follow-up for 102 weeks, but that patients were off the drug for a mean of 27 weeks after the end of the trial until relapse
Calin[26]	Etanercept 96 weeks Those who completed original trial 81/84 ASAS 20	Additional abstract provides X-ray data only; no extended reports on primary outcome					

continued

TABLE 8 *Open-label extension studies (cont'd)*

Study	Drug Duration Inclusion Primary outcome	Outcomes	Adverse events	Notes
Davis[48]	Etanercept 72 and 96 weeks All patients from original trial ASAS 20 response	72 and 96 weeks 257/270 enrolled 157/270 completed After 24 weeks' treatment 70% attained an ASAS 20 response Complete data not provided on ITT only on subgroups of those who continued		96 weeks Patients remaining: E/E 95/138 P/E105/139
Gorman[46]	Etanercept 10 months All patients from original trial ASAS 20	ASAS 20: 10 months E/E 16/17 6 months P/E 16/19 ASAS 50 and 70 scores also reported		Report decrease in rate of use of other NSAIDs and DMARDs

E, etanercept; I, infliximab; ITT, intention to treat; P, placebo.

Other sources of data

Other sources of patient information include registry data. The British Society for Rheumatology Biologics Register (BSRBR) was established in 2001 to capture data on the safety and efficacy of all patients with RA and other rheumatic diseases commencing biological therapy in the UK. It also facilitates the collection of data relating to patients with AS receiving these treatments. The data for AS patients are limited by the fact that the focus and funding of the register are not related to AS patients and complete data (such as BASDAI and BASFI) are not necessarily available in all cases. The register has data related to over [**Commercial-in-confidence information removed**] AS patients. It is anticipated that in the future interrogation of the database could include such comparisons as distribution of BASDAI and BASFI, change in these scores over a 6-month window, relationship of these changes to SF-36 and possibly comparisons of responses for differing treatments. [**Commercial-in-confidence information removed**] (Hogg M, Clinical Project Manager, British Society for Rheumatology: personal communication, 3 April 2006).

Discussion

Overview

Treatment with an anti-TNF-α agent resulted in statistically significantly better outcomes than placebo for every pooled and drug-specific meta-analysis conducted. When examining individual trials, very few failed to demonstrate statistically significant differences between drug and placebo.

Composite binary outcomes

The analyses indicate that treatment with anti-TNF-α therapy is associated with approximately 2.5- and 2.7-fold increases in the likelihood of patients improving by 20% in ASAS criteria at 12 and 24 weeks respectively, approximately 3.2- and 3.5-fold increases in the likelihood of a 50% improvement in ASAS criteria, and a 4- and 3.5-fold increase in achieving ASAS 70 (the latter analysis is based on adalimumab and etanercept only).

Adalimumab treatment was associated with approximately 2.4-, 3.2- and 5.5-fold increases in the likelihood of 20, 50 and 70% ASAS improvement at 12 weeks and 2.5-, 2.8- and 2.9-fold improvements in ASAS 20, ASAS 50 and ASAS 70 at 24 weeks, compared with those allocated to placebo.

Etanercept treatment resulted in approximately 2.1-, 3.5- and 3.4-fold increases in the likelihood of 20, 50 and 70% improvement in ASAS criteria at 12 weeks compared with the placebo group. At 24 weeks patients treated with etanercept had a 2.5-, 4.0- and 4.6-fold increase in the probability of experiencing an ASAS 20, ASAS 50 and ASAS 70 response.

Infliximab patients were 4.1 and 8.2 (one trial only) times more likely to experience ASAS 20 and ASAS 50 responses than those provided only with placebo.

Statistical indirect comparison composite binary outcome data failed to discriminate between anti-TNF-α agents.

Disease and functional outcomes

Reductions in disease-related scoring (BASDAI) were greater by approximately 2 points (at [**Commercial-in-confidence information removed**] 12 [**Commercial-in-confidence information removed**] weeks) for anti-TNF-α-treated groups than for the placebo group. Functional scores (BASFI) were reduced by a further 2 points for the anti-TNF-α-treated patient group than for the placebo grouping. LMA, which incorporated correlation data, produced similar estimates.

[**Commercial-in-confidence information removed**] of approximately [**Commercial-in-confidence information removed**] points in BASDAI score were estimated to be associated with adalimumab at 12 and 24 weeks. Functional scores reduced by [**Commercial-in-confidence information removed**] to [**Commercial-in-confidence information removed**] points for adalimumab at 12 and 24 weeks.

Etanercept was assessed for percentage change in BASDAI and BASFI scores. A further reduction in score of 18% for BASDAI and 22% in BASFI was observed in comparison to placebo at 12 weeks.

Disease scores [**Commercial-in-confidence information removed**] and [**Commercial-in-confidence information removed**] points at 12 and 24 weeks, respectively, with infliximab compared with placebo. Functional scores [**Commercial-in-confidence information removed**] 12 and 24 weeks.

Statistical indirect comparison of the three anti-TNF-α agents identified some differences between adalimumab compared with infliximab and

etanercept with infliximab at 12 weeks. However, differences in etanercept and infliximab converged by 24 weeks. Comparison of the efficacy of each anti-TNF-α agent on reduction in functional score failed to disseminate robustly between drugs.

Limitations

Although the reviewers are confident that all appropriate RCTs were included, not all data collected in these studies are presented within the trial reports. Available evidence on the effects of anti-TNF-α therapy is reported in a variety of detail and formats. Both of these issues may mean that not all data on the effects of anti-TNF-α agents have been presented in this review or included in the summative analysis.

Furthermore, it was not possible to determine whether patients included in the trials of etanercept and infliximab met the licence criteria for anti-TNF-α agents.

The main outcomes used in RCTs and therefore analysed in the review provide a number of potential challenges. Many of the trials selected ASAS 20 as principal outcome. Although appropriate for the statistical powering and conduct of the trials, 20% improvement may confer only a modest change in a patient's overall well-being. Similar scores or grades of improvement may be obtained by different combinations of patient outcomes and therefore considerable variability of experience may underlie outcomes that are apparently similar. The distribution of disease and functional scores may not be linear, further complicating the validity of statistical assessment. This issue will be discussed further in the critique of submitted economic evaluations. Measurement of change in score as trials progress is also problematic. Few data are available on how representative scores recorded at specific follow-up are of general or sustained disease activity (or function) for people with AS in their day-by-day experience.

This meta-analysis has a number of limitations. The analysis was structured at discrete periods of follow-up and it was assumed that there is no correlation between observations at different periods. This may not be the case. The LMA, which incorporated correlation data between observations, offered nearly identical results to independent time-point meta-analysis. The LMA considered only two discrete observation periods. LMA may offer additional information were a larger number of discrete observation periods subject to analysis. The authors also acknowledge that although the 'no correlation' assumption underpinning independent time-point meta-analysis was queried, these data were used for statistical indirect comparison of anti-TNF-α agents, rather than LMA-based data. The reason for this apparent inconsistency is that there are currently no methods for longitudinal indirect comparison of data.

In addition, moderate or medium statistical heterogeneity was detected for a number of the pooled analyses (e.g. pooled analysis of change in BASDAI; see *Figure* 7). That being said, after considering each incidence of moderate to medium statistical heterogeneity, the reviewers are confident that data were combined appropriately and the analyses are robust in this respect.

Clinical relevance

The authors believe that a clinically relevant improvement for those with active AS is represented by 50% or more improvement in ASAS criteria. Significant, three- to four-fold increases in the probability of achieving these improvements have been demonstrated by the anti-TNF-α drugs.

Clinically relevant differences in BASDAI and BASFI scores appear to have been demonstrated for each drug (if compared with data from Pavy and colleagues,[84] 22.5% change for BASDAI, 17.5% change for BASFI).

Summary

Nine RCTs were included in the clinical review. All compared anti-TNF-α with a placebo control group and aimed to enrol people with active AS. Two studies investigated adalimumab, five etanercept and two infliximab. All studies were of good and broadly comparable quality, and few significant variations in study conduct or patient characteristics were identified. It is not clear whether patients in the trials assessing infliximab and etanercept met current licence criteria for anti-TNF-α therapy.

Data were analysed up to 12 weeks for all three drugs, but only etanercept and infliximab at 24 weeks, owing to the early escape option operating (after 12 weeks) in the adalimumab trials.

Meta-analysis of available 12-week data on all three anti-TNF-α drugs, treated as a technology grouping, indicates that a 3.5-fold increase in

those achieving 50% improvement in ASAS criteria (considered a clinically relevant improvement) could be expected with anti-TNF-α treatment.

An additional 2-point improvement in disease and/or functional outcome with anti-TNF-α treatment for 12 weeks is predicted by the analysis.

Statistical indirect comparison of the three anti-TNF-α agents against one another was unable to distinguish between their clinical efficacies.

Few suitable long-term data were available of analysis across trials or anti-TNF-α agents.

Chapter 5
Economic review

Introduction

This chapter explores the published literature on the costs and benefits of anti-TNF-α therapy for AS. It begins by looking at the economic impact of AS in terms of both costs and health outcomes. The following section goes on to describe the results of a systematic literature review of the cost-effectiveness of treatments for AS.

Economic impact of AS therapy

Currently, AS patients are managed with a combination of NSAIDs and DMARDs; both treatments are inexpensive and of limited benefit to the patient. The introduction of anti-TNF-α therapy may offer patients additional clinical benefits, in terms of improving quality of life and functional capacity, but the costs of treatment can be expected to increase dramatically (*Table 9*). If one considers the relatively early onset of the disease then the costs of treating AS over a patient's lifetime could be considerable. Hence, the question is whether the increased costs of treatment can be justified by any extra benefits offered by this new technology. To address this issue, both the costs and benefits of TNF-α inhibitor therapy in AS need to be assessed.

Assessing the economic impact of AS

Two recent papers have attempted to assess the economic costs associated with AS.[85,86] In the Kobelt study,[85] the aim was to investigate the cost of AS in the UK. In the Ward study,[86] the authors attempt to describe the composition and distribution of the total costs of AS in the USA. Both studies present total costs from a societal perspective and include detailed analyses of cost categories used. Both studies conclude that functional disability is the main driver of total costs in AS.

To compare the costs presented by both studies, all costs have been converted to UK pounds using purchasing power parities (PPPs),[87] and inflated to 2006 using the consumer price index (CPI)[88] (see Appendix 4 for methods). Both papers are discussed in the sections below.

Costs in AS

Costs in any disease area can be divided into direct costs and indirect costs. Direct costs refer to those costs attributable to the treatment intervention, and include the value of all goods, services and other resources that are consumed in the provision of an intervention, any side-effects occurring, and all current and future consequences linked to the disease process. Direct costs can be further subdivided into direct healthcare costs and direct non-healthcare costs, where the former include the costs of tests, drugs, supplies, healthcare personnel and medical facilities, and the latter encompass the costs associated with an intervention but not directly arising from it, such as childcare costs, transportation, private nursing, including unpaid nursing by family members (home production), and the costs of 'time'.

Indirect costs pertain to productivity gains or losses related to mortality and morbidity, and are a specific type of time cost. There are two methods of calculating the productivity costs, the friction cost method and the human capital approach.

Perspective

In the cost assessment of AS, as with any disease area, the perspective taken has a significant impact on the costs considered in the analysis and the overall conclusions drawn. Several perspectives can be adopted, but for the purposes of this review only the health service perspective and the societal perspective are considered.

When taking a health service perspective, the only costs considered relevant are those that fall on the healthcare provider, that is to say the direct healthcare costs. From a societal perspective both the direct (healthcare and non-health care) and indirect costs are considered relevant to the total costs.

Direct healthcare costs

Kobelt and colleagues[85] estimated the mean direct annual healthcare costs per AS patient to be £1742, which is approximately £1854 when uplifted to 2006 prices (*Table 10*). These costs

TABLE 9 *Medication costs for an average adult AS patient based on BNF 51 prices (March 2006)*

Class	Drug	Dose	Cost of dose	Yearly cost
GI protectors	Misoprostal	200 mg four times daily	£23.40 for 140 tablets Dose £0.17	£243.36
	Omeprazole	20 mg once daily	£9.67 for 28 tablets Dose £0.35	£125.71
	Lansoprazole	30 mg once daily	£23.63 for 28 tablets Dose £0.84	£307.19
COX II selective NSAID	Meloxicam	7.5 mg once daily	£9.30 for 30 tablets Dose £0.31	£112.84
Indometicin	Indometicin	50 mg three times daily	£1.06 for 20 tablets Dose £0.16	£57.88
Standard NSAIDs	Naproxen	500 mg twice daily	£1.60 for 28 tablets Dose £0.11	£41.60
	Diclofenac sodium	75 mg twice daily	£1.52 for 84 tablets Dose £0.11	£39.52
	Ibuprofen	400 mg four times daily	£2.66 for 84 tablets Dose £0.03	£46.11
Analgesics	Paracetamol	500 mg four times daily	£0.31 for 20 tablets Dose £0.02	£22.59
	Codeine	30 mg four times daily	£1.67 for 20 tablets Dose £0.08	£121.58
Anti-TNF-α therapy	Adalimumab[a]	40 mg s.c. injection every 2 weeks	£357.50	£9,295.00
	Etanercept	25 mg s.c. injection twice weekly	£89.38	£9,295.52
	Infliximab	5 mg/kg by i.v. infusion, repeated at 2 weeks and 6 weeks after initial infusion, then repeated every 6 weeks (or 8 weeks not shown)	For a 75-kg adult, at a cost of £419.62 per 100 mg, requiring four 100 mg vials = £1678.48	£16,784.80 (in first year)

[a] Not licensed for AS, costs based on RA dose.
BNF, British National Formulary; COX, cyclooxygenase; GI, gastrointestinal.

TABLE 10 *Annual healthcare costs from the health service perspective*

Breakdown of direct healthcare costs	Mean annual costs per patient, UK £ 2006 (£ 2002)	% of direct healthcare costs	% of total costs[a]
Hospital care	£1,024 [£962]	55.2%	14.2%
Community care	£643 [£604]	34.7%	8.9%
Medication	£187 [£176]	10.1%	2.5%
Total direct healthcare costs	£1,854 [£1,742]	100%	25.6%

[a] Total costs are societal costs.
Table adapted from Kobelt[85] and inflated to 2006 prices.

include the cost of the drugs prescribed for AS, the cost of physiotherapy and the cost of doctors' time. Medication costs only accounted for 10.1% of the direct healthcare costs; however, these costs do not include the costs of anti-TNF-α agents. With the introduction of anti-TNF-α medications it is anticipated that costs will rise, which will ultimately lead to an increase in direct healthcare costs.

In Kobelt's study[85] the majority of healthcare costs (approximately 90%) are made up of hospital and community care costs. However, the total direct healthcare costs only accounted for approximately one-quarter of the total per-patient costs. Hence, if Kobelt[85] had only included a healthcare perspective rather than a societal perspective, nearly 75% of costs would have been omitted and the true cost of AS would have been obscured.

TABLE 11 *Annual costs of AS therapy from the societal perspective (all costs converted to UK £ 2006)*

Breakdown of mean per patient annual costs	Kobelt[85] [£ 2002] *n* = 1413 (% of total costs)	Ward[86] [US$ 1999] *n* = 241 (% of total costs)
Direct healthcare costs	£1854 [£1742] (25.6%)	£1094 [$1545] (22.9%)
Direct non-healthcare costs	£1183 [£1111] (16.5%)	£163 [$230] (3.4%)
All direct costs	£3037 [£2853] (42.1%)	£1257 [$1775] (26.4%)
Indirect costs (human capital approach)	£4166 [£3913] (57.9%)	£3502 [$4945] (73.6%)
Total costs	£7203 [£6766] (100%)	£4759 [$6720] (100%)

When comparing the results of both studies, it can be seen that the direct healthcare costs ranged from £1094 to £1854, and accounted for in excess of 25% of the total costs (*Table 11*). The direct non-healthcare costs were generally quite low, accounting for between 3.4 and 16.5% of the total costs. The resulting total direct costs ranged from £1257 to £3037, accounting for between 26 and 42% of total costs. The differences in the cost estimates between the different countries can in the main be attributed to the dissimilarities in the way the different healthcare systems manage AS, and the large differences in cost per unit resource. The UK study[85] reported the highest direct costs, more than double those of the USA study,[86] which can mainly be credited to higher hospital care costs and community care costs compared with other countries. However, it must be acknowledged that there are differences in how and what was included in the cost calculations of each of the studies, which makes direct comparison of the costs between the countries difficult at best.

In terms of the costs of medications (excluding anti-TNF-α drugs), a striking feature of both studies is that drug costs only account for between 2.6 and 11.1% of the total annual costs (*Table 11*). The reason for this is that the medications used are typically low-cost first line therapies, such as NSAIDs.

Indirect costs

AS patients generally have higher rates of sick leave, work disability and withdrawal from work than the general population.[86] This equates to a significant burden on society, as changes in productivity costs (i.e. indirect costs) are a major component of the total costs of AS.

Few studies report productivity costs; however, both studies estimated these costs using a human capital approach (*Table 11*). There were no significant differences in the way that indirect costs were calculated; however, the US study was the only study to include costs of inability to perform unpaid work, which accounted for 6.8% of the total indirect costs. The mean annual indirect per-patient costs were estimated to range from £3502 to £4166.

A striking feature is common to both studies: the indirect costs of AS far outstrip the direct costs. In the US study, 74% of the total costs could be attributed to the indirect costs of the disease. The same pattern is seen in the UK study, with the indirect costs accounting for 58% of the total costs. The large contribution of indirect costs to total costs in AS patients may in part be explained by the fact that AS predominantly affects men, who are valued higher in terms of productivity costs than women.

Total costs

The total societal costs are composed of both the direct healthcare costs and the direct non-healthcare costs together with the indirect costs. In the two studies, the total annual per patient costs ranged from £4759 to £7203, using a base year of 2006. These costs are relatively low compared with the total costs of RA; however, owing to the relatively young age of onset of AS in patients, resulting in disability and absence from work for a greater proportion of their lives, the lifetime costs of AS could be much higher. Furthermore, the introduction of anti-TNF-α therapy could increase these costs substantially depending on the eligible patient population. This is to be expected as when the healthcare costs of the disease are low and a new expensive technology is introduced, it is difficult to save on long-term total costs, even if the treatment is effective.

Commentary

The total costs of treating patients with AS are dominated by the indirect costs. If an analyst were to take a healthcare provider perspective only, a significant proportion of relevant costs would be overlooked. However, with the introduction of anti-TNF-α agents the cost of treating AS is set to soar, whether one takes a healthcare provider or a societal perspective. A recent study by Michaud and colleagues[89] in the USA demonstrates how the introduction of 'biological agents' (such as infliximab) has greatly increased the direct healthcare costs of RA. Studies on the costs of RA therapy before the introduction of biological agents estimated drugs to account for approximately 20% of direct healthcare costs. However, the recent study by Michaud[89] estimates drug costs in the current 'biological agent era' to account for approximately 60% of direct healthcare costs. This is a significant finding as it indicates that biological therapy is now itself a major determinant of RA treatment costs. If a similar pattern is seen with AS, then the introduction of anti-TNF-α therapies could have a considerable impact on the NHS, as the onset of AS is generally earlier than the onset of RA, implying that the lifetime costs of AS could increase upon the introduction of anti-TNF-α therapy.

Assessing health outcomes in AS

Adequately measuring health and health outcomes is an integral part of assessing the effectiveness and cost-effectiveness of healthcare technologies. The WHO defined health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".[90] Therefore, defining and assessing health and health outcomes are not simple processes.

Clinical trials of anti-TNF-α therapy for AS have reported a number of different health outcomes, including the ASAS 20, BASDAI and BASFI. However, all of these outcomes are clinical efficacy measures, and although important, they are insufficient to capture the true impact of the healthcare intervention upon a patient's life.

From a health economics perspective, a more meaningful health outcome is the QALY, which is a composite measure that takes into account both survival and quality of life. The QALY also aids decision-makers by providing them with a non-disease specific measure that allows comparisons of healthcare technologies both across and within different disease areas.

Review of the economic literature

The assessment group conducted a systematic search of the economic evidence concerning anti-TNF-α therapy for the treatment of AS. The aim was to identify published cost-effectiveness studies of anti-TNF-α therapy for the treatment of AS versus any other 'conventional therapy'.

Identification of studies

Using the search strategy outlined in the section 'Identification and selection of evidence: cost-effectiveness' (p. 10) (*Table 1*), 112 studies were selected and independently assessed (CM and ABol) for review using the inclusion criteria outlined in the section 'Inclusion criteria: cost-effectiveness' (p. 11).

Quantity and quality of included studies

Only two full papers[85,91] and four abstracts[92–96] met the review inclusion criterion and were subsequently reviewed. All six studies were quality assessed using a standard checklist by two independent reviewers (CM and ABol).

As four of the studies were available in abstract format only, it is acknowledged that owing to restrictions of space, the authors of these studies would have been unable to include all of the relevant cost and benefit information. Where checklist items where poorly scored (for example, no methods for the estimation of quantities and unit cost, no model details presented, no details of sensitivity analysis), the four abstracts scored equally poorly. Duff[92] included the results of both a CMA and a CEA, which suggests that the authors were unsure how to interpret the clinical data available.

The two full papers by Boonen[91] and Kobelt[85] scored highly on the item checklist. However, it was noted by the assessment group reviewers that the clinical data used in the economic evaluations did not always correspond with the data from the original clinical trials. After being contacted by the assessment group, both Boonen and Kobelt kindly supplied the correct clinical data. None of the cost-effectiveness ratios was affected by these errors, as they were mainly typographical in nature and were not transmitted into the model. In general, both papers were clearly written and addressed the majority of important economic issues. Only one weakness was apparent in both papers, in that neither provided enough detail regarding the calculation of indirect costs and Boonen failed to present these separately from the direct costs. In summary, there were only two

TABLE 12 *Characteristics of economic studies*

Study	Type of evaluation and synthesis	Interventions	Study population	Country	Duration of study
Boonen[91]	CEA and CUA	Etanercept Infliximab Usual care (NSAIDs and physiotherapy)	Adult patients with AS	Netherlands	5 years
Duff[92]	CMA and CEA	Etanercept Infliximab	Adult patients with AS	USA	1 year
Kobelt[85]	CUA	Infliximab vs placebo for 12 weeks followed by usual care (components of usual care not stated) up to 54 weeks	UK adult AS patients	UK	2-year cost-effectiveness model, with a 30-year follow-up in a hypothetical model
Kobelt[93]	CUA	Infliximab	Adult patients with AS	Canada	30 years
Sadri[94]	CEA	Etanercept and standard therapy (NSAIDs, DMARDs, steroids) Infliximab and standard therapy Standard therapy	Adult patients with AS	Canada	1 year
Singh[95,96]	CEA	Etanercept Infliximab Placebo (components of placebo not stated)	Adult patients with AS	USA	1 year

relevant fully published papers available, both of which were of high quality.

Characteristics of economic studies

Three of the studies carried out a CUA; one study included a CMA. The remaining studies presented CEAs (*Table 12*). The two studies by Kobelt[85,93] considered only infliximab, while the remaining studies looked at both infliximab and etanercept. Only one study[92] actually compared etanercept with infliximab; none of the economic evaluations considered adalimumab as a comparator. Only one of the studies was UK based;[85] the remaining studies originated from The Netherlands, Canada and the USA. Three of the studies attempted to extend beyond 1 year using observational data.

Economic models

Boonen[91] and Kobelt[85,93] used Markov modelling techniques to extrapolate to longer time-frames (*Table 13*). Sadri[94] used a decision-tree model for the 1-year results, and although there is mention of extrapolation to 10 years this is not described, nor are the results presented beyond 1 year. Duff[92] and Singh[95,96] did not describe their modelling methodology.

The societal perspective was adopted by both Boonen[91] and Kobelt,[85] who included both direct and indirect costs. A healthcare provider perspective was taken by both Duff[92] and Sadri,[94] who only included direct medical costs. The remaining studies did not adequately describe the perspective taken.

Cost data and data sources

Very little detailed information was given on individual cost items and their data sources (*Table 14*). Resource use was even more poorly described. All of the studies apart from Kobelt[93] and Singh[95,96] provided both a currency and price year.

Discounting of costs was applied by Boonen, Kobelt and Kobelt,[85,91,93] at rates of 4%, 6%, and 5%, respectively, which is in line with their individual countries' guidance. The earlier UK-based Kobelt study[85] is based on the previous NICE guide to methods of technology appraisal. The remaining studies did not apply discounting, which is appropriate as they were only of 1 year in duration.

Health outcome data and data sources

An array of clinical efficacy measures was used in the studies, ranging from the BASDAI and BASFI to the ASAS 20 and DCART 20 (*Table 15*). All of the studies used RCT data for efficacy values. Duff,[92] Sadri[94] and Singh[95,96] used data from the ASSERT[49] and Davis[48] trials, Boonen[91] used data from the studies by Braun[50] and Brandt,[47] and Kobelt[85,93] also used data from the Braun RCT.[50]

TABLE 13 *Economic model*

Study	Type of model	Perspective	Model assumptions	
			Outcomes	**Costs and resource use**
Boonen[91]	Markov model, cycle length of 3 months	Societal	Response to treatment defined as achieving a low disease activity state (BASDAI <4). Non-response was followed by stopping anti-TNF-α therapy and continuing with usual care. Toxicity could be followed by either continuation or discontinuation followed by relapse to active disease (BASDAI >4) and continuing usual care. There was no difference between infliximab and etanercept regarding relapse and toxicity	For costs assigned to health states, the time-averaged values over the 2-year observation period were used. Etanercept given twice weekly at a dose of 25 mg/kg. Infliximab dosage 5 mg/kg at weeks 0, 2 and 6, and then every 6 weeks for a 70-kg adult
Duff[92]	Unclear	US managed care organisation (MCO): direct medical costs	In CMA medication efficacy assumed to be similar. In CEA ASAS 20 assumed to capture efficacy	Dose of etanercept assumed to be 50 mg weekly. Dose of infliximab estimated as 5 mg/kg at weeks 0, 2 and 6, and then every 6 weeks for a 74-kg adult
Kobelt[85]	Non-parametric model for 2 years with a Markov model for 30 years' follow-up	Societal (direct, and indirect costs using human capital approach)	QoL correlated with disease activity and physical function	Costs correlated with disease activity and physical function. Dose of infliximab 5 mg/kg every 6 weeks, as in trial
Kobelt[93]	Markov model	Unclear	No progression while on treatment	Dose of infliximab 5 mg/kg every 6 weeks, as in trial
Sadri[94]	Decision tree for 1 year with extension. Mention of 10-year extension using spreadsheet model, but cost-effectiveness results only presented for 1-year horizon	Ontario provincial perspective	Unclear	Unclear
Singh[95,96]	Unclear	Unclear	Two trial populations are similar enough for comparison. Authors only identify concomitant medications as area of main difference between etanercept trial and infliximab trial. Etanercept trial patients were allowed to continue with HCQ, SSZ, MTX, NSAIDs corticosteroids and analgesics. Infliximab trial only stable doses of NSAIDs were allowed	Average number of infliximab vials per dose and total dose per year based on ASSERT. Etanercept was administered at a 25 mg/kg dose twice weekly, as in trial. Infliximab was given at a dose of 5 mg/kg at weeks 0, 2, 6, 12 and 18, as in trial

TABLE 14 *Cost data and cost data sources*

Study	Cost items	Cost data sources	Resource use	Resource data source	Currency, and currency year	Discount rate
Boonen[91]	Costs of screening and prophylaxis for TB = €82 Treatment toxicity costs = €2007 Treatment costs	Costs from 2 monthly questionnaires Toxicity from literature Usual care arm from Dutch 2-year longitudinal study	Not given	Not given	€, 2002	4%
Duff[92]	Drug costs Administration costs	Drug costs: USA average wholesale price Administration costs: Medicare 2004 reimbursement rates	Resources related to common treatments; no further details given	Literature and expert opinion	US$, 2004	NA, owing to study duration
Kobelt[85]	Hospital and community care, medication, non-medical resources and loss of work capacity Mean total annual costs per patient £6765 in table (or £6165 in text)	Public sources (BNF, PSSRU, CIPFA, national labour statistics and national schedule of reference costs). Costs earlier than 2002 were adjusted using the consumer price index	Annual use per patient: inpatient care 1.6 days, day cases 0.6 days, consultations 2.2 visits, healthcare professionals 8.1 visits, other services 1.0 service	Survey sent out to 3000 patients, of whom 1413 patients responded	UK£, 2002	6%, in SA 3%
Kobelt[93]	Not provided	Costs estimated from observational study of 545 AS patients in Canada	Not provided	Not provided	Can$, price year not given	5%
Sadri[94]	Mean annual costs: Drugs and monitoring Can$1589.80 (SD = Can$601.70) Medical imaging costs Can$140.20 (SD = Can$65.8) Physician visits Can$303.40 (average 3.4 ± 1.4 visits)	Unclear	Not provided	Not provided	Can$, 2003/04	NA, owing to study duration
Singh[95,96]	Costs based on the average dose for a patient receiving maintenance therapy over a 1-year period	Two trials: etanercept vs placebo, infliximab vs placebo	Not provided	Not provided	US$, price year not given	NA, owing to study duration

CIPFA, Chartered Institute of Public Finance and Accountancy; PSSRU, Personal and Social Services Research Unit; NA, not applicable.

TABLE 15 *Health outcome data and data sources*

Study	Efficacy data	Efficacy data sources	Health outcomes/utility	Health outcome data sources	Discount rate
Boonen[91]	Mean BASDAI: infliximab 6.4, etanercept 6.6 Mean BASFI: infliximab 5.3, etanercept 5.9	RCTs (Braun, Brandt), clinical opinion and literature	QALY. Utility measured using EQ-5D Utility if BASDAI $\geqslant 4 = 0.59$ Utility if BASDAI $< 4 = 0.76$ Utility if BASDAI < 4 and toxicity $= 0.5$	EQ-5D from Dutch longitudinal study	4%
Duff[92]	ASAS 20 response rates: 0.57 vs 0.22 for etanercept vs placebo 0.60 vs 0.18 for infliximab vs placebo	Respective package inserts. Package inserts for etanercept refer to ASSERT and for infliximab to the trial by Davis	No attempt made to estimate effectiveness from efficacy. ASAS was main outcome	Respective package inserts	NA, owing to study duration
Kobelt[85]	*Infliximab*: Baseline BASDAI = 6.5 Baseline BASFI = 5.5 12-week BASDAI = 3.4 12-week BASFI = 3.2 54-week BASDAI = 2.8 54-week BASFI = 2.8 *Placebo*: Baseline BASDAI = 6.3 Baseline BASFI = 5.1 12-week BASDAI = 5.0 12-week BASFI = 5.7 54-week BASDAI = not used 54-week BASFI = not used	RCT of 70 patients over 12 weeks (Braun), with 1-year open-label extension	QALYs. Mean utility estimated at 0.67	RCT of 70 patients over 12 weeks, with 1-year open-label extension. To extend beyond 1 year, survey and cohort data were used, which incorporated a mailed survey including EQ-5D, BASDAI and BASFI questions, with a 57% response rate resulting in 1413 participants. 1100 of these patients, who had previously been surveyed, were used to estimate disease progression	1.5%
Kobelt[93]	Not stated	3-month placebo-controlled trial (Braun) with 2-year open extension	QALYs. Mean utility estimated at 0.67 (range 0.2–0.87)	Observational study of 545 AS patients in Canada	5%

continued

TABLE 15 *Health outcome data and data sources (cont'd)*

Study	Efficacy data	Efficacy data sources	Health outcomes/utility	Health outcome data sources	Discount rate
Sadri[94]	ASAS 20 scores: Etanercept and standard therapy 0.57 Standard therapy 0.22 Infliximab and standard therapy 0.61 Standard therapy 0.19 BASDAI 50 scores: Etanercept and standard therapy 0.41 Standard therapy 0.14 Infliximab and standard therapy 0.51 Standard therapy 0.11	Unclear. Efficacy data indicate ASSERT for etanercept and the Davis trial for infliximab	Efficacy measures used: ASAS 20 and BASDAI 50	Unclear	NA, owing to study duration
Singh[95,96]	ASAS 20: Etanercept 57% vs placebo 22% Infliximab 61.2% vs placebo 19.2% ASAS partial response: Etanercept 17% vs placebo 4% Infliximab 22.4% vs placebo 1.3% DCART 20: Etanercept 33% vs placebo 7% Infliximab 45.5% vs placebo 10.7% BASFI improvement: Etanercept 30% vs placebo 2% Infliximab 38.5% vs placebo 0.1%	ASSERT and Davis RCTs	No attempt made to estimate effectiveness from efficacy. Outcomes used: ASAS 20, ASAS partial response, DCART 20 and BASFI	ASSERT and Davis RCTs	NA, owing to study duration

EQ-5D, EuroQoL 5 Dimensions.

Duff,[92] Sadri[94] and Singh[95,96] did not attempt to convert efficacy measures to health outcomes such as the QALY, nor did they apply discounting, which was appropriate as their studies did not exceed 1 year in duration.

Boonen[91] estimated utility values, using a mailed EQ-5D questionnaire as part of a Dutch longitudinal study, which were then mapped to BASDAI scores, to which a 4% discount rate was applied. Similarly, the two studies by Kobelt[85,93] estimated utility values, almost certainly by the same methods, which were described in the earlier of the two Kobelt studies.[85,93] Again, utilities were based on the scores from mailed EQ-5D questionnaires, which were then mapped to BASDAI and BASFI scores. For the UK-based Kobelt study,[85] outcomes were discounted at 1.5%, which was in line with NICE technology appraisal guidelines at the time of publishing. The Canadian Kobelt study[93] used a 5% discount rate.

Cost-effectiveness results

The cost-effectiveness results were difficult to compare owing to the different approaches adopted and the sparse details available in the abstracts (*Table 16*). However, both of the full papers[85,91] provided sufficient detail on how costs and outcomes were valued and both adopted a societal perspective, making comparison easier.

To enable results between the two studies to be interpreted more easily, the costs from Boonen[91] were transformed into UK£ 2006, using PPPs and the CPI. However, the base-case results for Boonen[91] are over 5 years, whereas Kobelt[85] presents results for 2 years. To account for this, the 2-year results for Boonen[91] were extracted and for ease of reference are presented alongside Kobelt[85] in *Table 17*.

As can be seen in *Table 17*, the cost-effectiveness ratios were very different across the two studies. Both studies considered placebo/usual care versus infliximab. Kobelt[85] estimated the incremental cost-effectiveness ratio (ICER) to be £35,400, while Boonen[91] estimated it to be in the region of £156,977. The difference seems to be mainly due to the way in which the costs of the placebo/usual care arm were calculated. Kobelt[85] estimated the total costs of placebo to be £25,126; this figure is approximately four times higher than the value estimated by Boonen[91] for usual care (£6,267). The reasons for this are unclear, but are likely to be mainly due to the different costing methods used.

Another difference between the two key studies, which may potentially account for some of the differences in the ICERs reported, is the choice of BASDAI and BASFI as outcomes by Kobelt,[85] as opposed to BASDAI only by Boonen.[91] Another potential factor is that in the base-case analysis Kobelt gave the intervention for 1 year and stopped; hence, there are no additional drug costs in the intervention arm past 1 year while the effect only slowly returns to preintervention.

However, differences between the incremental outcomes were also apparent, with Kobelt[85] estimating the incremental QALYs to be 0.175 and Boonen[91] estimating them to be 0.11. Again the reasons for this disparity are unclear, although differences between the health outcome data sources are likely to have played a significant role.

Sensitivity analysis

The reporting of sensitivity analysis among the abstracts was poor. Kobelt[93] and Duff[92] did not describe the method of sensitivity analysis, but concluded that the results were most sensitive to the dosing regimen of infliximab. Kobelt[93] also noted that results were sensitive to continuation rates and assumptions on disease progression (*Table 18*). Singh[95,96] and Sadri[94] did not provide any details of sensitivity analyses.

The two full articles[85,91] provided more information on the sensitivity analyses performed. Boonen[91] undertook one-way analysis and best case analysis, and concluded that only the price of the drugs had a significant impact. Similarly, Kobelt[85] undertook one-way SA, with the dropout rate impacting most significantly on the results.

Author conclusions

The conclusions of the authors were mixed (*Table 19*). Boonen[91] concluded that the high drug costs of etanercept and infliximab would restrict efficient use in AS patients. The two Kobelt studies[85,93] concluded that the costs of infliximab would be offset by reductions in the costs of the disease and increases in quality of life, leading to an acceptable cost-effectiveness ratio. Both Sadri,[94] and Duff[92] concluded that etanercept was likely to be more cost-effective than infliximab, whereas Singh[95,96] concluded that they were equivalent.

Conclusion

This chapter has reviewed and quality assessed a selection of the published literature on the costs and benefits associated with anti-TNF-α therapy

TABLE 16 *Cost-effectiveness results*

Study	Cost of anti-TNF-α therapy	Total costs	Total incremental costs	Total outcomes	Total incremental outcomes	Cost-effectiveness ratios
Boonen[91]	Etanercept €13,759 per patient per year [£9113][a] Infliximab €21,335 per patient per year [£14,131][a]	Usual care €21,261 [£14,082][a] Etanercept €52,137 [34,532][a] Infliximab €62,047 [£41,095][a] 5-year time-frame	Usual care vs etanercept €30,876 [£20,450][a] Usual care vs infliximab €40,786 [£27,014][a] 5-year time-frame	Usual care 2.89 QALYs Etanercept 3.16 QALYs Infliximab 3.11 QALYs 5-year time-frame	Usual care vs etanercept = 0.27 QALYs Usual care vs infliximab = 0.22 QALYs 5-year time-frame	Usual care vs etanercept = €118,022/QALY [£78,169][a] Usual care vs infliximab = €189,564/QALY [£125,553][a] 5-year time-frame/societal
Duff[92]		Total 1-year direct medical costs: Etanercept $14,636 Infliximab $25,543 1-year time-frame	Infliximab vs etanercept $10,907 per patient 1-year time-frame	ASAS 20 response rates: 0.57 vs 0.22 for etanercept vs placebo 0.60 vs 0.18 for infliximab vs placebo 1-year time-frame	Not provided	Cost-efficacy ratio of infliximab vs etanercept of $150,000 per additional ASAS 20 responder 1-year time-frame
Kobelt[85]	Infliximab £14,100 per patient per year	Placebo £25,126 Infliximab £31,340 2-year time-frame	Placebo vs infliximab £6214 2-year time-frame	Not provided	Placebo vs infliximab = 0.175 QALYs 2-year time-frame	£35,400 2-year time-frame £9,600 during the long term (30 years), societal
Kobelt[93]		Unclear	Not provided	Mean utility estimated at 0.67 (range 0.2–0.87) 30-year time-frame	Not provided	Over a 30-year time-frame the cost per QALY is Can$62,637, assuming patients do not progress while on treatment
Sadri[94]		Average expected costs: Etanercept and standard therapy Can$14,585 Standard therapy Can$1767 Infliximab and standard therapy Can$24,053 Standard therapy Can$1738 1-year time-frame	Not provided	ASAS 20 scores: Etanercept and standard therapy 0.57 Standard therapy 0.22 Infliximab and standard therapy 0.61 Standard therapy 0.19 BASDAI 50 scores: Etanercept and standard therapy 0.41 Standard therapy 0.14 Infliximab and standard therapy 0.51 Standard therapy 0.11 1-year time-frame	Not provided	Etanercept and standard therapy vs standard therapy: Can$36,622 per ASAS 20 Can$47,474 per BASDAI 50 Infliximab and standard therapy vs standard therapy: Can$53,130 per ASAS 20 Can$55,787 per BASDAI 50 1-year time-frame

continued

TABLE 16 *Cost-effectiveness results (cont'd)*

Study	Cost of anti-TNF-α therapy	Total costs	Total incremental costs	Total outcomes	Total incremental outcomes	Cost-effectiveness ratios
Singh[95,96]		Not provided	Not provided	ASAS 20: Etanercept 57% vs placebo 22% Infliximab 61.2% vs placebo 19.2% ASAS partial response: Etanercept 17% vs placebo 4% Infliximab 22.4% vs placebo 1.3% DCART 20: Etanercept 33% vs placebo 7% Infliximab 45.5% vs placebo 10.7% BASFI improvement: Etanercept 30% vs placebo 2% Infliximab 38.5% vs placebo 0.1% 24-week time-frame	ASAS 20: Etanercept vs placebo 35% Infliximab vs placebo 42% ASAS partial response: Etanercept vs placebo 13% Infliximab vs placebo 21.1% DCART 20: Etanercept vs placebo 26% Infliximab vs placebo 34.8% 24-week time-frame	Cost per responder Infliximab vs placebo: ASAS 20 $44,790 ASAS partial response $89,156 DCART 20 $54,057 Etanercept vs placebo: ASAS 20 $43,271 ASAS partial response $116,500 DCART 20 $58,250 Cost per BASFI responder: Infliximab $490 Etanercept $541 24-week time-frame

[a] Values in brackets indicate currency exchange.

TABLE 17 *Cost-effectiveness results for Boonen[91] and Kobelt[85] over a 2-year time-frame*

Study	Cost of anti-TNF-α therapy	Total costs	Total incremental costs	Total outcomes	Total incremental outcomes	Cost-effectiveness ratios
Boonen[91]	Etanercept €13,759 per patient per year [£9113][a] Infliximab €21,335 per patient per year [£14,131][a]	Usual care €9462 [£6267][a] Etanercept €25,675 [17,005][a] Infliximab €31,972 [£21,176][a]	Usual care vs etanercept €16,213 [£10,738][a] Usual care vs infliximab €22,510 [£14,909][a]	Usual care 1.26 QALYs Etanercept 1.39 QALYs Infliximab 1.37 QALYs	Usual care vs etanercept 0.13 QALYs Usual care vs infliximab 0.11 QALYs	Usual care vs etanercept €123,761/QALY [£81,970][a] Usual care vs infliximab €237,010/QALY [£156,977][a]
Kobelt[85]	Infliximab £14,100 per patient per year	Placebo £25,126 Infliximab £31,340	Placebo vs infliximab £6214	Not provided	Placebo vs infliximab 0.175 QALYs	Placebo vs infliximab £35,400

[a] Values in brackets indicate currency exchange.

TABLE 18 *Sensitivity analysis*

Study	Sensitivity analysis method	Sensitivity analysis results
Boonen[91]	One-way SA and best case analyses	5-year results: No response in health status in usual care arm Usual care vs etanercept = €77,088 cost/QALY Usual care vs infliximab = €120,369 cost/QALY Best case analysis with probabilities favouring anti-TNF-α agent Usual care vs etanercept = €73,368 cost/QALY Usual care vs infliximab = €122,780 cost/QALY Best case analysis with probabilities, costs and utilities favouring anti-TNF-α agent Usual care vs etanercept = €44,443 cost/QALY Usual care vs infliximab = €76,622 cost/QALY Best case analysis reducing costs of anti-TNF-α agent Usual care vs etanercept 1/4 of usual price = €18,950 cost/QALY Usual care vs infliximab 1/5 of usual price= €21,750 cost/QALY
Duff[92]	Type of SA unclear. Some form of SA was performed on "dose and other assumptions"	Results were most sensitive to infliximab dose and infusion frequency
Kobelt[85]	One-way SA	Long term: 30 years Discount rate 3% both costs and benefits = £4900 cost/QALY No progression for patients on treatment = £2800 Infliximab infusions every 8 weeks = £5600 Dropout rate 5% = £18,700 Dropout rate 15% = £700
Kobelt[93]	No details provided	Statement that results are sensitive to dosing regimen, continuation rates and assumptions concerning disease progression
Sadri[94]	No details provided	No details provided
Singh[95,96]	No details provided	No details provided

SA, sensitivity analysis.

TABLE 19 *Author conclusions*

Study	Conclusion	Industry author affiliation
Boonen[91]	High drug costs restrict efficient use of etanercept and infliximab in all patients with AS and BASDAI >4, although modelling has its limitations owing to an absence of insight into the natural course of AS	None
Duff[92]	The use of etanercept would result in 43% cost savings compared with infliximab, owing to the higher cost of infliximab compared with etanercept	Author affiliations with Covance and Amgen/Wyeth
Kobelt[85]	Cost of infliximab partly offset by reductions in cost of disease and increases in patients' QoL, leading to cost per QALY gained of £30,000 in short term, but potentially below £10,000 in long term	Schering-Plough grant. Author affiliations with Abbott, Amgen, Centocor, Schering-Plough and Wyeth
Kobelt[93]	Infliximab therapy should be cost-effective for Canadian patients with active AS (Can$21,887–84,780/QALY) (comparator not stated)	None declared, although evaluation in UK setting indicates industry affiliation with Abbott, Amgen, Centocor, Schering-Plough and Wyeth
Sadri[94]	Short-term results (1 year) show a reasonable cost-effectiveness ratio of etanercept vs standard therapy. Results suggest etanercept is more cost-effective than infliximab compared with standard therapy	Author affiliation with Amgen/Wyeth
Singh[95,96]	The cost-efficacy ratios for etanercept and infliximab compared with placebo were similar, but without actual head-to-head comparisons the cost-effectiveness ratios cannot be reliably estimated	Author affiliation with Centocor/Schering-Plough

for the treatment of AS. Only one abstract (Duff[92]) compares etanercept with infliximab, and concludes that etanercept is more cost-effective than infliximab. Adalimumab was not included as a comparator in any of the cost-effectiveness analyses. As none of the economic evaluations was based on the results of head-to-head drugs trials, it is difficult to conclude with any certainty that one of the drugs is significantly more cost-effective than the other.

The critical appraisal of the economic evaluations is summarised in *Table 20*.

TABLE 20 *Critical appraisal of economic evaluations*

Checklist item	Boonen[91]	Duff[92]	Kobelt[85]	Kobelt[93]	Sadri[94]	Singh[95,96]
1. The research question is stated	Yes	Yes	Yes	Yes	Yes	Yes
2. The economic importance of the research question is stated	Yes	Yes	Yes	Yes	Yes	Yes
3. The viewpoint(s) of the analysis are clearly stated and justified	Yes	Yes	Yes	No	Yes	Yes
4. The rationale for choosing the alternative programmes or interventions compared is stated	Yes	Yes	Yes	No	No	No
5. The alternatives being compared are clearly described	Yes	Yes	Yes	No	Yes	Yes
6. The form of economic evaluation used is stated	Yes	Yes	Yes	Yes	Yes	Yes
7. The choice of form of economic evaluation is justified in relation to the questions addressed	Yes	No	Yes	No	No	No
8. The source(s) of effectiveness estimates used are stated	Yes	Yes	Yes	Yes	Yes	Yes
9. Details of the design and results of effectiveness study are given (if based on a single study)	NA	No	NA	No	No	No
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	NA	NA	NA	NA	NA
11. The primary outcome measure(s) for the economic evaluation are clearly stated	Yes	Yes	Yes	Yes	Yes	Yes
12. Methods to value health states and other benefits are stated	Yes	NA	Yes	No	NA	NA
13. Details of the subjects from whom valuations were obtained are given	Yes	NA	Yes	No	NA	NA
14. Productivity changes (if included) are reported separately	No	NA	Yes	No	NA	NA
15. The relevance of productivity changes to the study question is discussed if included	No	NA	No	No	NA	NA
16. Quantities of resources are reported separately from their unit costs	No	No	Yes	No	No	No
17. Methods for the estimation of quantities and unit costs are described	Yes	No	Yes	No	No	No
18. Currency and price data are recorded	Yes	Yes	Yes	/ no price year	Yes	/ no price year
19. Details of currency price adjustments for inflation or currency conversion are given	Yes	No	Yes	No	No	No
20. Details of any model used are given	Yes	No	Yes	No	No	No
21. The choice of model used and the key parameters on which it is based are justified	Yes	No	Yes	No	No	No
22. Time-horizon of costs and benefits is stated	Yes	Yes	Yes	Yes	Yes	Yes
23. The discount rate(s) is stated	Yes	NA: 1 year	Yes	Yes	NA: 1 year	NA: 1 year

continued

TABLE 20 *Critical appraisal of economic evaluations (cont'd)*

Checklist item	Boonen[91]	Duff[92]	Kobelt[85]	Kobelt[93]	Sadri[94]	Singh[95,96]
24. The choice of rate(s) is justified	Yes	NA	Yes	No	NA	NA
25. An explanation is given if costs or benefits are not discounted	NA	NA	NA	NA	NA	NA
26. Details of statistical tests and confidence intervals are given for stochastic data	NA	NA	NA	NA	NA	NA
27. The approach to sensitivity analysis is given	Yes	No	Yes	No	No	No
28. The choice of variables for sensitivity analysis is justified	Yes	No	Yes	No	No	No
29. The ranges over which the variables are varied are stated	Yes	No	Yes	No	No	No
30. Relevant alternatives are compared	Yes	Yes	Yes	Yes	Yes	Yes
31. Incremental analysis is reported	Yes	/ no outcomes	Yes	No	No	/ no costs
32. Major outcomes are presented in a disaggregated as well as an aggregated form	Yes	No	Yes	No	Yes	Yes
33. The answer to the study question is given	Yes	Yes	Yes	Yes	Yes	Yes
34. Conclusions follow from the data reported	Yes	Yes	Yes	Yes	Yes	Yes
35. Conclusions are accompanied by the appropriate caveats	Yes	Yes	Yes	Yes	Yes	Yes

NA, not applicable; No, not addressed adequately; Yes, addressed adequately; /, partially addressed.

Chapter 6

Critical review of company economic submissions

Submitted models

Each of the three companies submitted an economic model to support their case for the cost-effectiveness of their product. Although the approaches taken to model design and construction are quite different, there is commonality of assumptions and sources of information from which to derive parameter values. All the models are narrowly focused on the limited clinical trial data associated with their own product, and none attempts to make direct or indirect comparisons to other anti-TNF-α agents.

In view of the underlying similarities of approach it is not surprising that the economic results obtained show substantial convergence, as illustrated in *Table 21*. This provides some reassurance that none of the three models is seriously defective in implementing its adopted framework, but should not be taken as confirmation that these shared assumptions are necessarily correct.

Table 22 compares key parameter values used in each company's reference case analysis, and demonstrates the extent of similarity between the models.

Overview of Wyeth model[53]

The health economic model presented by Wyeth compares the use of etanercept and NSAIDs versus NSAIDs for the treatment of patients with ankylosing spondylitis. The model is constructed using Microsoft Excel and Visual Basic for Applications. It generates a hypothetical patient population based on characteristics drawn from analysis of individual patient data (IPD) from Phase III RCTs of etanercept, together with other published clinical and economic evidence. Some clinical data used in the model are not currently in the public domain.

In the submission, results of a CUA are presented, including a range of incremental cost per QALY ratios. The results of both univariate and probabilistic sensitivity analyses are discussed. The model takes an NHS perspective and costs and benefits up to 25 years are identified, measured and valued. Costs and benefits are discounted at 3.5%.

Population and comparator

The model uses patient data from two RCTs and one open-label extension study. Patients in these clinical trials differ from UK patients in two ways. First, UK patients have lower BASDAI/BASFI

TABLE 21 *Base-case economic results reported in company submissions*

Model	Period	Incremental cost per patient	Incremental utility per patient (QALYs)	Incremental cost per QALY gained
Abbott: adalimumab	48 weeks	+£5,025	+0.107	£47,083
	5 years	+£13,273	+0.504	£26,332
	30 years	+£23,857	+1.033	£23,097
Schering-Plough: infliximab; Braun,[50] ASSERT[49]	Lifetime	+£29,399	+1.62	£18,192
	(70 years)	+£30,326	+1.58	£19,169
Wyeth: etanercept	1 year	+£6,174	+0.14	£44,684
	2 years	+£10,298	+0.33	£30,754
	5 years	+£19,136	+0.84	£22,844
	10 years	+£26,940	+1.50	£18,002
	15 years	+£29,782	+1.99	£14,978
	20 years	+£30,880	+2.26	£13,694
	25 years	+£31,365	+2.37	£13,201

TABLE 22 *Parameter values for each of the models*

Parameter	Abbott	Schering-Plough	Wyeth
Time-frame	Up to 30 years	Lifetime (70 years)	Up to 25 years
Discount rate	3.5%	3.5%	3.5%
Average age (years)	42.2	40	41
Mortality (SMR)	1.5	1.0	1.5
Baseline BASDAI	Anti-TNF-α agent 6.67/10, placebo 6.94/10	6.41/10	6.1/10
Baseline BASFI	Anti-TNF-α agent 56.4/100, placebo 60.4/100	5.75/10	5.9/10
Rate of progression in control arm	+0.05% p.a. BASFI	+0.07% p.a. BASFI	+0.3% p.a. for both BASDAI and BASFI
Annual long-term rate of anti-TNF-α agent withdrawal	10% p.a.	15%	10% p.a.
Incidence of TB	0.0026 per patient p.a.	Not included	Not included
Incidence of AEs	[**Commercial-in-confidence information removed**]	20% of anti-TNF-α agent withdrawals from AEs	Not included
Inclusion criteria for simulation	VAS ⩾4/10 BASDAI ⩾4/10	BASDAI >4/10	BASDAI >4/10
Criteria to remain on therapy in simulation	BSR eligibility and stopping rules	BSR eligibility and stopping rules	BSR eligibility and stopping rules
TB monitoring costs	£16 chest X-ray (initial and month 6), £25.36 skin test	Not included	Not included
Monitoring costs	£108 (per 6 months) + £49.60 monthly tests	Included in administration costs	£89.91 (0–3 months), then £75.16 p.a.
Administration costs	Not included	£124 per infusion	Not included
TB treatment costs	£5100 per treatment	Not included	Not included
AE costs	£61.56 per AE	£79.27 per AE	Not included
AS-specific healthcare costs	£708.45 + £750 per 1/10 BASDAI	Two-part model, approx. linear: £554.78 per 1/10 BASFI – £665.23	£351.31 p.a., × 1.0665 per 1/10 BASDAI, × 1.1707 per 1/10 BASFI

p.a., per annum.

scores (i.e. these patients have less severe AS). Secondly, the duration of disease in patients in the UK studies appears to be longer. UK data are representative of all UK patients with AS and not only those who may be eligible for anti-TNF-α therapies.

The model compares the use of etanercept plus NSAIDs versus NSAIDS. Other anti-TNF-α therapies do exist. However, as there are no head-to-head RCTs of these drugs and no indirect comparisons in the published literature, the use of NSAIDs as the comparator is appropriate.

Resource use

The dose of etanercept used in the model is 25 mg twice weekly; 25 mg of etanercept costs £89.38. The model uses patient data from two RCTs of 12 and 24 weeks' duration, respectively. The model has a time-frame of 25 years.

The costs used in the model are derived from a variety of sources. Drug, drug administration and monitoring costs appear to be based on the BSR recommendations.[3] Quantities of tests and investigations are presented in the submission, but whether or not these would be undertaken as part of a monitoring visit in a hospital setting is not clear.

Etanercept is associated with a small risk of developing TB.[97] Current practice suggests that all patients be screened for TB before commencing anti-TNF-α therapy (Robert Moots: personal communication, 2006). However, no specific costs of TB screening are included in the model.

TABLE 23 *Model assumptions concerning disease progression*

Model assumption	Detail
Size of the initial improvement	In the economic submission, models are used to predict BASDAI and BASFI scores for responders to therapy. This initial health gain is used for the period that patients respond to treatment
Rebound on withdrawal from treatment	There are two distinct scenarios modelled for patients who do not respond to treatment. They either return to their original BASDAI/BASFI scores or they rebound by the same magnitude to their initial improvement
Progression while on treatment	In the base case it is assumed that responders to etanercept do not progress while on treatment and that annual disease progression is 3% in non-responders (BASFAI and BASFI scores)

The derivation of the disease-related costs used in the model is more complex. To inform the CUA, a costing study was carried out on 147 AS patients attending the Staffordshire Rheumatology Centre, Haywood Hospital. Hospital records (December 2003 to June 2004) were reviewed retrospectively to estimate the costs associated with AS. There are several differences between the patients in the costing study and in the RCTs; for example, the patients in the costing study have substantially lower BASDAI and BASFI scores, patients are approximately 10 years older and the average time since diagnosis is longer. In line with the NHS perspective, only direct medical costs are included (e.g. clinic visits, inpatient care, scans). However, owing to a lack of data, GP visits are not included; the submission states that other potentially relevant costs are also omitted.

Costs in the model are influenced by the withdrawal rate used. As etanercept is a relatively new drug, there is very little evidence on long-term withdrawal rates. In the base case, the withdrawal rate is set at 10% per annum. In support of this figure, the authors quote the results of a Swedish study of RA patients taking etanercept for 24 months.

Within the model annual disease costs are predicted based on changes in BASDAI and BASFI measurements.

Health outcomes

In the Phase III RCTs of etanercept and NSAIDs versus NSAIDs, BASDAI and BASFI are used to measure disease activity and functional disability in the short term. In the long term, the model forecasts disease progression by making several assumptions, as outlined in *Table 23*.

The EQ-5D (n = 356 subjects) and SF-36 (n = 511 subjects) were used to collect patient quality of life data. To use these scores in the CUA, a series of regressions was undertaken to determine whether there was a relationship between BASDAI and BASFI and the quality of life scores. The EQ-5D regression was chosen for the base-case analysis on the grounds that it encompassed a wider range of utility values, although there is no further justification for this choice.

In the model, the life expectancy of patients with AS was reduced by an SMR of 1.5.

As the trials did not report statistically significant differences in adverse events, these were not considered in the economic evaluation.

Results

Cost-effectiveness ratios are presented for a range of time-points between 1 and 25 years. At year 25, the discounted incremental cost per QALY is approximately £13,000. Etanercept and NSAIDs yield an incremental 2.37 QALYs compared with NSAIDS alone for an additional cost of £31,365.

Sensitivity analysis

Over 30 different univariate sensitivity analyses were undertaken as part of the submission. The majority of the cost per QALY ratios presented ranged from £11,000 to £25,000. The variables that were identified as having the largest impact were the disease costs, annual progression rates use for the BASDAI and BASFI scores and the quality of life scores.

Disease costs

In the economic submission, the authors do not comment on why varying the disease costs has the largest impact on the size of the cost-effectiveness ratios. The authors simply state that "using the lower confidence intervals increases the ICER by 26% to 16.6k per QALY" (p. 49 in the Wyeth submission).

Annual disease progression

In the model, annual disease progression is forecast based on several different factors. In the sensitivity analysis, there are many different combinations of variations in assumptions that could have been performed. For example, if it is assumed that no patients progress in the model, then the ICER increases to £24,600 per QALY; if it is assumed that progression is the same for both responders and non-responders, the ICER increases to £17,000 per QALY. Whether or not BASDAI scores are stable, with only BASFI scores increasing, is also tested. The annual progression rate of 3% is not subjected to change in the univariate analysis.

Quality of life

The submission reports the effect of changing quality of life parameters based on both EQ-5D and SF-36 scores. However, the SF-36 values are then excluded from the tornado diagram as they are reported as having a 'floor' effect. Although, in the submission, it is argued that the SF-36 values are not comparable, the authors do report ICERs in the range of £17,000–70,000 per QALY.

Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis (PSA) appear to demonstrate 100% certainty that etanercept and NSAIDs are cost-effective at £18,000. The submission also reports 88% probability that etanercept is cost-effective at £15,000.

Quality assessment of Wyeth model

The economic model presented in the Wyeth submission was evaluated using the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) good practice checklist[98] as shown in *Table 24*. The submitted Excel model was examined to identify issues of particular concern and any confirmed or apparent implementational errors. Where possible, an assessment is made of the likely impact of each problem on cost-effectiveness results.

Specifying the patient cohort

The model generates a sample of 1000 hypothetical patients, which should be representative of the patients studied in the cited clinical trials. Unfortunately, several issues have been identified which suggest that economic results have been produced on the basis of an unsatisfactory cohort of hypothetical patients.

Gender

It appears that the gender of patients has been mislabelled in the model, so that the model generates predominantly female patients (76%), rather than the lower expected proportion (24%). There is no impact from this error in the first year, but differences will accumulate in subsequent years as differential mortality rates take effect. Nonetheless, it is probably unlikely that this error alone will have a significant impact on economic results.

Age range

The model produces a very wide range of patients' age, with several hypothetical patients under the age of 10 in the cohort. Since the modelled dose of etanercept is only valid for patients over 18 years of age, and paediatric use at reduced dose is only licensed for children aged 4 years and above, this is clearly inappropriate.

Duration of disease

The age and duration of disease for hypothetical patients are generated independently within the model, despite the obvious connection. This leads to glaring anomalies (see above), with paediatric patients being assigned values for disease duration greater than the assigned physical age.

BASDAI/BASFI values

The range of BASDAI and BASFI baseline values in the model cohort is very restricted and does not represent patients with BASDAI above 4.0. This appears to have arisen because the standard error of the estimated mean has been used to govern variability, instead of the standard deviation.

Correlation

Baseline values for BASDAI and BASFI are generated independently in the model cohort, which is in contradiction of the evidence of all studies and trial IPD that these measures are strongly correlated. Similarly, these values are also incorrectly uncorrelated with age and duration of disease in the sample.

Response rate

The assumed response rate to treatment is considered to be independent of the baseline values of disease activity and function. However, there is a significant negative correlation between baseline BASFI and response rate at 12 weeks (as seen in Abbott IPD data). It is likely that this omission will overstate the impact of etanercept in patients in the worst condition at baseline and may thereby bias economic results in favour of etanercept.

TABLE 24 *ISPOR checklist*

	Wyeth model	Abbott model	Schering-Plough model
Decision context			
Is there a full description of the decision question, its context, and the process by which this was identified?	Yes	Yes	Yes
Do the model structure and parameters adequately represent the key decision options and perspective?	Yes	Yes	Yes
Do the treatment options cover those of immediate interest to the decision-maker?	Only comparisons to conventional treatment are included, owing to lack of clinical evidence	Only comparisons to conventional treatment are included, owing to lack of clinical evidence	Only comparisons to conventional treatment are included, owing to lack of clinical evidence
Are there additional treatment options likely to be of interest in other decision and clinical contexts?	No	No	No
Is the model structure easily adaptable to include future developments?	Possibly	No. Reliant on specific IPD	Possibly
Health states and clinical outcomes			
Does the model structure fit (appropriate and relevant) with the clinical theory of the disease process?	Yes, although current understanding of progression is limited	Yes, although current understanding of progression is limited	Yes, although current understanding of progression is limited
Does the model appropriately capture the full impact and cost of treatments?	No. Adverse events are not modelled. Costs of screening for TB/TB treatment are not included	Yes	No. Adverse events are underestimated. Costs of screening for TB/TB treatment are not included. Safety monitoring costs assumed part of administration costs
Does the model appropriately represent the patient population(s) of concern?	No. It is based on populations of two RCTs and one open-label study	No. It is limited to populations of two clinical trials	No. It is limited to populations of two clinical trials
How has heterogeneity been included in the model?	No	Yes, implicitly through IPD, but much of this is lost by assuming an average age for all patients in long-term projection	No
Were appropriate methods used to include patients' treatment/disease history and effects on event rates?	No	No	No
Does the model clearly list and justify structural assumptions, and likely impacts on outcomes?	Most assumptions are described, and tested in sensitivity analyses	Most assumptions are described, and tested in sensitivity analyses	Most assumptions are described, and tested in sensitivity analyses
How were structural aspects tested by the modeller (e.g. clinical opinion, literature review, clinical guidelines)?	Not stated	Not stated	Not stated
Was the modelling methodology fully justified (e.g. Markov, decision tree, discrete simulation)?	Adequate in the circumstances but not ideal	Adequate in the circumstances but not ideal	Adequate in the circumstances but not ideal

continued

TABLE 24 *ISPOR checklist (cont'd)*

	Wyeth model	Abbott model	Schering-Plough model
Transparency			
Is the model structure transparent (structure, parameters and values)?	Yes	No. Reviewers had to restructure it before assessing its logic	No. Proprietary modelling package made assessment difficult
Is the physical model fully accessible to a non-modelling audience?	No	No	No
Timing			
Are time-horizons appropriate, given the disease, treatments and decision context (1-year, 10-year, lifetime)?	Yes. Results are presented for 1, 2, 5, 10, 15, 20 and 25 years	Yes. Results are presented for 48 weeks, 5 and 30 years	No. Results given for lifetime, 10, 20, 30, 40, 50 and 60 years. Other shorter time-horizons would be helpful
Are the model's cycle times appropriate to the disease and treatments of interest?	Yes	Yes	Yes
Have appropriate methods been used to extrapolate data over extended time-horizons?	No. BASDAI and BASFI used for progression, and exaggerated rates used	Yes	Yes
Data values			
Is there a full description of a thorough review process identifying data values?	Yes	Yes	Yes
Are the sources of data values fully described and appropriate?	Yes. Except for odd choice of progression rates	Yes	Yes
Are there clear criteria for data inclusion/exclusion?	No	No	No
Are there appropriately documented value ranges for data parameters for sensitivity analysis?	Yes. Mostly	Yes. Mostly	Yes. Mostly
Is there clear identification of areas in the model populated with clinical opinion? Is the approach appropriate?	Yes	Yes	Yes
Data preparation			
Are there full details on data preparation to generate parameter values (e.g. meta-analysis, relative risk rates, estimation of utility, calculation of transition rates)?	Yes	Yes	Yes
Were transition rates correctly calculated from interval data?	No. Life expectancy calculations wrong	Yes	Yes
Were survival data appropriately extrapolated/modelled (e.g. Weibull, exponential)?	NA	NA	NA
Are sensitivity analyses adequately handled and classified (e.g. probabilistic, one-way, multiway)?	Yes	Yes	Yes

continued

TABLE 24 *ISPOR checklist (cont'd)*

	Wyeth model	Abbott model	Schering-Plough model
Data incorporation			
Are data units, time intervals and patient characteristics consistent?	Yes	Yes	Yes
Was uncertainty adequately incorporated in the model using appropriate sensitivity structures and analyses?	Yes	Yes	Yes
Internal validation			
Was there a thorough and adequate quality control/error checking test plan?	No	No	No
Was the model replicated and compared using alternative software?	Not clear	Not clear	Not clear
Was there a clinical face-value reality check? How was this conducted (e.g. internal review, expert review)?	Not known	Not known	Not known
Was the model shown to replicate accurately data used in model construction?	Not relevant as long-term data do not exist	Not relevant as long-term data do not exist	Not relevant as long-term data do not exist
Cross-model validation			
Was the model directly compared and contrasted with existing models in the same disease area?	No	No	No
Were differences between models appropriately discussed, categorised and acted on?	No	No	No
External validation			
Was the model validated against independent data?	No	No	No
Were data suitable in terms of their context for comparison (patient group, treatments, timelines, outcomes)?	No. RCT populations are quite different from normal NHS patients	No. RCT populations are quite different from normal NHS patients	No. RCT populations are quite different from normal NHS patients
Which interim outputs were matched?	None	None	None

Disease progression

In the company submission, disease progression rates are based on a Finnish study of only 65 patients followed for 3 years. This is preferred over the main published and authoritative reference[85] on disease progression in AS based on data from 1100 UK patients over 8–10 years, and validated by 3-year data from a further 493 patients. They also quote and then dismiss another UK study carried out at Truro on 257 patients over 5 years. In both of these papers the estimated annual progression rates in BASFI are much lower than those in the Finnish paper. In addition, the Truro study showed no significant progression in BASDAI scores over 5 years, whereas the authors have adopted the same strong progression rate for BASDAI as for BASFI, again on the limited evidence of the Finnish paper. We do not believe that these are credible assumptions.

If one substitutes more realistic progression rates for BASFI, and assumes no progression in BASDAI over time, important changes are seen in the results generated by the Wyeth model. If BASFI increases by 0.7 per annum (0–100 scale) as used by Schering-Plough, the ICER at 25 years increases from £13,207 per QALY to £21,967, and if a rate of 0.5 per annum is used (as per the Abbott model), this increases further to £22,670 per QALY. Making these alterations brings the Wyeth results much more into line with those reported by the Abbott model (see *Table 21*, p. 55).

Regression models of BASDAI and BASFI

Justification for analysis

The rationale for carrying out these analyses is not presented, and may be open to question. In particular, it must be considered unlikely that relationships derived from limited trial data over no more than 24 weeks will remain unchanged for up to 25 years.

Appropriate predictors

There seems to be confusion between predictors and predicted variables in that response at 12 and 24 weeks is largely governed by the BASDAI and BASFI values at 12 and 24 weeks, so that the use of response as a predictor is tautological. The use of treatment as a predictor is also problematic:

- on pragmatic grounds in that it fails standard criteria for inclusion on several occasions
- on theoretical grounds in that the validation of a reasonable predictive model would be to compare predictions to observed data by treatment group as strata, treatment being excluded as an explanatory variable.

Causality

It is not clear what causal model (if any) is assumed here. Without this underpinning there is a serious danger of self-perpetuating errors propagating through the long-term model. If a causal loop is considered unavoidable, then two-stage regression may be required, leading to different results.

Linearity

The formulation of these models as simple linear models is also inappropriate, given that values are constrained between two limits. This usually necessitates non-linear functional forms, particularly where predictions are required close to the boundaries. Using the beta distribution as an approximation, it is clear that at least quadratic powers of the predictor variables should be tested, and some of these are likely to feature in the final models.

Utility model

Regression models

The models shown in the company submission disguise the very strong correlation between model parameter values or BASDAI and BASFI. In the long-term, BASFI appears to be correlated with disease duration, whereas BASDAI is not; this suggests that a BASFI-only model (possibly with quadratic terms) may be more suitable for long-term projection.

Choice of model

Using the EQ-5D utility model leads to a large proportion (>70%) of survivors on the lowest utility level 0.09 (BASDAI/BASFI = 100) in the long term. Since this is close to the value appropriate to death it may not be compatible with the reality of chronic disease. If this is conceded, then either the BASDAI/BASFI models are not appropriate in the long term, or the SF-6D utility model may be more realistic.

Regression models of AS costs

Choice of predictors

As with the utility model, the selected AS costs model uses both BASDAI and BASFI values to model long-term costs, despite the regression coefficient for BASDAI being clearly insignificant for inclusion. The evidence suggests that the BASFI-only model is superior and should be used. However, this yields less extreme cost values for high BASFI scores, which will tend to reduce the apparent cost savings from using the treatment.

Model structure

The use of a single 'compendium' cost model is questionable, particularly as use of a log-normal model necessarily involves producing biased cost estimates. It is often more reliable (and certainly easier to explain) if an attempt is made to subdivide costs on the basis of cost-driving events (e.g. via a two-part conditional model), rather than resorting to a logarithmic transformation just because of skewness.

Life expectancy

The estimation of life expectancy from life tables appears to have been wrongly calculated, failing to condition expectancy on the attained age of patients. This would tend to distort the balance of patients in the long-term projection period, and may contribute to erroneous results.

Overview of Abbott model[51]

Abbott developed a patient-based transition state health economic model comparing adalimumab and NSAIDs with NSAIDs for the treatment of patients with AS. The model is constructed using Microsoft Excel. Some clinical data used in the model are not currently in the public domain. The submission presents results of cost–utility analysis including a range of incremental cost per QALY ratios. An NHS perspective is taken in the base-case analysis, with societal costs explored in the sensitivity analysis. A discount rate of 3.5% is applied to both costs and benefits.

Population and comparator

The model incorporates IPD from the M03606 and M03607 Phase III trials for the first 48 weeks, and subsequently extrapolates future treatment careers for these patients for up to 30 years, using derived parameters and assuming that all patients have the same (average) age for mortality calculations.

In the base case, only the subset of patients deemed to satisfy BSR inclusion criteria are included in the analysis (315 from a total of 397; 79%). The average age for treatment initiation in the base-case model is 42.2 years, [**Commercial-in-confidence information removed**]% of patients are male, [**Commercial-in-confidence information removed**]% are white, and baseline BASDAI and BASFI scores are 6.8 and 5.8, respectively. No information is available for duration of disease for the base-case population; however, in the combined study samples mean duration was 11.8 years in the treated group and 10.6 years in the control group.

The Abbott model compares the use of adalimumab plus NSAIDs versus NSAIDS. This is appropriate as NSAIDS are the current standard treatment for AS. No indirect comparisons were attempted with other anti-TNF-α agents.

Resource use

Several resources are costed in the model. Drug costs are calculated as £357.50 per injection. No administration costs are included, as it is assumed that patients will self-inject without assistance. Efficacy monitoring costs are included at initiation. The cost of assessing response to treatment during the 48-week trial, and twice per year thereafter is included at £108 per visit.[99]

Routine safety monitoring (which includes one liver function test, one urea and electrolyte test and one full blood count, together with nursing and physician administration time) is estimated at a monthly cost of £49.60. Test costs are taken from Jobanputra and colleagues[100] and uplifted to 2005 prices, with 10 minutes of nursing time estimated at £34 per hour, and 10 minutes of physician time at £108 per hour. An additional routine chest X-ray (£16) before and 6 months after initiation of therapy, together with a TB skin test before initiation are also included in the model.

Unlike the other two models, the costs of adverse events were also included. It was estimated that all adverse events apart from TB would cost £61.56 per episode (which includes the cost of a physician visit, a liver function test, a urea and electrolyte test, a full blood count and a course of antibiotics for 37% of cases). The cost of an active case of TB was estimated at £5100, which was based on National Collaborating Centre for Chronic Conditions (NCCCC) data.

Disease-specific costs were based on ordinary least squares (OLS) regression of BASDAI and BASFI data from the OASIS study.[51] Only BASDAI measurements are used to predict total costs in the base-case analysis.

Health outcomes

Survival was factored into the model with an SMR of 1.5. Utility values were estimated by mapping the health utility index (HUI) values collected in the M03-606 and M03-607 trials to BASDAI, and BASFI scores.

No disease progression was assumed for patients receiving adalimumab. Patients who did not respond to adalimumab or patients receiving standard therapy were assumed to progress by 0.5% BASFI per year.

Patients were assumed to discontinue adalimumab at a rate of 10% per year. Once patients discontinued treatment, their BASDAI and BASFI scores rebounded to the average score of the conventional therapy patients.

Results

Cost-effectiveness ratios are presented at 48 weeks, 5 years and 30 years. Using an NHS perspective the incremental cost per QALY for adalimumab compared with placebo is £47,083 at 48 weeks, £26,332 at 5 years and £23,097 at 30 years. Using a societal perspective, the ICER at 48 weeks is £29,855; by 5 years this has decreased to £7742 and by 30 years to just £5093.

Sensitivity analysis

Univariate sensitivity analysis was undertaken as part of the submission, on a number of parameters including probability of discontinuation, costs and rate of progression, none of which increased the ICER above £30,000. PSA was also conducted, which indicated that there was a 69.7% chance of adalimumab being cost-effective at a £30,000 threshold, using the NHS perspective.

Quality assessment of Abbott model

The economic model presented in the Abbott submission was evaluated using the ISPOR good practice checklist,[98] as shown in *Table 24*. The submitted Excel model was examined to identify issues of particular concern and any confirmed or apparent implementational errors. Where possible an assessment is made of the likely impact of each problem on cost-effectiveness results.

Specifying the patient cohort

The model incorporates IPD relating to the two RCTs which support the application. It is recognised by the authors that the trial inclusion criteria do not match those of the BSR guidelines for treatment of AS, and therefore in the base case those trial patients who would not be eligible for treatment based on the guidelines were excluded.

The duration of disease of trial patients is not included in the IPD built into the model, and therefore no direct comparisons can be made. However, the summary data included in the company's submission indicate that the mean duration of disease was lower for placebo patients than for those randomised to adalimumab (10.6 versus 11.8 years). Although this difference did not achieve conventional statistical significance ($p = 0.24$), it could have an influence on the model results when extrapolated over 30 years, although the nature of such an effect is not obvious (shorter duration but similar disease severity could indicate either an earlier stage of disease progression, or alternatively more aggressive disease progression in the placebo arm).

Analysis of IPD for the base-case population does reveal differences between the two treatment groups in terms of the initial condition of patients. Patient-assessed pain was significantly worse in placebo patients (75.2 versus 71.0 on VAS, $p = 0.006$). Although not statistically significant, noticeable differences were also observed in the BASDAI score (6.94 versus 6.67, $p = 0.098$) and the BASFI score (6.04 versus 5.64, $p = 0.095$). Thus, it is likely that use of the selected subset of trial patients may bias outcome changes in favour of adalimumab.

In the submitted model, the authors have chosen to respecify the age of all patients to the mean age of the selected subset from 48 weeks onwards. This is a strange decision and effectively means that the results presented refer to the sum of two model simulations for patient groups with different characteristics. It is likely that this would result in some bizarre inconsistencies between various characteristics of some of the patients in the simulation. Thus, the oldest patient recorded in the trials, who was aged [**Commercial-in-confidence information removed**] at randomisation, has a [**Commercial-in-confidence information removed**] chance of still being alive at age 101 (through being redesignated as aged 42).

Response rate

The use of IPD to populate the model should avoid any problems in adequately incorporating heterogeneity in the model population with respect to modelling response to treatment. However, there are some difficulties in continuing efficacy of adalimumab as projected in this model. The authors do not accept that any long-term loss of efficacy is to be expected, which seems to be unduly optimistic. However, they do allow that discontinuation of therapy will occur at a low level owing to adverse events and other causes, and adopt a rate of 10% per annum as used in Kobelt's model[85] beyond 48 weeks. In the Abbott model discontinuation up to 48 weeks is assessed according to BSR criteria, [**Commercial-in-confidence information removed**] per annum,

but after week 48 this is switched to the long-term 10% rate. This appears to be an unwarranted and arbitrary assumption, which is internally inconsistent and serves to inflate the projected benefits of adalimumab.

By contrast, response in the placebo comparator remains unchanged from week 30 onwards at [**Commercial-in-confidence information removed**]%. This leads to an anomaly in the model, since by progressively reducing the number of responders to adalimumab annually while retaining a fixed level of response in the placebo arm, there is a break-even time after which the placebo arm performs better than the intervention arm. With the assumed adalimumab discontinuation rate of 10% per annum this occurs after 10 years, but with the modelled rate of [**Commercial-in-confidence information removed**]% per year (based on BSR criteria) the break-even efficacy occurs after only [**Commercial-in-confidence information removed**] years. If the authors' assumptions are sound, then this implies that continuation of adalimumab therapy beyond 10 years (or more consistently 4 years) would not be warranted.

Projected BASDAI and BASFI scores

Values of BASDAI and BASFI beyond the observed data are calculated differently for placebo and adalimumab patients: the former receive their last observed value indefinitely up to 30 years [last observation carried forward (LOCF)]. However, adalimumab patients who cease to receive treatment are assumed to return to BASDAI and BASFI values equivalent to the average value of the placebo patients. This means that there is much less variability in long-term scores in the adalimumab group than in the placebo group, who retain their initial wide range of values. This leads to two potentially important effects:

- the adalimumab group is guaranteed a cost advantage, even if the response rate has fallen below that of the placebo group (see the section 'Response rate', p. 58)
- in PSA the underlying (first order) variances are distorted by adopting a structure that compares individual patient simulation in one arm with group-averaged simulation in the other.

Utility model

A linear regression model is used to estimate health-related utility from BASDAI and BASFI scores which features only two additional parameters: gender and race. The analysis leading to this model is not described in any detail, but is stated to be based on the cross-sectional HUI data collected at a single time-point in the two trials. Using sample average values for gender and race, the possible range of utility scores corresponding to the worst and best possible disease scores is from [**Commercial-in-confidence information removed**] to [**Commercial-in-confidence information removed**]. The omission of age from the model formulation is potentially serious, since it prevents any consideration of the long-term modifying effects of ageing and growing co-morbidities on patient utilities, which must be important when projecting outcomes for three decades. Almost certainly, age will narrow the available range of utility so that later utility gains from the use of adalimumab would be reduced.

Cost regression models

The annual cost associated with AS was estimated from one of two simple regression models in which disease severity scores (BASDAI/BASFI) were related to average resource use (costed at UK prices), based on the OASIS study. This involved collecting data from 208 patients in four European (non-UK) countries over 2 years. As the authors did not have access to original OASIS data they were limited in the analysis they could carry out to that possible from stratified averages. The base case assumes that costs are solely related to the BASDAI score, with an equivalent BASFI model offered as an alternative. Both models yield predictor coefficients with very wide confidence intervals, indicating that their predictive accuracy is very limited. This is particularly worrying since the number of observations with high values of BASDAI and BASFI is very small, while the costs for such patients are very important in comparing treatments in the model.

Overview of Schering-Plough model[52]

The following commentary focuses on the methods used in the submission to produce cost-effectiveness estimates for infliximab from the NHS perspective only. A discussion of an analysis that incorporates costs other than those faced by the NHS, in particular the cost associated with informal care and days off work for individuals of working age, is not pursued since infliximab is clearly cost-effective under all reasonable values under these circumstances (see Table 18, p. 43, in the Schering-Plough submission).

The model prepared in support of the Schering-Plough submission is based on a combined decision tree and Markov chain structure, implemented within the TreeAge software package. To allow assessment of model logic on a comparable basis to the other submitted models, the assessment group attempted to replicate the model using Microsoft Excel. It proved difficult to obtain approximately comparable economic results to those submitted.

Population and comparator

The model looks at the costs and effects of infliximab therapy (5 mg/kg) once every 6 weeks over a period of 70 years after the start of therapy, compared with placebo. The experience of a cohort of individuals aged 40 years (on average), 80% of whom are male, is described for adult patients classified as having AS (by New York criteria) with a BASDAI score ⩾4 and with a spinal pain assessment score ⩾4 on VAS (range 0–10 cm). Two sets of results are presented, one based on the 24-week results in ASSERT[49] and another based on those reported by Braun and colleagues up to 12 weeks.[50]

Resource use and health outcomes

Costs and utilities were estimated on the basis of regression analysis of a cross-sectional postal survey data on 1413 and 1145 AS patients in the UK[85] using age, gender, BASFI and BASDAI covariate values in the respective trial sample.

Disease progression and long-term treatment

Since the analysis assumed that there was no effect on mortality, the difference in benefits between placebo (comparator) and infliximab was based entirely on morbidity differences driven by the extent to which the latter improved disease and functional activity, and delayed disease progression (based on functional score alone). The estimated effect on retardation of disease progression is based on actual data up to 2 years only.

The analysis is based on the assumption that patients drop out from treatment at an annual rate of 15%, which is derived from a 2-year follow-up study of 18 patients who qualified for treatment continuation after 12 weeks in the study by Braun and colleagues.[50] The same source was used to justify the assumption that disease activity (BASDAI) and its implications on functioning (BASFI) remained stable with infliximab. The 0.07 (annual) progression rate (in BASFI scores) estimate used in the analysis was based on 1100 participants in the same survey, for whom data on BASDAI and BASFI scores were also available from a previous population survey conducted in 1992–1994 at the University of Bath. Results on progression were also available using the BASFI score data for 495 patients followed up annually for up to 9 years.[85]

Results

Discounted cost–utility ratios are presented for the whole of remaining lifetime: £18,192 per QALY (Braun trial[50]) and £19,169 per QALY (ASSERT[49]). Infliximab and NSAIDs yield about 1.6 additional QALYs per patient for an incremental cost of about £30,000 per patient.

Sensitivity analysis

The results of a PSA are reported in graphical form, and appear to demonstrate, with 100% certainty, that infliximab and NSAIDs are cost-effective at £30,000 for both trials.

Quality assessment of Schering-Plough model

The economic model presented in the Schering-Plough submission was evaluated using the ISPOR good practice checklist[98] as shown in *Table 24*. The submitted model has been examined to identify issues of particular concern and any confirmed or apparent implementational errors. Where possible, an assessment is made of the likely impact of each problem on cost-effectiveness results.

Dosing costs

As acknowledged by the authors, dose and frequency of administration are important parameters in the model. The breakdown of results by number of vials used is clearly relevant to the NHS, but should be supported by observed usage patterns in the UK.

In the submitted model, the cost of infliximab has been erroneously inflated by 7.84% (a general price inflation factor used for NHS costs). However, the mean number of vials per infusion is set at 3.7, which assumes that there is no wastage at all due to extensive vial-sharing; this leads to an understating of infliximab costs by up to 7.5%. The net effect of these two issues is largely neutral.

Although sensitivity analysis considers the effects of varying doses and cycle lengths on costs, it does not account for the corresponding effects on health. This assumption of constant benefits at varying doses was justified on the basis of

TABLE 25 *Corrected base-case economic results for infliximab*

Model	Period	Incremental cost per patient	Incremental utility per patient (QALYs)	Incremental cost per QALY gained
Submitted model: Braun[50]	Lifetime (70 years)	+£29,399	+1.62	£18,192
ASSERT[49]		+£30,326	+1.58	£19,169
Corrected model: Braun[50]	Lifetime (70 years)	+£44,170	+0.877	£50,380
ASSERT[49]		+£39,914	+0.976	£40,889

observational and uncontrolled data on 43 patients in Spain and 34 patients in Canada, which requires more convincing validation.

Disease progression

As noted by the authors, apart from the cost of infliximab administration, the most important parameter was the effect of the drug on disease progression: changing the baseline value of no progression while on treatment to half the off-treatment rate (i.e. 0.035) takes the cost-effectiveness ratio close to £30,000 cost per QALY (see Figures 7 and 8, p. 45, in Schering-Plough submission). This highlights the need for further evidence on the effects of treatment beyond the first 6 months to confirm the results of the model. It is noted that the analysis of the Braun trial[50] data (the only source available to the authors for the purpose of populating the model) only used BASDAI and BASFI scores from the group of 13 patients who completed the 2-year follow-up; the data on BASFI scores while still on treatment for the five (28%) patients who withdrew from treatment appear to have been ignored (see p. 31).

The analyses presented are all based on an annual rate of progression (in terms of BASFI score) while off treatment of 0.07, derived from Kobelt.[85] According to this source, the progression rate for patients with active disease (i.e. BASDAI $\geq$4) was found to be 0.054 with the postal survey, and 0.059 in the regularly followed cohort at the Bath hospital. The rate adopted in the Schering-Plough model corresponds to that for all AS patients rather than to the population of patients with active disease studied by ASSERT[49] and Braun and colleagues.[50] Since a lower rate of progression off treatment implies lower benefits from infliximab therapy, the analysis appears to be biased (see comments in Kobelt[85], pp. 1163–1164, about the observed negative relationship between rate of progression and baseline BASFI score).

Detailed exploration of the submitted model, and replication of its logic in an Excel spreadsheet, revealed a serious flaw in the implementation of an important assumption. Contrary to the submission document, patients who are withdrawn from infliximab treatment have been assigned no off-treatment disease progression at all. This leads to an unwarranted and accumulating cost and outcome advantage for the infliximab arm of the model. When this error was corrected (*Table 25*), the lifetime ICERs for infliximab treatment increased dramatically.

Regression cost models

An interesting feature of the presented analysis is its use of regression methods to make cost projections for the sample in the ASSERT[49] and Braun[50] trials on which the analysis is based. In particular, the source publication does not report the age range in the estimating sample, but reports a sample mean age of 56 years with 22% of patients aged 65 or older, taken from Kobelt.[85] By contrast, the model covers a period of 70 years following initiation of infliximab therapy. Projections over such a timespan, derived from regression analysis of cross-sectional data for 1 year, may result in meaningless estimates, as suggested by the reported negative relationship between age and costs, on the one hand, and the positive one between age and utility, on the other (see Table 13, p. 36, and Appendix 3, Table 1, of company submission).

Model time-frame

While the rationale for chronic disease modelling is sound (i.e. to account for the long-term effects of treatment on disease activity and dysfunctional progression), the model time-frame may not be justified given the available evidence (see above). This is important given the observed influence of the time-frame on the results. When the authors assumed no effect beyond 10 years they obtained a cost per QALY ratio of £42,000 or £44,000, depending on whether the Braun[50] or the ASSERT[49] sample data are used (see Table 17, p. 42 of company submission).

Withdrawal of treatment

It is somewhat unclear what the dropout rate used in the model represents. Twenty per cent of the rate seems to relate to the effect of adverse events, although the type is not specified. This poses problems since, according to the authors' own assessment (see Table 17, p. 42 of company submission), a higher annual dropout rate makes the treatment more attractive in terms of the cost-effectiveness ratio. To obtain meaningful interpretations, the model should allow the separation of the effect on the cost-effectiveness ratio of an increase in treatment withdrawal due to AEs from that following the inability of the drug to control disease activity and maintain patient functioning.

Adverse events

The average cost of an AE was estimated by calculating the average cost of all AEs recorded in the Braun trial.[50] However, not all AEs are costed in the model, only those that were associated with treatment discontinuation. This implies that an unknown number of other events would be equally distributed between the two arms of the analysis, and would therefore not contribute to either incremental costs or outcomes. However, no evidence is presented to support this proposition. In ASSERT,[49] 82% of infliximab patients suffered at least one AE up to week 24, and 11% had an infusion reaction. Thus, when compared with 'no infusions' conventional therapy, AEs should be included for at least 11% of all treated patients, and possibly many more.

There also appears to be some inconsistency about the way adverse events are treated in the model. While a fixed cost is imputed to 20% of cases who withdraw from treatment with each annual cycle, no utility loss is assigned to such events, other than that which results from the discontinuation of treatment and its intended effect on disease activity and functioning.

Utility model

Given the absence of documented effects on mortality, the validity of results depends critically on the statistical methods used to estimate utility scores as a function of age, gender, disease activity and functional status. Given the limited range of possible utility values (i.e. from –0.59 to 1;[101]), using a simple linear regression to estimate a predicting equation for utilities will in general result in biased and inefficient estimates and predictions, since its predictions are not restricted to fall within the range of possible utility values (in principle, they could fall anywhere within the $-\infty$ to $+\infty$ range). For example, while the minimum estimate obtainable by the equation is 0.17, the maximum exceeds 1.0 for some combinations of values, suggesting a possible bias in the results. It is not clear whether values used in the model have been restricted to prevent this eventuality.

This problem is likely to be more serious when predictions are made using values for covariates in the linear model that are outside the ranges observed in the estimating sample (see problems discussed with regard to predictions on the basis of age, above). Therefore, as a minimum check, the sensitivity of results to alternative statistical specifications for utilities (and costs which can only take non-negative values and, typically, have a skewed distribution of positive values) should have been conducted. Possible statistical choices include regression methods for censored variables or non-normal distributions.

Summary

Although different in structure and methods, the three submitted models share a common set of assumptions governing how the anti-TNF-α drugs should be assessed for cost-effectiveness. In each case the initial treatment phase is followed by a long period of progressive chronic disease in which the original two treatments remain the only options.

All three models were disappointing in the quality of execution, particularly in terms of quality control and transparency. After the correction of serious errors and unusual parameter values, the cost-effectiveness of the two self-administered drugs appears to be closely comparable. By contrast, infliximab seems to be a far less attractive investment, with high long-term ICERs (£40,000–50,000 per QALY) and presumably even less appealing results over shorter periods.

Chapter 7

Economic evaluation

Key issues

Mortality

It has been documented that patients with AS are subject to increased mortality risks throughout life,[33] and this is reflected in the modified risk tables used in two of the three submitted models. Although there is evidence that anti-TNF therapy is effective in reducing disease activity and improving functional performance, as yet there is no basis on which to project improved survival in treated patients, although plausible pathways can be suggested (e.g. incidence of heart disease). Thus, the outcome benefits that can be legitimately modelled are restricted to health-related quality of life and associated utility gains. Should even modest survival benefits be identified in future, there is no doubt that the cost-effectiveness of anti-TNF-α agents in treating AS would be markedly improved. This is an important area for continuing research, but will necessarily take several years of data accumulation before any results could be expected. Even so, it will be necessary to rely on large-scale patient registry data, since the restrictive design of efficacy trials precludes meaningful long-term comparisons.

Co-morbidities

AS is associated with a range of co-morbidities which impact on patients' quality of life and the cost of their care throughout their lives. Lack of reliable information prevents explicit recognition of these distressing conditions in models. Instead, they are represented implicitly through the intermediate patient assessment tools, and the cost models that use these to reflect variations in healthcare expenditure variations. Clearly, these are blunt instruments and inevitably lead to potentially large estimation errors, especially in projecting future healthcare costs. This position can only be remedied in the long term by careful and extensive research, which should aim to identify the principal clinical events, patient subgroups and disease patterns that govern poor patient experience and high resource use.

Intermediate outcomes

The submitted and published models rely heavily on the two Bath indices of self-assessed patient condition (BASDAI and BASFI). Although validated and well regarded, these tools suffer from some limitations:

- Self-completed questionnaires may be vulnerable to subjective bias.
- The absence of explicit definitions and guidance for responders permits interpretive heterogeneity.
- 'Ceiling' and 'floor' effects can make interpretation of extreme values problematic in longitudinal data of chronic conditions.

It is disappointing that the Bath metrology index (BASMI) has not been more widely used, and correlated with the other indices and with direct observations of morbidity and cost, although this is presumably because of the additional time and cost involved in carrying out the clinical measurements required by the BASMI. Using the BASMI would facilitate an objective measure of physical deterioration.

The central issue for economic evaluation is the suitability of these measures as the principal basis for estimating both outcome changes and disease-related costs. This is particularly important when considering long-term changes dependent on our very limited understanding of the natural progression of AS. Ideally, new targeted indices should be developed, framed where possible around verifiable events or functional restrictions and with clear associations with the main sources of resource use and disutility.

However, these are long-term research aspirations. At present, BASDAI and BASFI are the best tools available. Because they were not designed for use in economic evaluation, it is important to be cognisant of potential difficulties, including enhanced scope for variability, inherent non-linearity of the scales, and the influence of the assumptions involved in linking index scores to utilities and costs.

Continuous or intermittent therapy

The three submitted models all assume that patients will continue on anti-TNF-α therapy indefinitely unless withdrawn because of loss of efficacy or adverse events. This is a very optimistic basis on which to evaluate cost-effectiveness.

Indeed, it appears to conflict with the guidance on continuation included in the BSR guidelines:

> "Once a consistent response has been achieved, treatment should be reviewed periodically to assess the need for continued treatment, the dose of drug to be used and the intervals between dosing, in order to ensure that patients receive the minimum effective treatment."

Unfortunately, this fails to provide specific detail as to the appropriate period between assessments, and the criteria that should govern the decision to (dis)continue treatment. As a result, modelling of alternative scenarios is somewhat speculative and must be subject to the test of clinical realism and practicality. Nonetheless, the general principle is valid that open-ended treatment without reappraisal of efficacy and safety cannot be supported on either clinical or economic grounds.

This raises a more fundamental question about the therapeutic objectives of anti-TNF-α drugs in the treatment of AS. The reported trials are all designed to demonstrate short-term benefit in controlling the symptoms of severe active disease, with principal outcomes assessed at 12 (or 24) weeks. Long-term continuation involves a second implicit objective; that of prophylaxis against subsequent symptomatic relapse. However, there is no conclusive evidence of efficacy in this respect, nor has any consideration been given to appropriate indications for such prophylaxis, or to the dosages necessary to achieve success. If successful prophylaxis can be demonstrated in RCTs then it might prove beneficial gradually to reduce the dose or frequency of treatment, while monitoring a patient's condition for symptom stability.

Treatment strategy

There is evidence that some patients whose initial treatment is unsuccessful on one anti-TNF-α drug will have a better response when offered a second or third agent. Indeed, in some centres this staged trial and error approach is an accepted treatment strategy. It may therefore be more realistic to compare different strategies distinguished by the sequence of drugs that are offered to patients, aiming to maximise benefit while minimising overall cost.

Other possible elements of a treatment strategy might include episodic treatment (i.e. treat only when severe symptoms are present and for a limited period after resolution), prespecified waiting/monitoring periods and scheduled dose adjustments (as discussed above).

Analysis of IPD

The Abbott model included a valuable subset of the IPD for two RCTs, which can be used to explore the nature and dynamics of response to treatment with one anti-TNF-α drug. Data relating to 397 patients (246 adalimumab, 151 placebo) were available concerning:

- patient characteristics (age, gender, race and weight)
- disease measures at intervals up to 52 weeks (BASDAI, BASFI and VAS pain score)
- efficacy measures (response according to BSR guidelines, HUI, whether and when patient exercised an early escape option).

A series of analyses has been carried out to gain general insights to inform the design of economic evaluation, and key findings are reported in the following sections.

Inherent variability in BASDAI

The natural measurement error associated with self-reported observations of BASDAI scores can be estimated by considering the recorded differences between scores at prebaseline assessment and at baseline (usually only a few days apart). The pattern of changes is shown in *Figure 9*, and represents a near-normal distribution with a mean difference of –0.04 points (on a 0–10 scale) and standard deviation of 1.13. This implies that following an initial measurement of 4.0, a second measurement could be much lower or higher without any real change in condition having occurred; 50% of second scores would fall outside the range 3.2–4.8, and 1 in 20 outside the range 1.8–6.2 purely by chance. The inherent variability in BASDAI scores is likely to arise from a variety of sources, but particularly from a combination of genuine very short-term alterations in the patient's condition and transitory perceptual and cognitive fluctuations.

At the level of the individual patient this poses severe problems for the clinical decision-maker, since no single BASDAI score can be taken as a reliable test against a preset threshold. Moreover, there is evidence from the IPD that variability for individual patients is highly heterogeneous within the AS population, so that few reliable inferences can be made without first obtaining an extended history of BASDAI scores. Thus, establishing eligibility to commence therapy would require multiple observations separated in time.

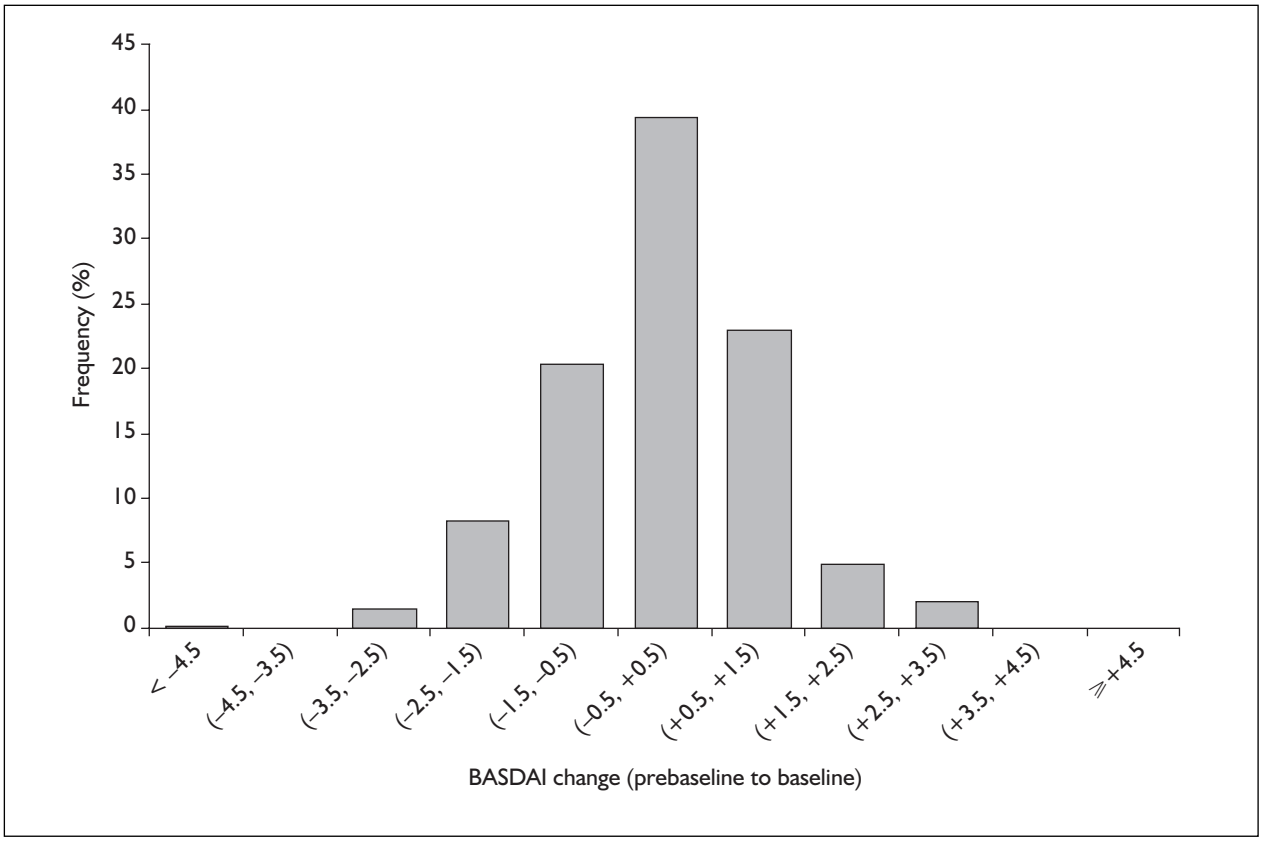

FIGURE 9 *Distribution of BASDAI changes between prebaseline and baseline assessments in two RCTs*

Similarly, confirming that a response has occurred would need several distinct measurements. This problem is compounded because it appears that during the period when a substantial change in condition is occurring (e.g. during the first 12–20 weeks of therapy) BASDAI scores may show much greater interobservation variability than at other times.

There must therefore be serious concerns about whether the BSR criteria for anti-TNF-α therapy are meaningful or practical as a means of distinguishing those patients most likely to benefit, either in deciding whether to commence treatment, or whether to discontinue treatment for non-response.

Non-linearity in outcome gains

All Wyeth and Schering-Plough submitted models adopt an average measure of benefit in terms of reduction in BASDAI score, which is independent of the initial condition of the patient. This is a crude assumption and does not take account of the closed nature of the BASDAI scale, which imposes non-linearity on the measured scores through floor and ceiling effects, resulting in important deviations from linearity in the vicinity of the extreme values (0 and 10). Using the beta distribution as an analogy for a double-bounded stochastic process, it was reasoned that in the vicinity of a boundary, relationships between measurements separated in time should be approximately quadratic in form.

To assess how response to treatment (measured by change in BASDAI over the first 12 weeks) varies with the initial condition of patients (i.e. baseline BASDAI score), the former was plotted and regressed as a function of the latter. The results for adalimumab are shown in *Figure 10* together with equivalent results for the placebo group. Regression trends were fitted by OLS on the patient-level data. Since the bulk of placebo data fell within the central portion of the scale for both variables, a linear trend line yielded a good fit to the data. By contrast, tests showed that a quadratic model was superior in presenting the adalimumab data, where more observations occurred at the lower end of the scale at 12 weeks.

For placebo patients it is noticeable that the observed values at 12 weeks do not follow the line of equivalence that might be expected if the patients' condition remained broadly unchanged

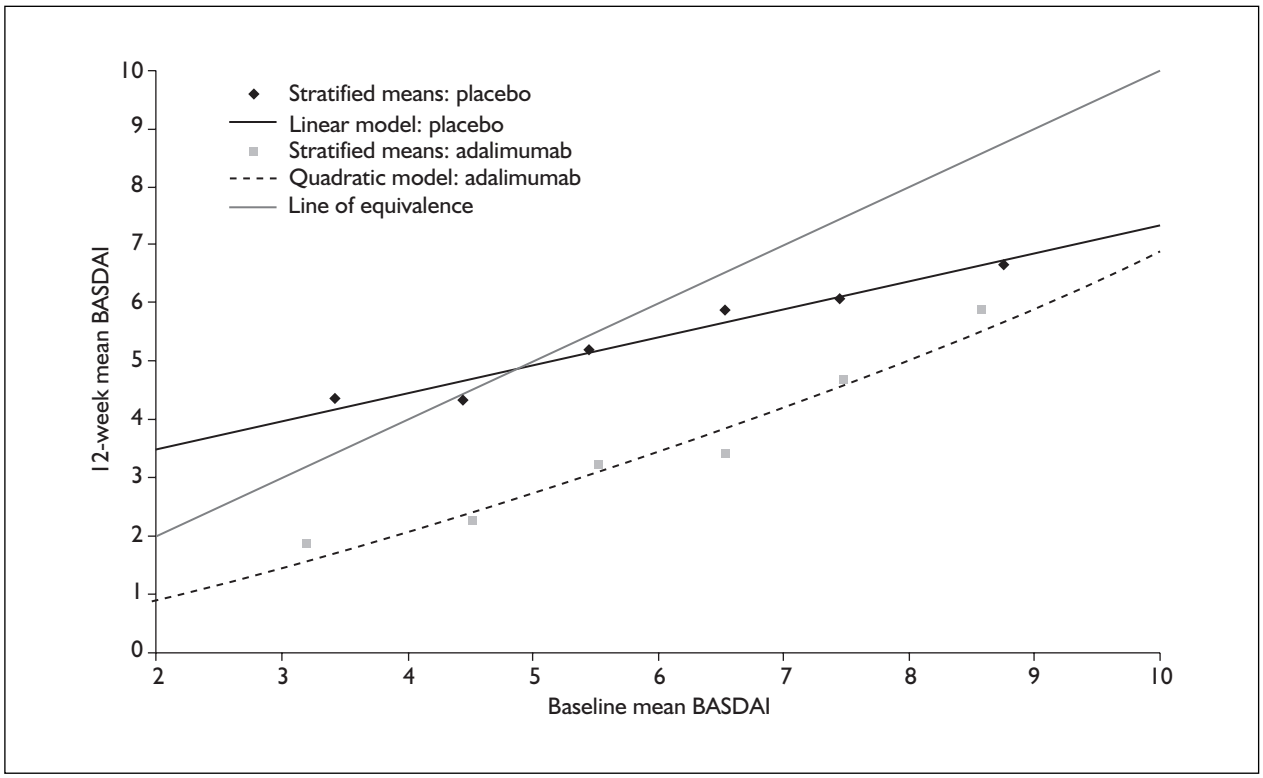

FIGURE 10 *Relationship between BASDAI scores at baseline and after 12 weeks in two RCTs*

over the period; most placebo patients experienced reductions in BASDAI scores, most notably among those with the higher initial scores. By contrast, there was a tendency for those with the lowest initial scores to exhibit increases in scores by 12 weeks. This suggests that regression to the mean may be involved, where patients with the most extreme values (high or low) will show a tendency to converge towards the centre of the distribution when remeasured. However, since the trendline crosses the line of equivalence well below the population median, it appears that there is also an important process of spontaneous improvement taking place in some placebo patients.

By comparing the two trendlines, it is possible to estimate the size of treatment benefit (i.e. the attributable reduction in BASDAI scores) and how this varies with the baseline BASDAI. As shown in *Figure 11*, it appears that the benefit is greatest for patients with less severe BASDAI score, and steadily diminishes with increasing baseline score. This effect is principally because patients with the highest scores are more likely to experience important improvements without treatment, so that much of the apparent gain from initiating anti-TNF-α therapy would have occurred anyway.

Spontaneous resolution without anti-TNF-α therapy

The trials of adalimumab featured an early escape option which allowed patients to opt for open-label treatment after a period on the randomised therapy. No patients could exercise this choice before 12 weeks had elapsed. 'Early escape' may be considered to reflect a patient's belief that they had not achieved a satisfactory response, and/or they believed that open-label treatment offered the possibility of better treatment. The relationship between this and the BSR guideline definition of response is explored in *Figure 12*, where it is apparent that responders and non-responders who were content to continue with randomised treatment fared consistently better. This is particularly clear in the case of pain assessments, suggesting the strong influence of pain on patients' decisions. The trends are similar in each category for both adalimumab and placebo patients, implying that benefit is gained mainly by the relative case-mix of patients falling into each group. Comparing those patients in each arm who chose to continue in the randomised trial for at least 36 weeks (*Figure 13*), the trends are very similar and have certainly converged by week 30. In this data set, this included about 20% of all placebo patients, who

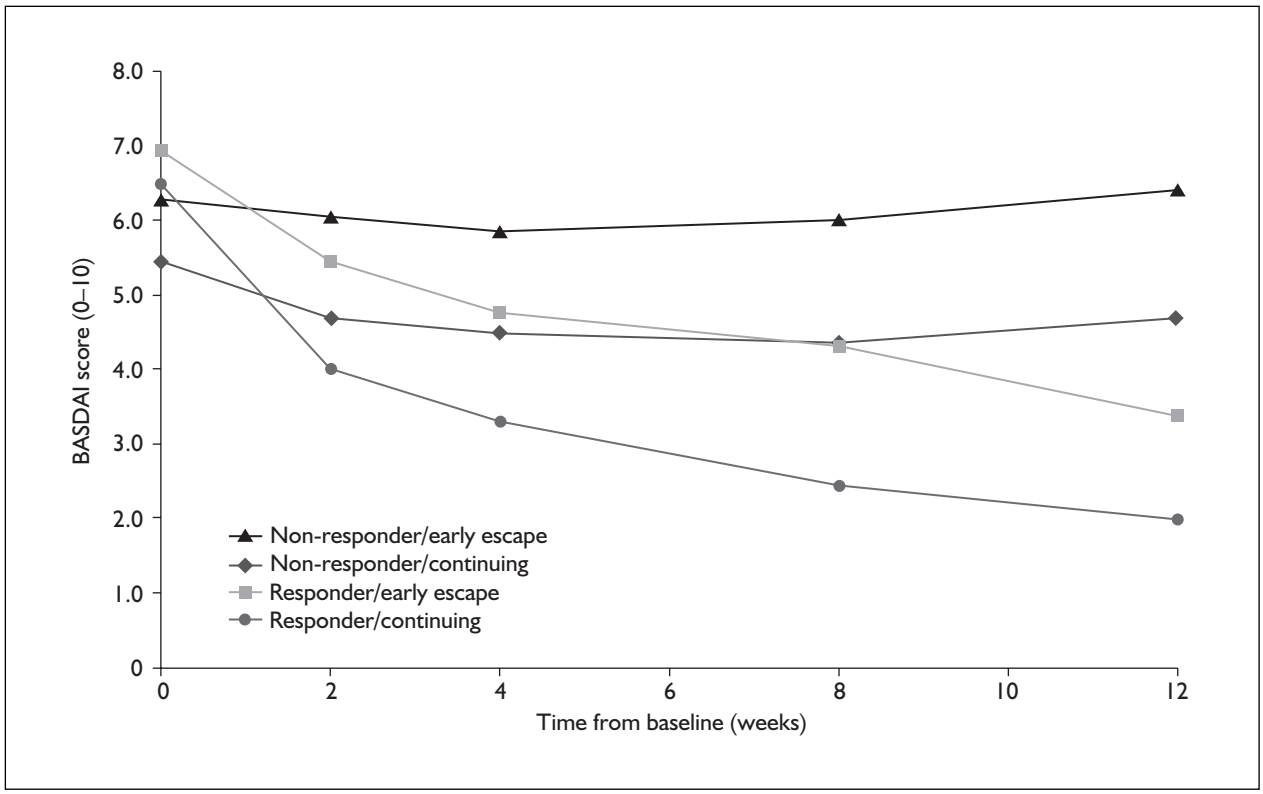

FIGURE 11 *Trends in mean BASDAI scores by response and early escape choice*

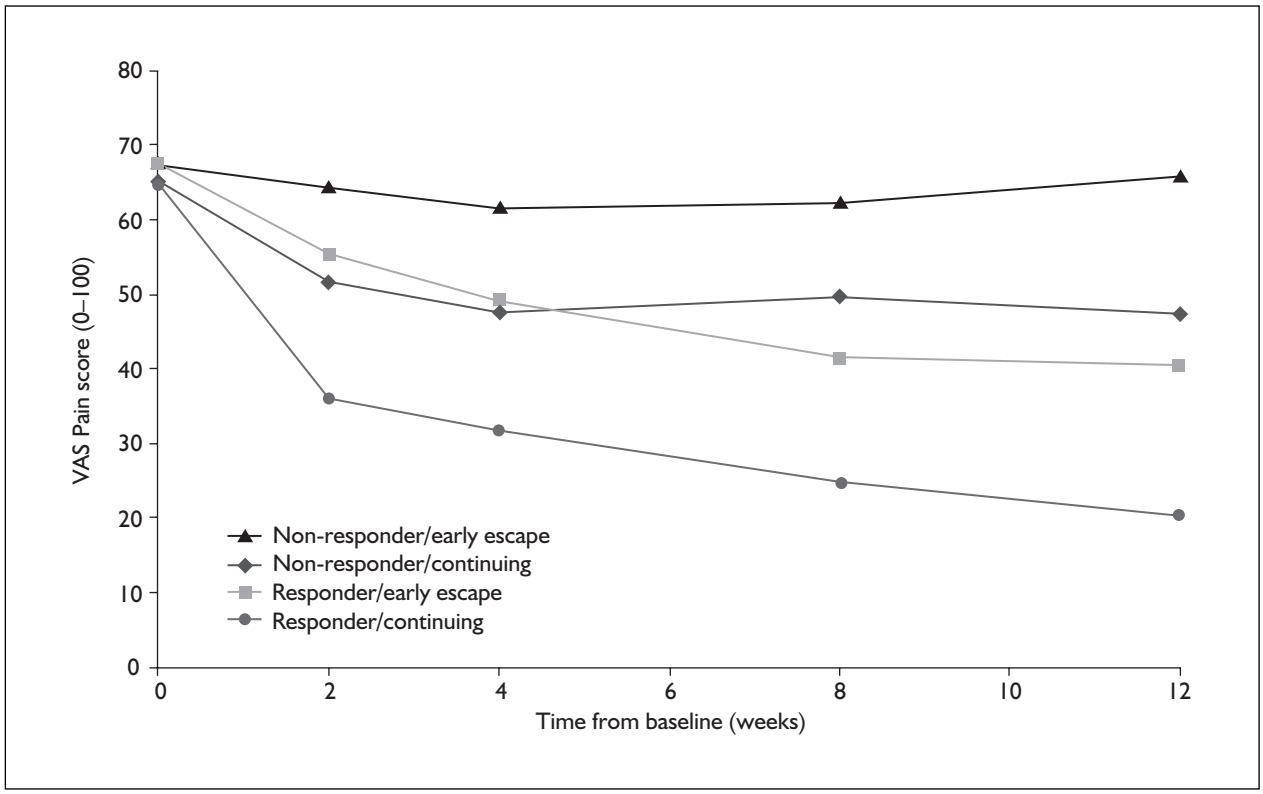

FIGURE 12 *Trends in mean VAS pain scores by response and early escape choice*

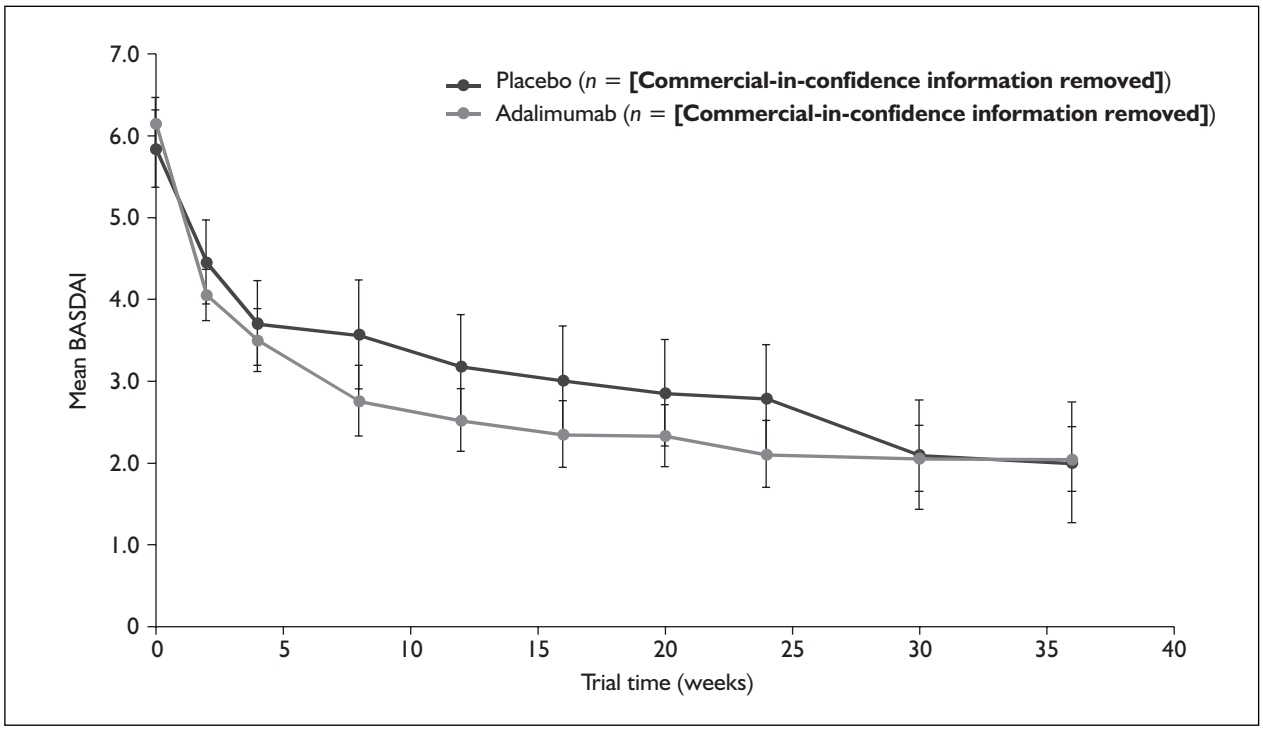

FIGURE 13 *Trends in mean BASDAI scores for patients remaining on randomised treatment to 36 weeks (CIC)*

met the criteria to be classed as responders and did not choose to exercise the early escape option. It may be concluded that a proportion of patients considered eligible for treatment with anti-TNF-α therapy are likely to achieve equally good outcomes without any additional treatment. If a decision protocol can be devised that identifies some or all of this group, it is possible that long-term unnecessary medication could be avoided for some, and the costs and cost-effectiveness of anti-TNF-α treatment for other patients considerably improved.

Pragmatic criteria for withdrawal of long-term therapy

The BSR clinical guidelines offer clear criteria governing the initiation of anti-TNF-α therapy, and the conditions for continuing treatment upon assessment of early response (after 12 weeks initially). However, although recommending periodical review of the need to continue treatment, no interval between reviews is suggested, and no criteria are given by which to determine whether the treatment remains effective.

One pragmatic approach to setting a threshold for withdrawal of long-term therapy is based on analysis of the trial IPD. From a patient perspective the decision made by patients randomised to adalimumab to exercise the escape option and transfer to open-label therapy suggests dissatisfaction with the effect of the unknown treatment. By examining different measures of patients' current condition it is possible to identify a factor or combination of factors that can predict whether patients will opt to continue treatment or wish to switch to a more effective alternative.

Three candidate factors were tested (BASDAI, BASFI and VAS pain score) for this purpose and each performed well on an individual basis:

- BASDAI at 12 weeks with a threshold of 4.2 (0–10 scale) accurately predicted 77% of cases.
- VAS pain score at 12 weeks with a threshold of 42 (0–100 scale) accurately predicted 77% of cases.
- BASFI at 12 weeks with a threshold of 3.75 accurately predicted 71% of cases.

In addition, a simple combined criterion of BASDAI and pain scores at 12 weeks (BASDAI + pain/10 > 8.4) achieved a slightly better result, accurately assigning 79% of cases. This is broadly consistent with current BSR guidelines.

The latter threshold used at annual intervals may be helpful in illustrating a strategy for withdrawal of long-term anti-TNF-α treatment for lack of effectiveness. [**Commercial-in-confidence information removed**.]

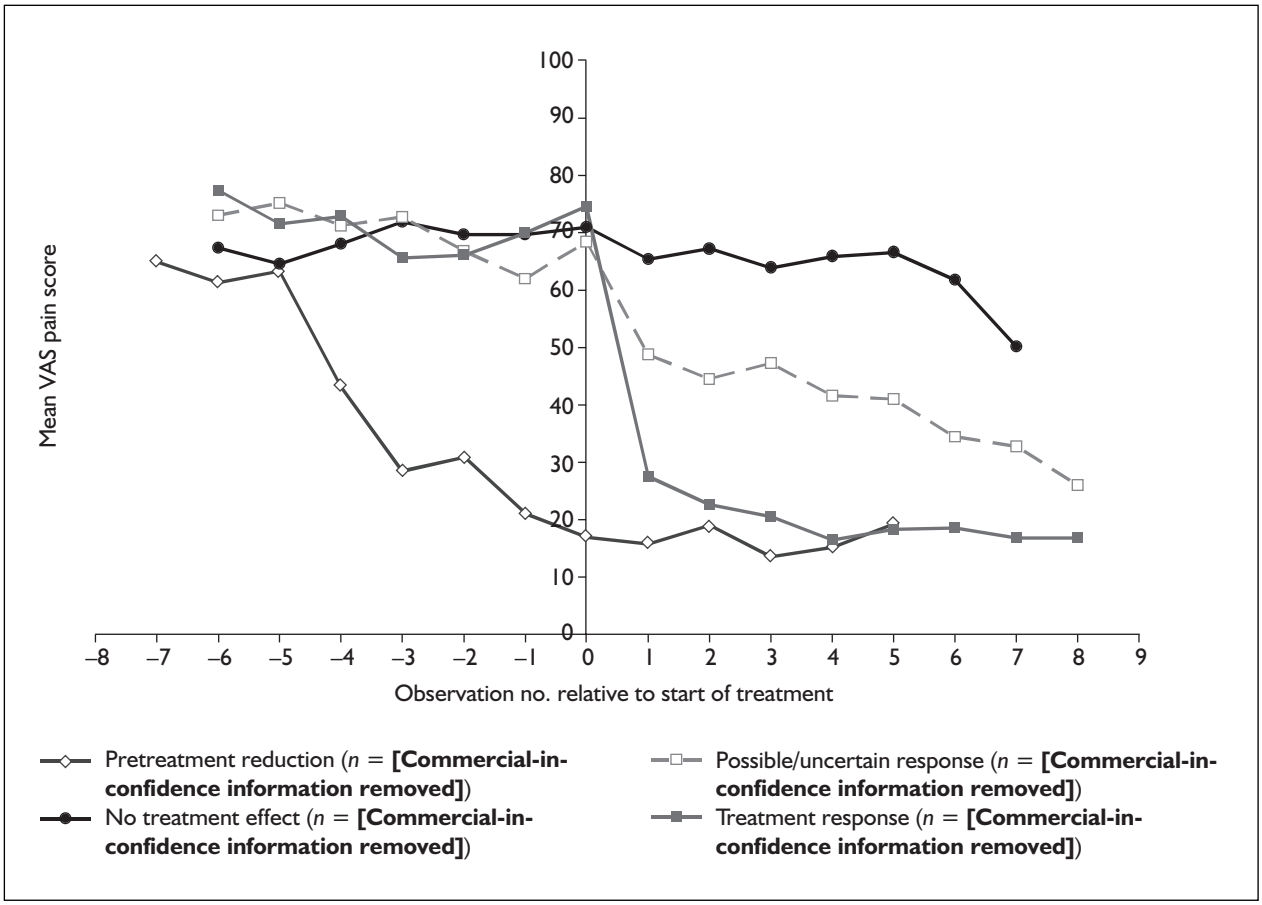

FIGURE 14 *Response to treatment in placebo early escape patients*

Profiling heterogeneity in AS patients

It is helpful to consider the nature of differences between patient experience of treatment with anti-TNF-α agents, as the basis for projecting benefits beyond the immediate observation period of available trials. The unusual design of the adalimumab trials permits such analysis (after some manipulation of the IPD) among patients randomised to placebo but who may exercise the option to switch to open-label adalimumab at any time from 12 weeks onwards. The reviewers selected these patients and examined the sequence of recorded pain scores, looking for evidence of a substantial and sustained reduction in pain during the course of the trial. This involved exercise of subjective judgement since allowance has to be made for inherent variability in measurement (as described above) as well as evidence in many patients of occasional short-term flares in pain superimposed on the medium-term trend. It proved possible to assign patients to one of three subgroups:

- those with no evidence of any change in pain scores over the period
- those with clear evidence of a substantial and sustained reduction in pain
- those where some improvement in pain scores was possible, but the variability in the evidence made the determination inconclusive.

In *Figure 14* mean VAS pain scores of placebo patients exercising the early escape option are plotted for each subgroup after standardising patients to a common reference observation point when open-label treatment began. No benefit from open-label treatment could be detected in [**Commercial-in-confidence information removed**] of [**Commercial-in-confidence information removed**] patients. By contrast, [**Commercial-in-confidence information removed**] patients showed clear evidence of important reductions in pain (mostly within 4 weeks) after beginning anti-TNF-α treatment. A small number of patients demonstrated equally large improvements, but all achieved well before the treatment change, showing clear evidence of spontaneous recovery. For the indeterminate subgroup there is an intriguing suggestion that the decision to opt for open-label treatment may often

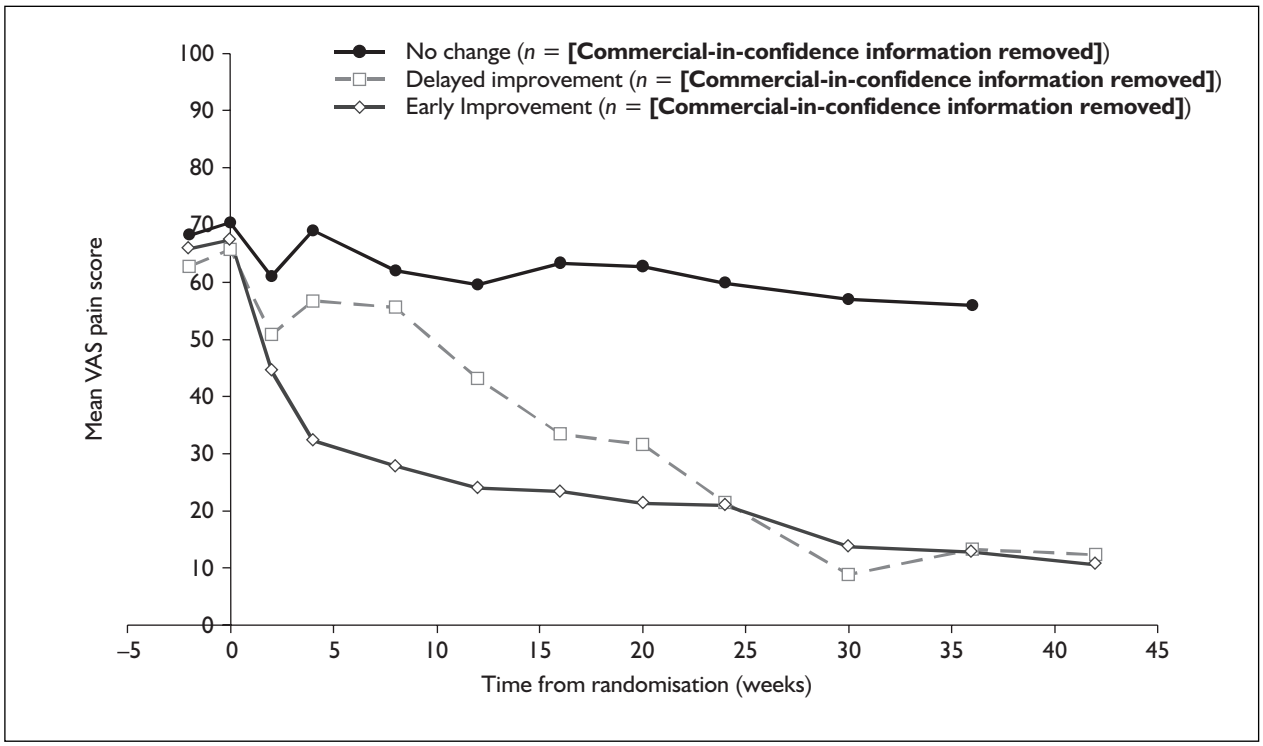

FIGURE 15 *Changes in pain among placebo patients not using escape option*

have been triggered by a short-term increase in pain. The subsequent downward trend in mean scores may be attributable to the new regimen, or arguably could be seen as a continuation of downward trend already evident before the switch. *Figure 15* shows the equivalent results for the patients who chose not to opt for open-label therapy during the trial. The pattern is very similar to that seen in *Figure 14* excluding the treatment response subgroup, suggesting that the three remaining subgroups reflect genuine differences in patient temporal experience of pain.

Taken overall, these data lead to a broad classification of the AS patients in the adalimumab trials as follows:

- About 30% suffer persistent severe pain which is not affected by anti-TNF-α treatment.
- About 18% of patients benefit from a rapid and sustained improvement in pain levels with conventional treatments alone.
- About 42% of patients benefit from a rapid and sustained improvement in pain levels only when anti-TNF-α therapy is used.
- About 10% of patients experience a more gradual or variable improvement in pain levels over several months, but where it is difficult to determine whether or not anti-TNF-α therapy assists the rate or extent of improvement.

Exploratory economic modelling: assumptions and parameter values

Various assumptions must be made to allow economic modelling to be attempted, including the choice of specific parameter values on the balance of available evidence or expert advice. This is set out in this section, and the baseline parameter values are summarised in *Table 26*.

Age and gender

To demonstrate explicitly the effect of age and gender on cost-effectiveness, model structures were adopted that allow individual age/gender cohorts to be analysed. For the purposes of presenting representative overall results, weighted averages are computed based on distributions drawn from the principal trials undertaken by the three companies.

Standardised mortality ratio

Two of the three submitted models use an SMR of 1.5 for all AS patients, based on credible published sources. The authors have adopted the same value for their modelling.

Initial disease activity and functional index scores

Each of the three submissions uses slightly different initial mean BASDAI and BASFI scores

TABLE 26 *Baseline parameter values for exploratory modelling*

Factor	Wyeth model	Abbott model	Schering-Plough model	LRiG baseline model
Age (years)	41	42.2	40	Various ages 20–80
Gender				Model men and women separately
Mortality (SMR)	1.5	1.5	1.0	1.5
Baseline BASDAI	6.10	6.67/6.94	6.41	Various scores 4.0–9.0
Baseline BASFI	5.90	5.64/6.04	5.75	Various scores 4.0–9.0
Long-term therapy withdrawal rate	10% p.a.	10% p.a.	15% p.a.	15% (vary between 7% and 24%)
Incidence of TB	–	0.0026 per person-year	–	0.0026 per person-year
Incidence of AEs	–	[**Commercial-in-confidence information removed**]	20% of anti-TNF-α therapy withdrawals	0.7856 per person-year
Inclusion criteria	BASDAI $\geqslant$4.0	BASDAI $\geqslant$4.0 and VAS pain $\geqslant$40 mm	BASDAI $\geqslant$4.0	BASDAI $\geqslant$4.0 and VAS pain $\geqslant$40 mm
TB monitoring costs	–	£32 (2 $\times$ CXR) + £25.36 skin test	–	£32 (2 $\times$ CXR) + £25.36 skin test
Monitoring costs	£89.91 (3 months) + £75.61 p.a. thereafter	£108 per 6 months + £49.50 per month for tests	Assumed to be included in admin. costs	Infliximab: included in admin. cost; etanercept and adalimumab: £25 tests per quarter, £25 twice per year tests by GP/nurse
Acquisition costs	£89.38 twice weekly	£357.50 fortnightly	£1552.59 per 6 weeks (plus loading dose)	Etanercept: £178.76 per week; adalimumab: £178.75 per week; infliximab: £1570.28 per 6 weeks (plus loading dose)
Administration costs	None (self-administered)	None (self-administered)	£124 per infusion	£267 per infusion (vary between £91 and £453)
TB treatment costs	–	£5100 per treatment	–	£5100 per treatment
AE costs	Assumed equal in both arms, so not included	£61.56 per AE, 1.548 AEs per patient-year = £95.29 per year	£79.27 per patient in first year, £15.80 per patient-year thereafter	£95.29 per patient-year in first year, £47.65 per patient-year thereafter
AS-specific cost model	£351.31 p.a., $\times$ 1.0665 per 1 point increase in BASDAI, $\times$ 1.1707 per 1 point increase in BASFI	£708.45 + £750 $\times$ BASDAI	Two-part model approx. linear for BASFI and BASDAI $\geqslant$3: £554.78 $\times$ BASFI – £665.23	£1585.30 $\times$ exp(0.1832 $\times$ BASFI)
Utility model	0.9234688 – 0.040190 $\times$ BASDAI – 0.043188 $\times$ BASFI	0.948857 – 0.041528 $\times$ BASDAI – 0.034481 $\times$ BASFI + 0.047080 $\times$ Male – 0.063801 $\times$ White	0.8772129 – 0.0384087 $\times$ BASDAI – 0.0322519 $\times$ BASFI – 0.0278913 $\times$ Male + 0.0016809 $\times$ Age	Use Schering-Plough model
Long-term progression in mean BASFI score	+0.30 p.a.	+0.05 p.a.	+0.07 p.a.	+0.07 p.a.

CXR, chest X-ray; LRiG, Liverpool Reviews and Implementation Group.

TABLE 27 *Pooled short-term BSR response rates*

Agents	Trials	Arm	Week 12	Week 24	Notes
Etanercept and adalimumab	All except AS314	Anti-TNF-α	52.1%	43.5%	–
		Placebo	22.3%	14.1%	–
	All including AS314	Anti-TNF-α	59.0%	49.2%a	12-week figures adjusted pro rata to results excluding AS314
		Placebo	22.5%	14.2%a	
Infliximab	Braun and ASSERT	Anti-TNF-α	50.6%	?	–
		Placebo	?	?	–

drawn from their own trials. Since clinical effectiveness (i.e. change in BASDAI/BASFI) appears to vary by initial value, it is important to consider a range of values explicitly. For the purposes of presenting representative overall results, weighted averages are computed based on available distributions drawn from the principal trials undertaken by the three companies.

Short-term effectiveness

In accord with the findings, reported in Chapter 4, of meta-analyses of treatment effects for the three products, including both direct comparisons with placebo and indirect comparison between agents, no distinction is made between the products in terms of effectiveness. Instead, estimates of benefit are assumed based on pooling of all available data at each time-point.

Response rate

Modelling the impact of anti-TNF-α agents when used according to the BSR guidelines requires an estimate to be made of the proportion of patients achieving a clinical response (at least a 2-point reduction on BASDAI) at various times during the first few months of treatment. If followed rigidly, the guidelines lead to a complex network of possible decision pathways (as shown diagrammatically in the Abbott submission). However, little accuracy is lost if instead short-term effectiveness is indicated by BSR response rates at two time-points (12 and 24 weeks), which correspond to reporting periods in the main RCTs. *Table 27* summarises the values obtained: full details are available for the etanercept and adalimumab trials at 12 weeks, and for all trials except for AS314 at 24 weeks. By contrast, the company's submission provided infliximab response figures only in respect of the anti-TNF-α arms at 12 weeks. For modelling, the pooled week 12 response rates from etanercept and adalimumab trials were adopted, and also week 24 rates after pro rata imputation of missing AS314 data. The 12-week response rate for infliximab is a little lower than those reported for the other products, so that adopting the pooled estimates for all three drugs does not disadvantage infliximab in any way.

These values are generally consistent with the patient subgroups identified in the IPD analysis, given that the trial assessments are made on single observations, rather than multiobservation trends.

Long-term effectiveness

Since all the RCT evidence is short term, projection of outcomes beyond the first year is founded on assumptions and some reports from patient registries and open-label follow-up studies. There is currently little evidence to suggest that effectiveness differs among the three drugs in the long term.

The most important measure of long-term potential to benefit is the probability of withdrawal from treatment owing either to loss of efficacy or to AEs and patient preferences. Compared with RA, there is no consistent reporting of reasons for withdrawal in published sources for AS patients. *Table 28* summarises the sources cited in support of model parameters used in the company submissions, alongside evidence from other sources. Comparison of medium-term continuation rates beyond the first year in the French and Spanish studies suggests that both are consistent with a constant annual risk of withdrawal, although at different rates. The wide range of annual rates indicates the degree of uncertainty involved in choosing a suitable value for this important aspect of any model. A central value of 15% per annum is adopted here, but it is important to explore the full range from 7% to 24% per annum in sensitivity analyses.

However, there is a technical problem associated with the implementation of this feature in a model, owing to the identification in the IPD analysis of an apparently stable subset of

TABLE 28 *Long-term anti-TNF-α treatment discontinuation rates*

Patient group	No. studied	Annual loss rate	Detail
SpA	1467	7.2%	Spanish BIOBADASER registry (Carmona[102])
AS	230	12%	French single-centre registry (Duclos[103])
RA	233	10%	Combined Swedish and UK open-label studies cited in Wyeth submission
AS	18	15%	Open-label extension to Braun trial cited in Schering-Plough submission
AS	220	22.3%	Danish DANBIO registry (Linde[104])
AS	[**Commercial-in-confidence information removed**]	23.7%	Adalimumab IPD analysis of continuation for weeks 24–48

SpA, spondyloarthropathies.

conventionally treated patients which maintains a steady mean outcome measure comparable to those of responders in the anti-TNF-α arm, that is, about 17% of 'responders'. The simple application of a fixed dropout rate to the total number of treated responders in a model leads to a medium-term anomaly by which after several years there are more untreated 'responders' than treated responders, implying that anti-TNF-α treatment would become detrimental rather than beneficial over time for which there is no evidential basis. This might be resolved if there were long-term evidence of progressive failure of conventional therapies for this subgroup, but this does not exist and longitudinal studies suggest that average BASDAI scores probably remain steady over many years. To overcome this difficulty the convention is adopted of applying an annual withdrawal rate to the difference in response rate between the two arms of the evaluation, rather than the absolute number of responders. This requires a calibration adjustment to reconcile the rate parameter in the model to the equivalent absolute rate. Since actual rates are used for the first 12 months of the model, this device is only used in second and subsequent years.

TB monitoring, treatment and costs

The Abbott model correctly acknowledges a recognised risk of TB as a potential adverse event associated with use of anti-TNF-α agents, and the authors have included the costs of pretherapy TB testing and of treating a notional small number of TB episodes. The estimation of these risks is not founded on a secure evidence base and the size of the calculated costs is relatively small; it is important for consistency to use a common set of costs for all three products, and therefore the Abbott calculations were adopted without modification.

Drug acquisition and administration costs

Etanercept and adalimumab

The acquisition cost of these drugs is virtually identical (etanercept costs £89.38 per 25 mg given twice weekly, and adalimumab costs £357.50 per injection given every fortnight, equivalent to weekly costs of £178.76 and £178.75 respectively) and since both are self-administered at home without supervision, no additional healthcare costs are incurred for administration.

Infliximab

Patients receive supervised infusions dosed by weight at 5 mg/kg. Initially, treatment is given at 0, 2 and 6 weeks, and thereafter every 6–8 weeks. In the submitted model patients receive maintenance therapy every 6 weeks, so that treatment is given every week with an additional loading dose at 2 weeks.

A patient with the average body weight of 73.6 kg would require 4 vials per infusion; however, the distribution of body weight shown on the BSRBR suggests that an average of 3.74 vials would be required costing £1570.28 per infusion (based on £419.62 per 100-mg vial). This assumes that no vial sharing takes place, which is realistic except in centres with a large number of patients. The maximum average saving from full vial sharing is unlikely to be more than about 0.3 per patient, equivalent to a potential reduction of about £126 per infusion. For sensitivity analysis, a reduction of £65 per infusion is tested.

The company's submission assumes that each infusion involves an outpatient attendance which is costed at £124: this is derived from the original Technology Assessment Report for rheumatoid arthritis (2001),[105] which has now been updated to current prices. The 2004/05 NHS reference costs tables[99] show the cost of a rheumatology (code 410) follow-up attendance as £108, and the cost of a rheumatology ward attendance as £135. However, the 2005/06 mandatory NHS tariff for rheumatology costs a follow-up outpatient attendance at only £91, but a regular attender visit for "chemotherapy with musculoskeletal primary diagnosis" (H98) at £267 and for "inflammatory spine, joint or connective tissue disorder" (H26) at £453. It is very likely that similar patients receiving infliximab infusions in different hospitals will be coded and costed differently depending on local circumstances and interpretation of definitions. On the basis that attendance for infusion is likely to involve treatment and clinical monitoring for a period of several hours, it seems inappropriate to treat these events for costing purposes as a routine follow-up consultation in an outpatient clinic. The authors therefore adopt the regular attender cost for chemotherapy (H98) of £267 for infliximab infusions, but allow this to encompass the additional treatment monitoring costs (tests and staff time). The impact of alternative assumptions is also tested, from a minimum of £91 per visit plus testing costs to a maximum of £453.

Treatment monitoring costs

There is general inconsistency among the three submissions and also between published guidelines and assessment reports concerning the nature and frequency of regular treatment monitoring. The Abbott model adopts the Prodigy guidelines, which derive from a US source, involving monthly testing of full blood count (FBC), liver function test (LFT) and urea and electrolytes (U&E). The Wyeth model assumes quarterly monitoring with FBC, ESR and biochemical profile. In the Schering-Plough model monitoring takes place every 6 months and is based on FBC, ESR, LFT and U&E. The West Midlands TAR for Rheumatoid Arthritis assumes that monitoring takes place at every infliximab infusion visit, and every 4–6 weeks for patients receiving adalimumab or etanercept; it is limited to FBC, LFT and U&E, as well as antinuclear antibodies and anti-DNA antibodies twice-yearly for infliximab patients.

Unit costs for individual tests are equally varied, being based on data from individual trusts in the absence of reliable national sources. Thus, the cost per FBC ranges from £2.42 [Centre for Reviews and Dissemination/Centre for Health Economics (CRD/CHE)] to £12.06 (Abbott), and per LFT from £0.61 (CRD/CHE) to £6.07 (Abbott).

From this confusion it is necessary to adopt a consistent set of assumptions for modelling monitoring costs. The authors have opted for quarterly monitoring for patients receiving long-term treatment. As discussed above, the cost of administration was allowed to include all associated monitoring costs in the case of infliximab. For etanercept and adalimumab patients it was assumed that testing will be carried out twice per year at the patient's routine follow-up outpatient visit, so that the additional costs involved are those of the tests themselves. It was assumed that the other two monitoring sessions are carried out at a GP's surgery. In each case, the tests carried out will be FBC, ESR, LFT and U&E. Using a mid-range estimate, it was assumed that this set of tests costs £25 per quarter, and the cost of nurse and GP time is £25 per GP monitoring visit.

Treatment-related adverse event incidence and treatment costs

The Wyeth model makes a simplistic assumption that etanercept is not associated with any additional adverse events and related costs. This is justified on the grounds that there were no statistically significant differences in moderate or severe AEs in the trials, although acknowledging an increase in injection-site reactions. These claims are not inconsistent with the AE detail provided by Abbott in their submission, yet the Abbott submission includes AE costs. Therefore, it must be assumed that cost differences are probable for all three agents.

In the Abbott model it is assumed that the rate of AEs observed in the first year of treatment persists indefinitely: this appears to be unduly pessimistic, given that some early AEs resolve within a short time, and that patients with persistent problems may be more likely to discontinue treatment in the first year. In contrast, the assumption made in the Schering-Plough model that only those AEs that are associated with later discontinuation should be costed almost certainly understates long-term AE-related costs. The present assessment adopted the Abbott figure of £95.29 in the first year of treatment, reducing by 50% (to £47.65) per patient-year thereafter.

Disease-related treatment costs

Modelling heavily skewed cost distributions is notoriously difficult. Each of the submitted models uses a different method to represent data from different sources.

The Wyeth modellers relied on a retrospective survey of 147 AS patients at a single UK centre in Stoke. To cope with the long tail on the cost distribution they carried out regression analysis on log-transformed cost data and obtained a predictive model that uses both BASDAI and BASFI scores as predictors. Unfortunately, this approach is fundamentally flawed as a basis for modelling disease-related costs over the full spectrum of patient experience. Regressing logarithmically transformed costs yields a model of the geometric rather than arithmetic mean, and leads to a systematic underestimation of true costs in skewed data. In addition, retrospective data collection over an extended period (12 months in this case) is very likely to underestimate resource use, especially where it relies on patients' long-term memory to recall multiple health professional contacts.

For the Schering-Plough model, resource-use data from a retrospective cross-sectional survey of 1413 AS patients in the UK (Bath) were costed, and then modelled as a function of current BASDAI and BASFI scores. The authors used a more sophisticated two-part conditional model to cope with the skewed distribution. A logit model predicts the probability of incurring any expenditure at all (predicted by BASDAI and BASFI), then a conventional regression estimates the magnitude of those costs (predicted by BASFI only). It appears that cost data were only requested for a period of 3 months, and then inflated to an annual equivalent. The presence of so many zero responses on resource use from chronically ill patients should be a serious cause for concern to the researchers, and may indicate selective non-response rather than zero returns. In any case the model obtained predicts that the mean cost of healthcare should be less than zero before the disease activity and functional indices reach the bottom of the scale: a result which is intuitively unreasonable. The maximum predicted cost is £4881 per annum, well short of the values of £10,000 or greater seen in other surveys.

The Abbott model relies on resource-use data held in the OASIS database, which was obtained in a 2-year prospective study of 208 AS patients from four centres in France, Belgium and The Netherlands. Clinical assessments and economic questionnaires were completed every 6 months, and BASDAI/BASFI scores collected every 2 months. A simple linear regression model was fitted to aggregated data, using either BASDAI or BASFI as a predictor (the former for the preferred Abbott model). The OASIS data should be considered a more reliable source than either Stoke or Bath, being prospective and over a longer period. However, the use of a linear regression model does not accord with the impression given by other studies that costs increase in a sharp, non-linear fashion for the highest BASDAI/BASFI scores. In addition, it is preferable to weight aggregated data points by the number of grouped observations where possible to minimise potential bias. Since the primary use of these models is to estimate costs of care over the long term, it seems more appropriate to use BASFI as the major predictor since it reflects long-term disease progression, rather than BASDAI, which appears to fluctuate but not increase over time.

Therefore, an exponential cost model was fitted to the weighted OASIS aggregate data, as a function of BASFI (*Figure 16*), as follows:

> Annual mean AS-related NHS cost = £1585.30 × exp(0.1832 x BASFI)

Health-related utility estimation

Each of the three submitted models uses a linear regression model to generate utility estimates depending on measures of patient characteristics and condition, primarily BASDAI and BASFI scores. The Wyeth model derives from EQ-5D data collected in the AS314 trial (n = 355), and uses BASDAI and BASFI scores only as independent predictors. The Abbott model uses HUI data collected in its two trials regressed on BASDAI and BASFI as well as gender and race. By contrast, the Schering-Plough model incorporates a regression model developed from the Bath survey dataset (n = 1144) and features BASDAI, BASFI, age and gender as predictor variables.

There are questions of technical validity concerning all of these regression models (floor and ceiling effects, the non-linear nature of utility scales, and the high degree of correlation between BASDAI and BASFI regression parameters). However, without direct access to source data it is not possible to undertake the necessary analysis to address these concerns. The authors chose to adopt the Schering-Plough utility model on the grounds that it draws on a much larger sample of

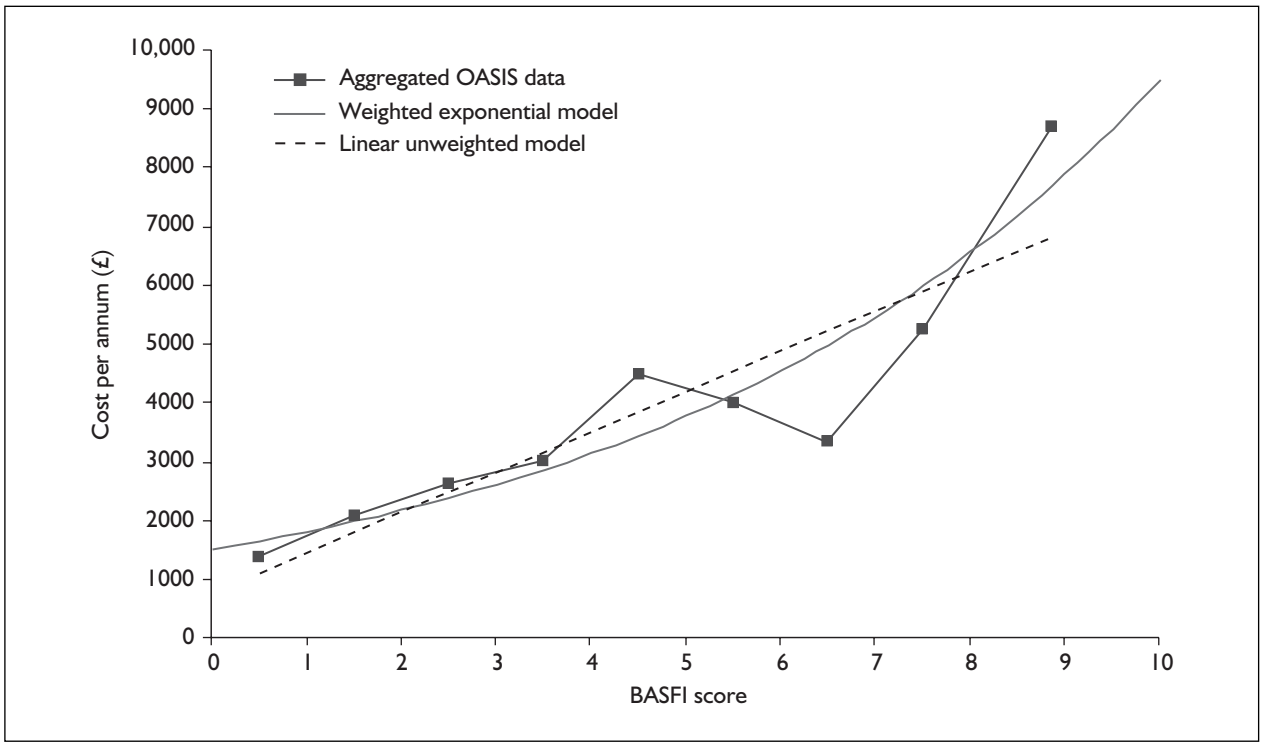

FIGURE 16 *Disease-related NHS costs modelled from OASIS data*

UK AS patients, and because the formulation incorporates age and gender variables, allowing a wider exploration of alternative scenarios.

Effect of discontinuing treatment and the disease process

The consequences of withdrawal from treatment for either loss of efficacy or adverse reactions impact significantly on long-term economic results. However, this is an area of minimal research evidence. All three company submissions assume that BASDAI and BASFAI scores return rapidly to their baseline values, with or without an adjustment to BASFI for long-term progression. Neither Abbott nor Schering-Plough offers any evidence to support this assumption. The Wyeth submission cites limited evidence for RA patients, which is of questionable relevance. They also refer to open-label extension data for AS trials to support their contention that there is no disease progression (i.e. no increase in BASFI scores) while on etanercept therapy.

It is disappointing that no attempt is made to base model assumptions on a reasonable assessment of the behaviour of the disease, and responses to clinical events. A study of AS patients' experiences[106] is instructive here. Group discussions involving 214 patients (25 years average duration of disease) suggested that normal experience consists of periods of relative stability interrupted by unpredictable flares of disease activity lasting from a few days to a few weeks. The dominant symptom of all flares was reported to be severe pain. Two types of flare were identified: localised flares affecting one or more specific areas, and general flares involving the whole body. All patients experienced the former at frequencies of one to five per annum, whereas only 40% of patients reported experiencing general flares at less frequent intervals. In either case, resolution was reported to be sudden, with return to the pre-existing condition. If the symptoms persisted for months it was suggested that this indicated a progression in disease severity rather than a flare.

This perspective accords with the evidence obtained from IPD analysis:

- that patient choices to switch to open-label treatment were normally associated with a sudden worsening of condition, particularly the pain score
- that many patients showed evidence of a natural improvement in condition over time, to the extent that some achieved a very good recovery while remaining on placebo
- that individual patient series of BASDAI/BASFI/pain scores regularly show short-term 'blips' of activity lasting for a few weeks before returning to the normal level.

This raises some important issues affecting the way that anti-TNF-α drugs are used, and the way that treatment is modelled. The notion of 'loss of efficacy' may be wrongly assigned in some cases on the basis of an isolated transient event breaching an arbitrary threshold. The use of baseline measurements to establish the 'normal experience' of AS patients may be flawed, since it is more likely that patients recruited into trials are suffering the effects of an abnormal flare event. This calls into question the nature and magnitude of the true treatment effect of anti-TNF-α treatment, which may be rather less than appears in trial results. It is then unclear to what extent rebound of patient scores should be included in AS models; it may be that the primary benefit of these drugs for some patients is to accelerate the recovery time from flare events, rather than to alter the normal quiescent condition of the patient. Moreover, if this is the case then continuation of treatment for extended periods may not be appropriate unless it can be shown to reduce the frequency or severity of subsequent flare events.

In the absence of much more longitudinal evidence on the normal treatment career of AS patients, the difficulties faced by the modeller are serious and profound. There is no doubt that important short-term benefits have been demonstrated for many patients from anti-TNF-α treatments. However, the claims for cost-effectiveness rely heavily on assumptions about the reality and magnitude of long-term efficacy in a few patients, which is most clearly seen in assessing an appropriate value for the size of the rebound effect to be included in a model when treatment ceases. In the submitted models this is set to a maximum level, to be consistent with their most optimistic assumption that without treatment baseline disease activity and pain experience are normal and persistent, rather than transient and self-resolving. This question cannot be resolved without a much improved evidence base. The present authors can only exemplify extreme positions and their implications for cost-effectiveness.

For the long-term increase in BASFI scores the model adopted the survey estimate used by Kobelt of +0.07 per annum for the conventional treatment comparator and this is applied for all periods after week 20 in the model. In the baseline analysis the same value was used in the intervention arm adjusted pro rata to the proportion remaining of the maximal excess response seen at 12 weeks. In effect, this implies that patients withdrawn from treatment are assumed to incur an increase in functional score which returns them to the trajectory of non-responders. An alternative option is also considered in which the size of this long-term increase can be scaled down to provide an enduring benefit to responders.

Exploratory economic modelling: short-term model

To make a direct comparison between the three products on the basis of the available RCT evidence, a simple spreadsheet model was constructed, limited to a period of 12 months from treatment decision (anti-TNF-α versus placebo plus conventional treatments). Only direct healthcare costs applicable to the NHS were modelled, and it should be understood that personal and societal indirect costs (e.g. loss of earnings) may be much greater, so that relatively modest gains in these elements would most probably lead to strongly positive cost-effectiveness results, particularly for patients of working age.

The model represents a cohort of 1000 patients of specific age and gender, with prescribed baseline BASDAI and BASFI scores, and combines life-table adjusted mortality rates with Markov-like transitions between anti-TNF-α treatment and reversion to conventional therapy. The model incorporates the common assumptions and parameter values described above, and draws on the available IPD to provide information on effectiveness measures over the first 12 months of treatment experience (response rates, treatment withdrawals and BASDAI/BASFI scores). As a consequence, the sources of uncertainty are limited, providing a starting point for the less secure projective modelling outlined in subsequent sections. However, it should be noted that this model is based on the use of a single agent used once only with no possibility of switching to other agents when the first is withdrawn, and is likely to be unrealistic in practice.

In this initial period no discounting of either costs or benefits is appropriate.

Baseline results are presented in *Table 29* and are estimated for a cohort of males aged 40 years with initial mean BASDAI/BASFI scores of 6.5 and 5.6, respectively. Since effectiveness is assumed to be the same for all three agents, the differences in economic results are determined by the cost of drugs and their administration.

TABLE 29 *Baseline results from short-term model (12 months undiscounted) for a cohort of males aged 40 years*

	Treatment			
Costs per patient	**Conventional**	**Adalimumab**	**Etanercept**	**Infliximab**
Drug acquisition	–	£5,453	£5,454	£9,856
Drug administration	–	£0	£0	£1,796
Therapy monitoring	–	£92	£92	£92
TB testing	–	£89	£89	£89
TB treatment	–	£8	£8	£8
AEs	–	£44	£44	£44
Disease-related	£213	£173	£173	£173
All costs	£213	£5,860	£5,860	£12,059
Incremental costs		+£5,647	+£5,647	+£11,845
Mean BASDAI	6.020	4.403	4.403	4.403
Mean BASFI	5.282	4.123	4.123	4.123
Mean utility	0.531	0.631	0.631	0.631
Total QALYs	521.7	620.3	620.3	620.3
Incremental QALYs per patient		+0.099	+0.099	+0.099
Incremental cost per QALY gained	**–**	**£57,258**	**£57,261**	**£120,109**

TABLE 30 *Sensitivity of baseline results from short-term model (12 months undiscounted) to age and gender*

Treatment	**Gender**	**Male**			**Female**		
	Age	**20**	**40**	**60**	**20**	**40**	**60**
Adalimumab	Incremental costs	£5,650	**£5,647**	£5,612	£5,652	£5,649	£5,628
	Incremental QALYs	0.099	**0.099**	0.098	0.099	0.099	0.098
	ICER	£57,249	**£57,258**	£57,347	£57,244	£57,251	£57,305
Etanercept	Incremental costs	£5,651	**£5,647**	£5,612	£5,652	£5,650	£5,628
	Incremental QALYs	0.099	**0.099**	0.098	0.099	0.099	0.098
	ICER	£57,252	**£57,261**	£57,350	£57,247	£57,254	£57,309
Infliximab	Incremental costs	£11,851	**£11,845**	£11,787	£11,854	£11,850	£11,814
	Incremental QALYs	0.099	**0.099**	0.098	0.099	0.099	0.098
	ICER	£120,075	**£120,109**	£120,448	£120,058	£120,085	£120,292

Table 30 shows summary economic results for a two-way sensitivity analysis of age/gender combinations: it is apparent that short-term model results are insensitive to age and gender variations.

The one-way sensitivity analysis for the cost parameters in *Table 31* demonstrates clearly the dominant effect of acquisition costs on cost-effectiveness. If the dosing frequency for infliximab were to be reduced from 6-weekly to 8-weekly (reducing from ten to eight doses in the first year), this would produce a reduced ICER of £100,507.

The impact of univariate variations in additional parameters or assumptions is set out in *Table 32*. The magnitude of the SMR assumed for AS patients has little effect in the first year of treatment. Similarly, assumptions about the effect of anti-TNF-α treatment on long-term BASFI scores are not important in the short term. Both of the alternative utility regression models proposed by the Wyeth and Abbott modellers and based on smaller studies suggest larger incremental gains and therefore reduced ICERs to those obtained with the present baseline model. Most striking is the range of variation in utility gains obtained when the baseline BASDAI/BASFI scores are varied from the eligibility threshold for anti-TNF-α treatment (BASDAI = 4.0) up to more severe disease activity levels (BASDAI = 8.0). This effect reflects the differential changes detected in the IPD analysis, and suggests counter-intuitively that

TABLE 31 *One-way sensitivity of baseline results from short-term model (12 months undiscounted) to cost parameters*

Cost element	Variation	Treatment					
		Adalimumab		Etanercept		Infliximab	
		Incr. cost	ICER	Incr. cost	ICER	Incr. cost	ICER
Drug acquisition	+25%	£7,010	£71,082	£7,011	£71,085	£14,309	£145,093
	–25%	£4,284	£43,434	£4,284	£43,436	£9,381	£95,125
Drug administration	£453 per infusion	£5,647	£57,258	£5,647	£57,261	£13,097	£132,796
	£91 per infusion	£5,647	£57,258	£5,647	£57,261	£10,661	£108,105
Therapy monitoring	+50%	£5,693	£57,726	£5,693	£57,729	£11,892	£120,578
	–50%	£5,601	£56,789	£5,601	£56,792	£11,799	£119,641
TB testing	+50%	£5,692	£57,711	£5,692	£57,714	£11,890	£120,562
	–50%	£5,602	£56,805	£5,602	£56,808	£11,801	£119,656
TB treatment	+50%	£5,651	£57,297	£5,651	£57,301	£11,849	£120,149
	–50%	£5,643	£57,218	£5,643	£57,221	£11,841	£120,070
Adverse events	+50%	£5,669	£57,482	£5,669	£57,485	£11,867	£120,334
	–50%	£5,625	£57,033	£5,625	£57,037	£11,823	£119,885
Disease-related	+50%	£5,733	£58,134	£5,734	£58,137	£11,932	£120,986
	–50%	£5,560	£56,381	£5,561	£56,385	£11,759	£119,233
All costs	+25%/+50% combined	£7,214	£73,143	£7,214	£73,147	£15,764	£159,842
	–25%/–50% combined	£4,080	£41,372	£4,080	£41,374	£7,994	£81,059

Incr., incremental.

treatment may be less cost-effective for patients with the most severe symptoms at initiation, presumably because in these circumstances there appears to be a greater probability of early natural improvement independent of anti-TNF-α treatment.

Summary

During the first year of anti-TNF-α treatment costs are high because many patients are treated for a minimum of 12 weeks before treatment is withdrawn from a large number of non-responders. This imposes a large front-loading on costs and ensures that none of the three agents is likely to be considered cost-effective in the first year. However, this is the only period for which direct unbiased RCT evidence is available. It is already apparent that infliximab has much higher costs than the self-injected drugs, and therefore yields much poorer economic results. Although age and gender do not appear to be important factors, it is noticeable that the initial severity of symptoms may be a significant influence on effectiveness and cost-effectiveness.

Exploratory economic modelling: long-term model extension

The simple short-term model may be extended to explore the cost-effectiveness of anti-TNF-α treatments for longer periods. The extended model is subject to the same caveats with respect to assumptions about the natural history of the disease and the mode of action of the treatments, but is rendered far more speculative since trends and parameter values must be projected far beyond the available evidence, with consequent loss of precision. Indeed, such use of modelling is unlikely to yield meaningful quantitative results, but can be valuable in revealing qualitative insights into the key features of a decision problem. Again, it is important to emphasise that the treatment strategy considered here of a single treatment option, attempted once only in the lifetime of a patient, is unlikely to be realistic for this chronic disease.

For periods beyond the first year, the model is modified from the weekly time intervals used during the first year to calculation at four quarterly intervals per year, from the beginning of year 2 to the end of year 20. The same logic is maintained for each element of the model. Implicit in this switch is the assumption that short-term fluctuations in condition are of no consequence, and that all relevant changes can be approximated by smoothed trendlines.

Results

Table 33 shows the baseline results of *Table 29* extended for periods of up to 20 years. For clarity

TABLE 32 *One-way sensitivity of baseline results from short-term model for non-cost parameter values and assumptions*

Parameter/assumption	Variation	Treatment								
		Adalimumab			Etanercept			Infliximab		
		Incr. cost	Incr. QALYs	ICER	Incr. cost	Incr. QALYs	ICER	Incr. cost	Incr. QALYs	ICER
SMR	1.0	£5,649	0.099	£57,252	£5,649	0.099	£57,255	£11,849	0.099	£120,089
	2.0	£5,645	0.099	£57,263	£5,645	0.099	£57,266	£11,842	0.099	£120,130
Initial BASDAI/BASFI	4.0/3.7	£5,656	0.112	£50,308	£5,656	0.112	£50,310	£11,855	0.112	£105,441
	5.0/4.5	£5,652	0.109	£52,041	£5,653	0.109	£52,044	£11,851	0.109	£109,111
	6.0/5.2	£5,649	0.103	£55,081	£5,649	0.103	£55,084	£11,847	0.103	£115,522
	7.0/5.9	£5,645	0.094	£59,883	£5,646	0.094	£59,886	£11,844	0.094	£125,634
	8.0/6.6	£5,642	0.084	£67,353	£5,642	0.084	£67,357	£11,840	0.084	£141,351
Utility model	Wyeth	£5,647	0.114	£49,515	£5,647	0.114	£49,518	£11,845	0.114	£103,868
	Abbott	£5,647	0.121	£46,800	£5,647	0.121	£46,803	£11,845	0.121	£98,172
Proportion of full BASFI progression on treatment	50%	£5,647	0.099	£57,222	£5,647	0.099	£57,225	£11,845	0.099	£120,035
	0%	£5,647	0.099	£57,187	£5,647	0.099	£57,190	£11,845	0.099	£119,961

TABLE 33 *Baseline results from LRiG model for males aged 40 years (2–20 years discounted at 3.5% for costs and outcomes)*

	Treatment														
	Conventional					Adalimumab/etanercept					Infliximab				
Period (years)	**0–2**	**0–3**	**0–5**	**0–10**	**0–20**	**0–2**	**0–3**	**0–5**	**0–10**	**0–20**	**0–2**	**0–3**	**0–5**	**0–10**	**0–20**
Drug acquisition	–	–	–	–	–	£8,750	£11,479	£15,791	£23,146	£32,339	£14,855	£18,544	£25,113	£35,782	£49,284
Drug administration	–	–	–	–	–	£0	£0	£0	£0	£0	£2,664	£3,302	£4,435	£6,262	£8,563
Therapy monitoring	–	–	–	–	–	£162	£220	£311	£468	£665	£162	£220	£311	£468	£665
TB testing	–	–	–	–	–	£89	£89	£89	£89	£89	£89	£89	£89	£89	£89
TB treatment	–	–	–	–	–	£13	£16	£23	£33	£46	£13	£16	£23	£33	£46
Adverse events	–	–	–	–	–	£58	£69	£86	£115	£153	£58	£69	£86	£115	£153
Disease-related	£425	£632	£1,033	£1,962	£3,546	£354	£539	£913	£1,823	£3,413	£354	£539	£913	£1,823	£3,413
All costs	£425	£632	£1,033	£1,962	£3,546	£9,425	£12,411	£17,212	£25,675	£36,705	£18,194	£22,779	£30,969	£44,573	£62,213
Accumulated incremental costs						+£9,000	+£11,780	+£16,179	+£23,713	+£33,159	+£17,769	+£22,147	+£29,936	+£42,610	+£58,667
Total QALYs	1015.6	1489.2	2378.6	4292.3	7009.0	1186.9	1711.7	2662.5	4624.2	7344.2	1186.9	1711.7	2662.5	4624.2	7344.2
Accumulated incremental QALYs	–	–	–	–	–	+0.171	+0.223	+0.284	+0.332	+0.335	+0.171	+0.223	+0.284	+0.332	+0.335
Incremental cost per QALY gained	**–**	**–**	**–**	**–**	**–**	**£52,534**	**£52,932**	**£56,976**	**£71,454**	**£98,910**	**£103,721**	**£99,516**	**£105,423**	**£128,399**	**£175,000**

of presentation, only results for adalimumab are shown as also being representative of those for etanercept. In the second year a reduction in ICERs occurs when the large initial treatment costs of the early efficacy-proving period are no longer incurred. However, in subsequent years in the base case the annual rate at which additional treatment costs accrue is greater than the accumulation rate of outcome gains for patients who continue on anti-TNF-α treatment. As a consequence, ICERs increase steadily from year 2 onwards, in contrast to the results of the submitted models, which show the opposite trend.

Sensitivity analyses

Not surprisingly, at younger ages neither gender nor age has an important effect on model results (*Table 34*). However, for older patients the differential life expectancy between men and women, and the reduced life expectancy of older patients generally have the effect of restricting future need for treatment, leading to slightly reduced estimated ICERs.

As before, the only cost parameters to which results are sensitive in the long term (*Table 35*) are drug acquisition costs, administration costs (infliximab only) and, to a lesser extent, the disease-specific costs.

Univariate sensitivity analyses for the seven non-cost parameters and other assumptions (*Table 36*) show more important changes; most lead to moderate or large alterations in the model ICER, with the sole exception of SMR.

To allow exploration of the full range of possible economic results with this model, a full six-way sensitivity analysis was conducted for both adalimumab/etanercept (*Table 37*) and infliximab (*Table 38*). The baseline results obtained with each company's assumptions and the authors' own are highlighted in bold type (see *Table 26*, p. 77, for baseline parameters used in each model). From this, some valuable insights can be drawn:

- It is difficult to envisage a set of conditions under which infliximab could be considered a cost-effective long-term treatment for AS.
- The cost-effectiveness of the other two agents depends critically on the assumption that none of the spontaneous recovery identified in the IPD analysis persists in the long term, and to a lesser extent that there is a very low withdrawal rate from treatment from any cause (adverse events, loss of efficacy, non-compliance or other factors) during a 20-year period.

The three most important factors considered in relation to PSA were:

- whether or not a patient's condition can self-resolve
- whether or not disease progression continues during anti-TNF-α treatment
- the type of utility model that is appropriate.

All of these are qualitative judgements rather than parameter-driven factors. Therefore, PSA results would be misleading, so PSA was not conducted.

Cost-effectiveness under annual review

Figure 17 considers the long-term trends in model ICERs as costs and benefits accumulate for up to 20 years. In the second year of treatment, costs invariably reduce to a steady level without the costs of the initial effectiveness trial period. Using the baseline assumptions, and for most univariate variations, the long-term trend is strongly upwards. This implies that the year-on-year conditional cost-effectiveness of continuing treatment at each annual review becomes progressively less attractive over time. In other words, if a cost-effectiveness test were to be applied each year for continuation of treatment, then all treatment would be terminated after the first year.

Only by combining alternative assumptions on the three most sensitive issues is it possible to obtain a slowly decreasing ICER trend, but even so it may take up to 10 years before the conditional ICER falls within the range of acceptable cost-effectiveness as conventionally used by NICE (£30,000 per QALY).

Sequential use strategies

The authors understand from clinical advice that in practice patients failing to respond to one anti-TNF-α agent will often be offered a second and then a third agent until an effective treatment is found. Limited evidence in RA and some AS patients suggests that non-response or loss of efficacy to one agent is not strongly predictive of lack of efficacy with other agents.[107,108] Thus, the reported sequential treatment strategy appears to be clinically appropriate. However, it has profound implications for the cost-effectiveness of anti-TNF-α therapy, since after each treatment failure it is necessary to expose the patient to another personal effectiveness trial of at least 12 weeks incurring substantial costs before a response (if any) is eventually obtained. Hence, for those

TABLE 34 *Sensitivity of extended model results to age and gender (2–20 years discounted at 3.5% for costs and outcomes)*

Treatment	Gender	Male									Female								
	Age	20			40			60			20			40			60		
	Period	CIC	CIQ	ICER	CIC	CIQ	ICER	CIC	CIQ	ICER	CIC	CIQ	ICER	CIC	CIQ	ICER	CIC	CIQ	ICER
Adalimumab/ etanercept	0–2	£9,011	0.172	£52,525	**£9,000**	**0.171**	**£52,534**	£8,885	0.169	£52,618	£9,017	0.172	£52,521	£9,008	0.171	£52,528	£8,938	0.170	£52,579
	0–3	£11,802	0.223	£52,927	**£11,780**	**0.223**	**£52,932**	£11,550	0.218	£52,980	£11,814	0.223	£52,924	£11,795	0.223	£52,928	£11,656	0.220	£52,958
	0–5	£16,233	0.285	£56,991	**£16,179**	**0.284**	**£56,976**	£15,644	0.275	£56,830	£16,259	0.285	£56,998	£16,213	0.285	£56,984	£15,890	0.279	£56,897
	0–10	£23,898	0.333	£71,667	**£23,713**	**0.332**	**£71,454**	£22,057	0.317	£69,627	£23,971	0.334	£71,735	£23,817	0.333	£71,563	£22,800	0.324	£70,451
	0–20	£33,933	0.337	£100,733	**£33,159**	**0.335**	**£98,910**	£27,728	0.320	£86,721	£34,131	0.338	£101,107	£33,538	0.336	£99,752	£29,899	0.327	£91,480
Infliximab	0–2	£17,789	0.172	£103,689	**£17,769**	**0.171**	**£103,721**	£17,571	0.169	£104,055	£17,799	0.172	£103,672	£17,783	0.171	£103,698	£17,663	0.170	£103,900
	0–3	£22,184	0.223	£99,483	**£22,147**	**0.223**	**£99,516**	£21,770	0.218	£99,857	£22,203	0.223	£99,466	£22,172	0.223	£99,493	£21,944	0.220	£99,698
	0–5	£30,028	0.285	£105,423	**£29,936**	**0.284**	**£105,423**	£29,026	0.275	£105,439	£30,072	0.285	£105,421	£29,994	0.285	£105,420	£29,444	0.279	£105,430
	0–10	£42,922	0.333	£128,719	**£42,610**	**0.332**	**£128,399**	£39,818	0.317	£125,696	£43,046	0.334	£128,818	£42,786	0.333	£128,560	£41,072	0.324	£126,911
	0–20	£59,979	0.337	£178,054	**£58,667**	**0.335**	**£175,000**	£49,465	0.320	£154,702	£60,316	0.338	£178,671	£59,310	0.336	£176,405	£53,143	0.327	£162,597

CIC, cumulative incremental costs; CIQ, cumulative incremental QALYs; ICER, cumulative incremental cost per QALY gained.

TABLE 35 *One-way sensitivity analysis of LRiG extended model results to cost parameter values*

Period	Cost element	Treatment				Cost element	Treatment			
		Adalimumab/etanercept		Infliximab			Adalimumab/etanercept		Infliximab	
		Incr. cost	ICER	Incr. cost	ICER		Incr. cost	ICER	Incr. cost	ICER
0–2	Drug acquisition	£11,187	£65,302	£21,483	£125,400	TB treatment +50%	£9,006	£52,570	£17,776	£103,758
0–3	+25%	£14,649	£65,827	£26,783	£120,348		£11,788	£52,968	£22,153	£99,544
0–5		£20,127	£70,878	£36,215	£127,533		£16,191	£57,016	£29,948	£105,463
0–10		£29,499	£88,891	£51,556	£155,356		£23,729	£71,504	£42,627	£128,449
0–20		£41,244	£123,026	£70,988	£211,752		£33,182	£98,979	£58,690	£175,068
0–2	Drug acquisition	£6,812	£39,765	£14,055	£82,043	TB treatment –50%	£8,994	£52,497	£17,763	£103,685
0–3	–25%	£8,910	£40,036	£17,511	£78,684		£11,771	£52,895	£22,140	£99,488
0–5		£12,232	£43,075	£23,658	£83,314		£16,168	£56,937	£29,925	£105,384
0–10		£17,926	£54,017	£33,665	£101,443		£23,696	£71,404	£42,594	£128,350
0–20		£25,074	£74,794	£46,346	£138,247		£33,136	£98,841	£58,644	£174,931
0–2	Drug administration	£9,000	£52,534	£19,625	£114,553	AEs +50%	£9,029	£52,701	£17,798	£103,889
0–3	at £453 per infusion	£11,780	£52,932	£24,447	£109,852		£11,814	£53,085	£22,176	£99,645
0–5		£16,179	£56,976	£33,026	£116,302		£16,222	£57,128	£29,979	£105,575
0–10		£23,713	£71,454	£46,972	£141,544		£23,770	£71,628	£42,668	£128,573
0–20		£33,159	£98,910	£64,632	£192,793		£33,235	£99,138	£58,743	£175,227
0–2	Drug administration	£9,000	£52,534	£16,013	£93,473	AEs –50%	£8,971	£52,366	£17,740	£103,554
0–3	at £91 per infusion	£11,780	£52,932	£19,970	£89,735		£11,745	£52,778	£22,118	£99,387
0–5		£16,179	£56,976	£27,013	£95,129		£16,136	£56,825	£29,894	£105,272
0–10		£23,713	£71,454	£38,483	£115,962		£23,655	£71,280	£42,552	£128,225
0–20		£33,159	£98,910	£53,023	£158,162		£33,083	£98,683	£58,591	£174,772
0–2	Therapy monitoring	£9,081	£53,006	£17,850	£104,194	Disease-related +50%	£9,177	£53,566	£17,946	£104,754
0–3	+50%	£11,889	£53,425	£22,257	£100,009		£12,049	£54,142	£22,324	£100,311
0–5		£16,335	£57,524	£30,092	£105,971		£16,636	£58,583	£30,393	£107,030
0–10		£23,947	£72,160	£42,844	£129,105		£24,624	£74,200	£43,521	£131,145
0–20		£33,492	£99,903	£59,000	£175,992		£34,865	£104,000	£60,373	£180,089
0–2	Therapy monitoring	£8,919	£52,061	£17,688	£103,249	Disease-related –50%	£8,823	£51,501	£17,592	£102,689
0–3	–50%	£11,670	£52,438	£22,037	£99,023		£11,510	£51,721	£21,970	£98,721
0–5		£16,024	£56,429	£29,781	£104,876		£15,723	£55,370	£29,480	£103,817
0–10		£23,478	£70,749	£42,376	£127,694		£22,801	£68,708	£41,699	£125,653
0–20		£32,826	£97,918	£58,334	£174,007		£31,452	£93,820	£56,961	£169,910

continued

TABLE 35 *One-way sensitivity analysis of LRiG extended model results to cost parameter values (cont'd)*

Period	Cost element	Treatment				Cost element	Treatment			
		Adalimumab/etanercept		Infliximab			Adalimumab/etanercept		Infliximab	
		Incr. cost	ICER	Incr. cost	ICER		Incr. cost	ICER	Incr. cost	ICER
0–2	TB testing +50%	£9,045	£52,794	£17,814	£103,982	All costs +25%/+50%	£11,525	£67,272	£23,676	£138,201
0–3		£11,824	£53,132	£22,191	£99,717	combined	£15,116	£67,922	£29,549	£132,779
0–5		£16,224	£57,134	£29,981	£105,581		£20,838	£73,381	£40,015	£140,915
0–10		£23,757	£71,589	£42,655	£128,534		£30,763	£92,701	£57,182	£172,310
0–20		£33,203	£99,044	£58,712	£175,133		£43,427	£129,538	£79,136	£236,058
0–2	TB testing –50%	£8,955	£52,273	£17,725	£103,461	All costs –25%/–50%	£6,475	£37,795	£11,962	£69,824
0–3		£11,735	£52,731	£22,102	£99,315	combined	£8,444	£37,941	£14,868	£66,809
0–5		£16,135	£56,819	£29,892	£105,266		£11,521	£40,572	£20,024	£70,517
0–10		£23,668	£71,320	£42,566	£128,265		£16,662	£50,207	£28,273	£85,196
0–20		£33,114	£98,777	£58,622	£174,866		£22,891	£68,282	£38,518	£114,898

TABLE 36 *One-way SA of LRiG extended model results to non-cost parameter values and assumptions*

Period (years)	Parameter/assumption	Treatment					
		Adalimumab/etanercept			Infliximab		
		Incr. cost	Incr. QALYs	ICER	Incr. cost	Incr. QALYs	ICER
0–2	SMR = 1.0	£9,007	0.171	£52,529	£17,781	0.171	£103,702
0–3		£11,793	0.223	£52,929	£22,169	0.223	£99,496
0–5		£16,211	0.284	£56,985	£29,990	0.284	£105,422
0–10		£23,812	0.333	£71,561	£42,778	0.333	£128,558
0–20		£32,743	0.337	£97,258	£57,913	0.337	£172,023
0–2	SMR = 2.0	£8,993	0.171	£52,539	£17,757	0.171	£103,741
0–3		£11,766	0.222	£52,934	£22,125	0.222	£99,536
0–5		£16,148	0.283	£56,968	£29,883	0.283	£105,425
0–10		£23,614	0.331	£71,348	£42,443	0.331	£128,242
0–20		£32,097	0.335	£95,872	£56,823	0.335	£169,728
0–2	Initial BASDAI/BASFI	£9,017	0.193	£46,839	£17,786	0.193	£92,392
0–3	= 4.0/3.7	£11,802	0.249	£47,401	£22,169	0.249	£89,038
0–5		£16,209	0.317	£51,165	£29,966	0.317	£94,592
0–10		£23,747	0.370	£64,180	£42,644	0.370	£115,255
0–20		£32,449	0.375	£86,538	£57,395	0.375	£153,066
0–2	Initial BASDAI/BASFI	£9,004	0.178	£50,697	£17,773	0.178	£100,075
0–3	= 6.0/5.2	£11,784	0.230	£51,128	£22,152	0.230	£96,106
0–5		£16,186	0.294	£55,064	£29,943	0.294	£101,867
0–10		£23,720	0.344	£69,049	£42,617	0.344	£124,061
0–20		£32,424	0.348	£93,241	£57,370	0.348	£164,980
0–2	Initial BASDAI/BASFI	£8,991	0.147	£61,123	£17,760	0.147	£120,740
0–3	= 8.0/6.6	£11,768	0.192	£61,398	£22,135	0.192	£115,489
0–5		£16,164	0.245	£65,979	£29,921	0.245	£122,135
0–10		£23,695	0.286	£82,812	£42,592	0.286	£148,858
0–20		£32,400	0.289	£112,269	£57,346	0.289	£198,709
0–2	Wyeth utility model	£9,000	0.198	£45,479	£17,769	0.198	£89,792
0–3		£11,780	0.257	£45,854	£22,147	0.257	£86,209
0–5		£16,179	0.327	£49,406	£29,936	0.327	£91,416
0–10		£23,713	0.382	£62,093	£42,610	0.382	£111,578
0–20		£32,417	0.385	£84,189	£57,363	0.385	£148,976
0–2	Abbott utility model	£9,000	0.209	£42,995	£17,769	0.209	£84,889
0–3		£11,780	0.272	£43,356	£22,147	0.272	£81,513
0–5		£16,179	0.346	£46,725	£29,936	0.346	£86,455
0–10		£23,713	0.404	£58,752	£42,610	0.404	£105,574
0–20		£32,417	0.407	£79,718	£57,363	0.407	£141,065
0–2	Only 50% of BASFI	£8,999	0.172	£52,391	£17,769	0.172	£103,442
0–3	progression rate for	£11,779	0.224	£52,699	£22,146	0.224	£99,082
0–5	anti-TNF patients	£16,177	0.286	£56,548	£29,934	0.286	£104,637
0–10		£23,706	0.337	£70,357	£42,604	0.337	£126,443
0–20		£32,403	0.345	£93,883	£57,349	0.345	£166,160
0–2	0% of BASFI	£8,999	0.172	£52,248	£17,768	0.172	£103,164
0–3	progression rate for	£11,778	0.224	£52,468	£22,145	0.224	£98,652
0–5	anti-TNF patients	£16,174	0.288	£56,125	£29,932	0.288	£103,862
0–10		£23,700	0.342	£69,292	£42,597	0.342	£124,545
0–20		£32,390	0.355	£91,350	£57,336	0.355	£161,706
0–2	BASFI annual progression	£9,000	0.172	£52,430	£17,769	0.172	£103,518
0–3	rate = +0.05	£11,779	0.223	£52,763	£22,146	0.223	£99,201
0–5		£16,178	0.285	£56,694	£29,936	0.285	£104,904
0–10		£23,710	0.335	£70,824	£42,608	0.335	£127,273
0–20		£32,411	0.341	£95,133	£57,357	0.341	£168,355

continued

TABLE 36 *One-way SA of LRiG extended model results to non-cost parameter values and assumptions (cont'd)*

Period (years)	Parameter/assumption	Treatment					
		Adalimumab/etanercept			Infliximab		
		Incr. cost	Incr. QALYs	ICER	Incr. cost	Incr. QALYs	ICER
0–2	BASFI annual progression	£9,003	0.167	£53,754	£17,772	0.167	£106,117
0–3	rate = +0.30	£11,786	0.214	£54,951	£22,153	0.214	£103,289
0–5		£16,192	0.268	£60,443	£29,949	0.268	£111,796
0–10		£23,752	0.298	£79,621	£42,650	0.298	£142,970
0–20		£32,530	0.279	£116,762	£57,476	0.279	£206,302
0–2	50% of trial control arm	£8,882	0.191	£46,590	£17,571	0.191	£92,164
0–3	long-term 'response'	£11,383	0.251	£45,423	£21,518	0.251	£85,869
0–5		£14,932	0.323	£46,287	£27,829	0.323	£86,263
0–10		£19,825	0.379	£52,263	£36,070	0.379	£95,090
0–20		£24,415	0.385	£63,412	£43,852	0.385	£113,895
0–2	0% of trial control arm	£8,765	0.210	£41,739	£17,373	0.210	£82,734
0–3	long-term 'response'	£10,985	0.279	£39,425	£20,888	0.279	£74,967
0–5		£13,684	0.361	£37,881	£25,720	0.361	£71,200
0–10		£15,936	0.427	£37,339	£29,528	0.427	£69,187
0–20		£16,412	0.434	£37,789	£30,340	0.434	£69,857
0–2	Long-term withdrawal	£9,155	0.178	£51,517	£18,043	0.178	£101,525
0–3	rate = 7%	£12,306	0.244	£50,375	£23,000	0.244	£94,149
0–5		£17,720	0.348	£50,961	£32,577	0.348	£93,687
0–10		£27,586	0.492	£56,014	£49,205	0.492	£99,913
0–20		£38,108	0.572	£66,607	£67,079	0.572	£117,244
0–2	Long-term withdrawal	£8,813	0.164	£53,865	£17,439	0.164	£106,589
0–3	rate = 24% p.a.	£11,218	0.199	£56,276	£21,229	0.199	£106,497
0–5		£14,857	0.229	£64,820	£27,670	0.229	£120,721
0–10		£21,444	0.238	£90,193	£38,738	0.238	£162,929
0–20		£29,902	0.231	£129,240	£53,066	0.231	£229,355

patients who fail to respond to two agents, the application of BSR guidelines requires that they receive at least 36 weeks of continuous treatments before it can be determined whether or not any anti-TNF-α therapy will be of value. In practice, this means that in the first year very few patients will not be receiving one of the three agents throughout the whole period, greatly increasing the initial cost of the strategy with only partially compensating outcome gains.

It may be concluded, therefore, that the exploratory analysis outlined above must be considered especially optimistic, since in normal clinical practice the average patient can expect to spend at least 20 weeks in aggregate on one, two or three anti-TNF-α agents in the hope of achieving a response, rather than the 12 weeks required by BSR guidelines.

Possible approaches to improving cost-effectiveness

Despite the caveats raised as a consequence of this analysis of IPD data and exploratory modelling, there is little doubt that anti-TNF-α agents do provide important benefits to some AS patients. Some approaches that could offer ways to improve the economic performance of the agents for these patients are considered here.

Subgroups

In many situations it is possible to identify groups of individuals in whom good or poor clinical response to treatment may be predicted from prior information of patient characteristics, prior history or predisposing risk factors. Unfortunately, the evidence submitted by the manufacturers does not provide any basis for distinguishing between patients; it seems that success for a particular patient treated with a particular agent is akin to a random lottery with the present state of knowledge.

Patient records

The insights gained through exploration of IPD suggest that there are indeed quite distinct types of patient, as defined by the nature of response. If risk factors cannot be identified for targeting treatment, a potential alternative approach may be

TABLE 37 *Multiway SA of LRiG model results to non-cost parameter values and assumptions: adalimumab/etanercept*

Annual anti-TNF-α withdrawal rate	Utility model	Baseline BASDAI/ BASFI averages	BASFI progression continues on anti-TNF-α treatment						BASFI progression prevented on anti-TNF-α treatment					
			Early response rate without anti-TNF-α treatment 17.1%			0%			17.1%			0%		
			BASFI progression rate p.a.			BASFI progression rate p.a.			BASFI progression rate p.a.			BASFI progression rate p.a.		
			0.05	0.07	0.30	0.05	0.07	0.30	0.05	0.07	0.30	0.05	0.07	0.30
24%	Schering-Plough	8.0/6.6	£151,601	£155,609	£223,702	£38,557	£39,236	£49,373	£145,266	£146,432	£161,408	£36,703	£36,599	£35,408
		6.5/5.6	£129,864	£132,792	£179,411	£40,011	£40,735	£51,583	£125,189	£126,054	£136,989	£38,039	£37,930	£36,686
		4.0/3.7	£115,808	£118,126	£153,530	£48,841	£49,904	£66,671	£112,086	£112,777	£121,421	£45,987	£45,834	£44,112
	Wyeth	8.0/6.6	£131,010	£135,029	£208,646	£33,601	£34,289	£44,990	£124,725	£125,876	£140,892	£31,741	£31,639	£30,471
		6.5/5.6	£113,279	£116,269	£167,025	£34,832	£35,565	£47,036	£108,552	£109,422	£120,586	£32,856	£32,749	£31,528
		4.0/3.7	£101,826	£104,230	£143,145	£42,461	£43,538	£61,526	£97,999	£98,706	£107,672	£39,608	£39,457	£37,769
	Abbott	8.0/6.6	£123,807	£127,721	£200,709	£31,813	£32,485	£43,037	£117,698	£118,815	£133,444	£30,001	£29,901	£28,769
		6.5/5.6	£107,274	£110,199	£160,599	£32,971	£33,687	£45,002	£102,660	£103,508	£114,429	£31,047	£30,942	£29,758
		4.0/3.7	£96,601	£98,961	£137,688	£40,180	£41,231	£59,034	£92,852	£93,544	£102,347	£37,402	£37,256	£35,620
15%	Schering-Plough	8.0/6.6	£112,996	£115,041	£145,425	£35,549	£35,966	£41,707	£107,770	£107,600	£105,638	£33,696	£33,363	£29,794
		6.5/5.6	£97,396	**£98,910**	£120,562	£37,386	£37,844	£44,148	£93,492	£93,364	£91,885	£35,368	£35,008	£31,198
		4.0/3.7	£87,414	£88,627	£105,552	£46,876	£47,585	£57,697	£84,266	£84,164	£82,978	£43,808	£43,274	£37,836
	Wyeth	8.0/6.6	£97,386	£99,421	£131,007	£30,936	£31,358	£37,296	£92,233	£92,068	£90,168	£29,085	£28,756	£25,308
		6.5/5.6	£84,731	£86,267	£109,078	£32,477	£32,938	£39,456	£80,807	£80,681	£79,221	£30,465	£30,110	£26,435
		4.0/3.7	£76,657	£77,908	£95,977	£40,601	£41,314	£51,829	£73,442	£73,338	£72,146	£37,560	£37,038	£31,828
	Abbott	8.0/6.6	£91,976	£93,956	£124,983	£29,281	£29,692	£35,520	£86,975	£86,815	£84,978	£27,479	£27,160	£23,827
		6.5/5.6	£80,192	£81,692	£104,167	£30,727	£31,176	£37,572	£76,367	£76,244	£74,826	£28,769	£28,425	£24,874
		4.0/3.7	£72,681	£73,907	£91,764	£38,389	£39,083	£49,412	£69,535	£69,434	£68,272	£35,433	£34,927	£29,902
7%	Schering-Plough	8.0/6.6	£77,379	£78,185	£88,917	£32,877	£33,089	£35,786	£73,733	£73,069	£66,023	£31,174	£30,717	£26,027
		6.5/5.6	£67,092	£67,697	£75,582	£34,998	£35,238	£38,294	£64,338	£63,833	£58,405	£33,099	£32,596	£27,516
		4.0/3.7	£60,598	£61,089	£67,410	£44,995	£45,391	£50,549	£58,354	£57,942	£53,496	£41,971	£41,194	£33,763
	Wyeth	8.0/6.6	£66,523	£67,322	£78,178	£28,576	£28,790	£31,553	£62,950	£62,306	£55,587	£26,878	£26,429	£21,946
		6.5/5.6	£58,223	£58,833	£66,944	£30,342	£30,584	£33,703	£55,471	£54,972	£49,691	£28,457	£27,964	**£23,122**
		4.0/3.7	£53,010	£53,513	£60,113	£38,835	£39,231	£44,471	£50,730	£50,315	£45,911	£35,858	£35,104	£28,096
	Abbott	8.0/6.6	£62,794	£63,569	£74,166	£27,039	£27,249	£29,953	£59,329	£58,707	£52,231	£25,387	£24,952	£20,629
		6.5/5.6	£55,073	£55,668	£63,615	£28,695	£28,930	£31,981	£52,395	£51,909	£46,798	**£26,862**	£26,384	£21,718
		4.0/3.7	£50,232	£50,725	£57,213	£36,690	£37,074	£42,195	£48,004	£47,600	£43,320	£33,801	£33,072	£26,335

Combinations with ICER ⩽£30,000 per QALY are shaded; companies' and LRiG preferred combinations in bold type.

TABLE 38 *Multiway SA of LRiG extended model results to non-cost parameter values and assumptions: infliximab*

Annual anti-TNF-α withdrawal rate	Utility model	Baseline BASDAI/ BASFI averages	BASFI progression continues on anti-TNF-α treatment						BASFI progression prevented on anti-TNF-α treatment					
			Early response rate without anti-TNF-α treatment 17.1%			0%			17.1%			0%		
			BASFI progression rate p.a.			BASFI progression rate p.a.			BASFI progression rate p.a.			BASFI progression rate p.a.		
			0.05	0.07	0.30	0.05	0.07	0.30	0.05	0.07	0.30	0.05	0.07	0.30
24%	Schering-Plough	8.0/6.6	£269,046	£276,124	£396,031	£73,395	£74,662	£93,318	£257,855	£259,916	£286,312	£69,938	£69,749	£67,604
		6.5/5.6	£230,432	£235,604	£317,693	£76,079	£77,433	£97,503	£222,177	£223,704	£242,978	£72,392	£72,192	£69,929
		4.0/3.7	£205,429	£209,523	£271,924	£92,688	£94,686	£125,989	£198,851	£200,073	£215,321	£87,326	£87,040	£83,854
	Wyeth	8.0/6.6	£232,503	£239,605	£369,377	£63,961	£65,248	£85,034	£221,393	£223,429	£249,919	£60,484	£60,296	£58,178
		6.5/5.6	£201,004	£206,288	£295,760	£66,231	£67,606	£88,908	£192,649	£194,188	£213,884	£62,529	£62,330	£60,098
		4.0/3.7	£180,625	£184,876	£253,532	£80,580	£82,606	£116,267	£173,859	£175,110	£190,940	£75,212	£74,930	£71,797
	Abbott	8.0/6.6	£219,719	£226,638	£355,326	£60,557	£61,816	£81,342	£208,920	£210,897	£236,708	£57,168	£56,985	£54,928
		6.5/5.6	£190,349	£195,518	£284,380	£62,693	£64,036	£85,062	£182,193	£183,694	£202,964	£59,085	£58,891	£56,724
		4.0/3.7	£171,358	£175,531	£243,867	£76,252	£78,230	£111,556	£164,729	£165,953	£181,496	£71,024	£70,750	£67,711
15%	Schering-Plough	8.0/6.6	£199,984	£203,582	£256,859	£65,806	£66,566	£76,878	£190,790	£190,497	£187,142	£62,451	£61,854	£55,570
		6.5/5.6	£172,335	**£175,000**	£212,965	£69,121	£69,955	£81,331	£165,468	£165,247	£162,718	£65,453	£64,805	£58,037
		4.0/3.7	£154,602	£156,739	£186,448	£86,476	£87,773	£106,159	£149,064	£148,886	£146,847	£80,873	£79,903	£70,094
	Wyeth	8.0/6.6	£172,356	£175,941	£231,394	£57,267	£58,037	£68,748	£163,285	£162,999	£159,736	£53,905	£53,313	£47,203
		6.5/5.6	£149,926	£152,630	£192,679	£60,044	£60,886	£72,688	£143,019	£142,799	£140,291	£56,380	£55,739	£49,178
		4.0/3.7	£135,578	£137,782	£169,535	£74,902	£76,206	£95,361	£129,915	£129,735	£127,678	£69,339	£68,388	£58,965
	Abbott	8.0/6.6	£162,782	£166,270	£220,753	£54,203	£54,954	£65,474	£153,977	£153,700	£150,542	£50,927	£50,353	£44,439
		6.5/5.6	£141,893	£144,535	£184,004	£56,809	£57,630	£69,217	£135,160	£134,947	£132,509	£53,241	£52,620	£46,273
		4.0/3.7	£128,546	£130,706	£162,093	£70,819	£72,091	£90,915	£123,005	£122,829	£120,822	£65,412	£64,490	£55,396
7%	Schering-Plough	8.0/6.6	£136,257	£137,673	£156,436	£59,061	£59,442	£64,245	£129,894	£128,745	£116,676	£56,067	£55,275	£47,294
		6.5/5.6	£118,100	£119,161	£132,951	£62,782	£63,211	£68,654	£113,294	£112,420	£103,122	£59,434	£58,556	**£49,827**
		4.0/3.7	£106,592	£107,454	£118,514	£80,519	£81,226	£90,393	£102,673	£101,959	£94,313	£75,160	£73,790	£60,805
	Wyeth	8.0/6.6	£117,142	£118,544	£137,543	£51,334	£51,719	£56,646	£110,897	£109,781	£98,232	£48,341	£47,559	£39,879
		6.5/5.6	£102,488	£103,559	£117,755	£54,431	£54,863	£60,422	£97,680	£96,814	£87,736	£51,099	£50,236	£41,871
		4.0/3.7	£93,245	£94,129	£105,685	£69,496	£70,202	£79,525	£89,259	£88,539	£80,941	£64,213	£62,881	£50,599
	Abbott	8.0/6.6	£110,574	£111,937	£130,485	£48,574	£48,950	£53,773	£104,519	£103,440	£92,303	£45,659	£44,901	£37,484
		6.5/5.6	£96,944	£97,988	£111,900	£51,475	£51,897	£57,335	£92,262	£91,421	£82,628	£48,235	£47,398	£39,328
		4.0/3.7	£88,359	£89,224	£100,587	£65,656	£66,343	£75,455	£84,463	£83,761	£76,373	£60,530	£59,241	£47,426

Companies' and LRiG preferred combinations in bold type.

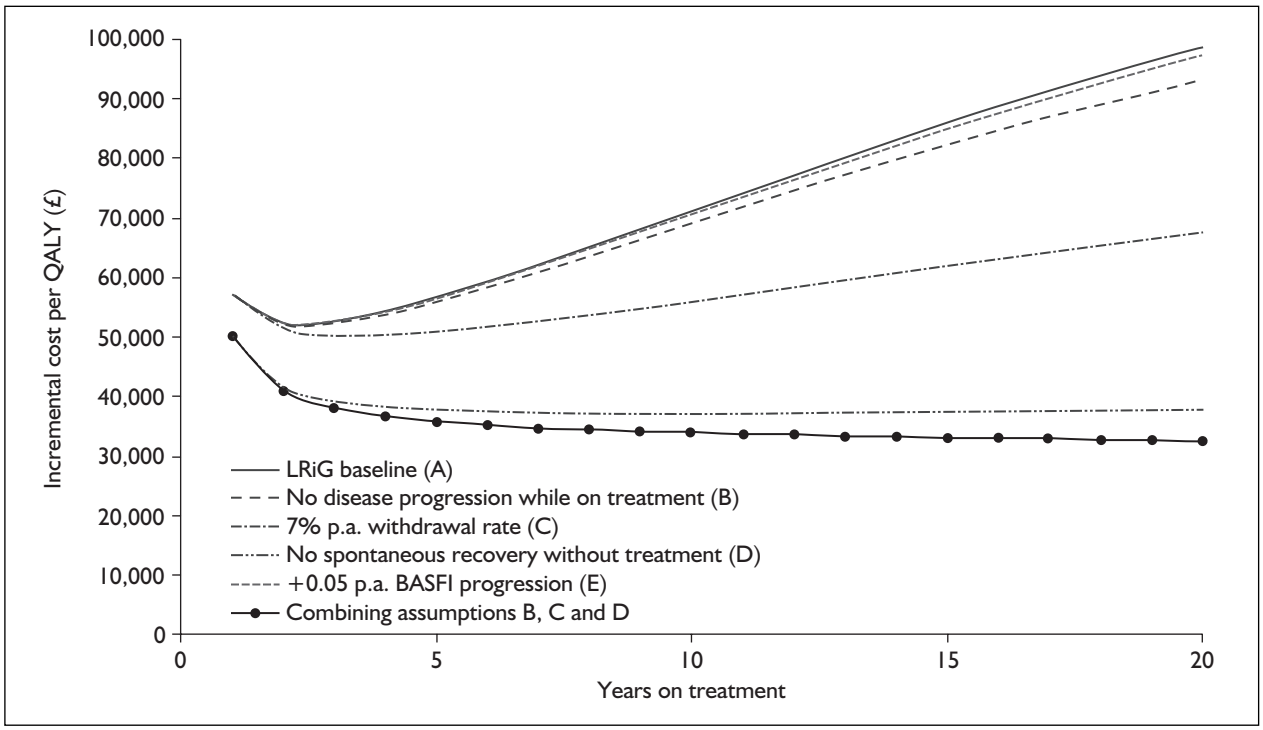

FIGURE 17 *Cumulative ICER of adalimumab/etanercept using various alternative assumptions in the LRiG model*

possible through resort to long-term patient data series. If some AS patients are able and willing to maintain a regular record of disease activity (by BASDAI or pain VAS score), together with a personal log of significant disease events, it may be possible to establish for each patient the 'normal' quiescent level of disease activity, and the normal variability of the condition, together with the frequency, severity and duration of disease activity flares. This information would then offer opportunities to target treatment better:

- Knowing the normal duration of flares and the speed with which they resolve may help patient and physician jointly to judge an appropriate period of watchful waiting before attempting a new treatment. This may avoid beginning long-term medication when the immediate symptoms may resolve spontaneously very soon.
- Monitoring experience over time may give an early indication of progressive worsening in the quiescent level of disease activity. Statistical process control (SPC) methods may be applicable here.
- An objective history of previous flare activity may avoid premature abandonment of a treatment during a random period of increased activity, which can mask continuing effectiveness of an agent in maintaining a reduction in the normal level of activity.
- The possibility of occasional use of anti-TNF-α agents could also be explored in which these drugs are reserved for especially severe episodes and withdrawn on recovery, with the objective of preserving effectiveness against exposure-related tolerance.

Summary

The consideration of cost-effectiveness of anti-TNF-α treatments for AS is overshadowed by the unfortunate absence of evidence concerning both the dynamics of the disease as experienced by patients at different stages in the progression of the condition, and the mode of action of the anti-TNF-α agents. In particular, it is far from clear whether we should expect benefits in any or all of these aspects of AS:

- providing immediate relief of symptoms, especially pain
- altering the normal level of disease activity
- accelerating recovery from flare episodes
- reducing the severity of flare episodes
- reducing the frequency of flare episodes
- preventing or delaying long-term disease progression.

In addition, there is no substantive RCT evidence of the performance of anti-TNF-α agents when used sequentially, or even in combination. This

means that the models submitted by the companies are based on a large number of assumptions, and framed in structures that are unlikely to apply in practice, and which tend to present the new products in a favourable light.

This modelling exercise (also using the same non-realistic single-agent framework) has explored the various assumptions and choice of parameter values, to indicate where the submitted economic results sit in relation to the wider universe of possible alternatives. Not surprisingly, the manufacturers seem to have presented scenarios that occupy positions at the more favourable end of the spectrum of possibilities.

It is not possible to make a definitive assessment of economic performance in the face of these wide-ranging uncertainties; however, three clear conclusions can be drawn:

- In the absence of any evidence of differences in effectiveness between the three drugs, it is evident that the higher costs associated with infliximab (even if given less frequently) make it a much less favourable option than either adalimumab or etanercept.
- Unusually in chronic diseases, it seems unlikely that extending the period of continuous treatment over decades will automatically improve cost-effectiveness, since it requires a particular coincidence of assumed effects for this to be the case.
- Without proven criteria by which to identify those patients most likely to benefit, the sequential trial and error approach to finding an effective agent for a patient will lead to less attractive economic results than those exemplified above.

It is evident that there is a large and important research agenda waiting to be addressed to remedy the many gaps in our understanding of AS. Some of these may be resolved by analysis of registers of patients receiving anti-TNF-α agents, but others will only be amenable to RCTs of various designs.

Chapter 8

Budgetary and resource consequences

This chapter considers the financial and service implications of adopting anti-TNF-α therapy for AS in England and Wales based on the BSR guidelines.[1] The very severe data limitations regarding key epidemiological measures in AS, together with the wide-ranging uncertainties already described in the previous chapter, mean that it is not possible to estimate costs and other effects with any precision. However, the figures presented below may allow some useful conclusions to be drawn.

Incidence, prevalence and patient numbers

No information could be identified that directly estimates the incidence and prevalence of AS in the UK. The strong association between the HLA-B27 antigen and AS points to a genetic origin for the majority of AS cases diagnosed.[7,109] As a consequence, one should expect considerable variations in incidence and prevalence between populations, with apparently higher levels in Caucasians in northern Europe.

Incidence

The BSR guidelines report the incidence of AS to be 7.3 per 100,000 person-years (range 6.1–8.4) in the USA;[1] however, this derives from a single historic source reporting experience from Rochester, Minnesota, between 1935 and 1989.[2] There must be serious doubts about the relevance of this estimate to the UK in 2006, given the likely dissimilarity in population characteristics, and the probable development of diagnostic criteria over the past 17–71 years. In 1997, a Finnish study was published relating to diagnosed AS patients aged 16 years or above on medication in the three years 1980, 1985 and 1990.[110] An annual incidence for this group was estimated as 6.9 per 100,000 (range 6.0–7.8).

Based on the more recent nature of the latter study, its European location and lower standard error, the present authors prefer the Finnish study result as the basis for calculating budget impact. Applying this rate to the estimated populations of England and Wales in mid-2004[111] suggests that about 2300±300 new cases are identified each year (*Table 39*).

Prevalence

The BSR guidelines offer a wide range for the estimated prevalence of AS in adults, between 0.05%[5] and 0.23%.[4] The reference given for the lower value is a paper by West published in 1949,[5] which is seriously outdated and of dubious quality. The higher estimate was obtained from an epidemiological study of AS in Hungary published in 1977[4] and related to people aged over 15 years of age. Estimates have also been traced from other locations:

- The Finnish study[110] reports 'clinically significant AS' in 0.15% (0.08–0.27%) of the population aged 30 and above.

TABLE 39 *Estimation of AS incident and prevalent cases*

	Estimate				Estimate		
	Lower	**Central**	**Upper**		**Lower**	**Central**	**Upper**
Annual incidence rate	0.0060%	0.0069%	0.0078%	Prevalence rate	0.08%	0.15%	0.27%
Mid-2004 population 16+				Mid-2004 population 30+			
England		40,338,700		*England*		31,451,500	
Wales		2,380,100		*Wales*		1,879,400	
Incident cases				Prevalent cases			
England	2,420	2,783	3,146	*England*	25,161	47,177	84,919
Wales	143	164	186	*Wales*	1,504	2,819	5,074
England & Wales	2,563	2,948	3,332	*England & Wales*	26,665	49,996	89,993

- In 1979, a prevalence estimate of 0.129% was reported for Rochester, Minnesota, for the period 1935–1973 based on 102 cases.[112]
- A study published in 2004[113] combined magnetic resonance imaging results in a screened sample of blood donors with the prevalence of HLA-B27 in the Berlin population to derive an estimated prevalence of 0.86%. It is not known how many of these were already diagnosed.
- A combination of questionnaires, interviews and examinations in Brittany, France, published in 1999[114] gave an overall prevalence estimate of 0.53% (0.16–0.90%).
- A comparison study between blood donors with a genetic marker, and a control group without (published in 1975[115]) suggested a very high rate of undiagnosed AS in the apparently normal population, suggesting a true prevalence rate of 1.0–1.5%.

The case for using either of the sources cited in the BSR guidelines does not seem to be particularly strong. Again, the authors consider the Finnish study the most reliable, since the other papers report figures that clearly include a large number of undiagnosed and untreated individuals, who would certainly not be relevant to the use of anti-TNF-α agents.

The estimated prevalent stock of AS patients is therefore between 26,700 and 90,000, with a mid-range value of 50,000 (*Table 39*). Since this parameter is central to subsequent budget calculations, calculated estimates for each of these three values are shown below, combined with the corresponding values for incidence.

Eligibility and response

The three manufacturers present very different estimates of the proportion of AS patients who would present for anti-TNF-α therapy and be found to satisfy the BSR eligibility criteria: 7% (Abbott), 19% (Wyeth) and 33% (Schering-Plough).

For incident cases, there are nine possible combinations of incidence and eligibility rates, leading to estimated numbers starting treatment of 169 (minimum), 529 (middle value) and 1038 (maximum). The equivalent figures for the prevalent stock of patients are 1761 (minimum), 8964 (middle value) and 28,023 (maximum).

For consistency with cost calculations the authors adopted the response rate in the LRiG base-case (40% at 12 months) combined with the base-case withdrawal rate (15% p.a.) to estimate that on average 20% of patients will be receiving continuing anti-TNF-α treatment in any year. Thus, in a steady-state environment between 352 (minimum) and 5605 (maximum) patients would be expected to be receiving long-term treatment in any year after the first (middle value 1793).

Cost estimates

All cost estimates are based on generalisations from the undiscounted LRiG model base-case scenario, adjusted as appropriate to the relevant estimated caseloads.

Initial treatment year

In the first year of treatment high costs are incurred as all patients are subject to a trial period of at least 12 weeks before it can be determined whether or not a significant response has been achieved. The estimated treatment costs for each annual incident cohort are shown in the left-hand portion of *Table 40*.

If anti-TNF-α therapy becomes generally available, there would be a large number of existing patients requiring initiation onto the new treatments, and the aggregated first year costs for this group are shown in the right-hand section of *Table 40*.

Continuing treatment

After the first year, responding patients continue on long-term treatment unless they are withdrawn owing to loss of effectiveness, or for other reasons. The estimated annual costs of anti-TNF-α treatment in each subsequent year assuming a steady state are shown in *Table 41*.

Combined estimates

To arrive at an overall estimate for the additional costs that may be incurred by the NHS from the use of anti-TNF-α treatment, it is necessary to propose a realistic time-frame during which one would expect current patients eligible for the new drugs to be assessed and initiated onto treatment. For the purpose of this exercise it was assumed that this would occur in equal proportions over a period of 3 years. On this basis, the combined cost estimates are displayed in *Table 42*.

Several important conclusions can be drawn from these figures:

- The uncertainty in the basic epidemiology of the condition and the eligibility of patients to be offered anti-TNF-α treatment leads to an extremely wide range of potential additional costs to the NHS.

TABLE 40 *Estimated treatment costs in the initial year on anti-TNF-α therapy*

Annual incident cases	Estimate (£ 000)			Prevalent case	Estimate (£ 000)		
	Lower	Central	Upper		Lower	Central	Upper
England				**England**			
No. of cases	169	529	1,038	No. of cases	1,761	8,964	28,023
Adalimumab/etanercept				*Adalimumab/etanercept*			
Drug cost	924	2,884	5,662	Drug cost	9,605	48,882	152,820
TB testing	15	47	93	TB testing	157	801	2,504
Monitoring	16	49	96	Monitoring	163	828	2,590
TB treatment	1	4	8	TB treatment	14	70	220
AE treatment	7	23	46	AE treatment	78	397	1,240
AS costs	–7	–21	–42	AS costs	–71	–362	–1,130
Total extra cost	957	2,986	5,863	*Total extra cost*	9,946	50,616	158,243
Infliximab				*Infliximab*			
Drug cost	1,670	5,212	10,234	Drug cost	17,359	88,345	276,194
Drug administration	304	950	1,865	Drug administration	3,163	16,099	50,330
TB testing	15	47	93	TB testing	157	801	2,504
Monitoring	16	49	96	Monitoring	163	828	2,590
TB treatment	1	4	8	TB treatment	14	70	220
AE treatment	7	23	46	AE treatment	78	397	1,240
AS costs	–7	–21	–42	AS costs	–71	–362	–1,130
Total extra cost	2,007	6,264	12,299	*Total extra cost*	20,863	106,178	331,946
Wales				**Wales**			
No. of cases	10	31	61	No. of cases	105	536	1,675
Adalimumab/etanercept				*Adalimumab/etanercept*			
Drug cost	55	170	334	Drug cost	574	2,921	9,132
TB testing	1	3	5	TB testing	9	48	150
Monitoring	1	3	6	Monitoring	10	50	155
TB treatment	0	0	0	TB treatment	1	4	13
AE treatment	0	1	3	AE treatment	5	24	74
AS costs	0	–1	–2	AS costs	–4	–22	–68
Total extra cost	56	176	346	*Total extra cost*	594	3,025	9,456
Infliximab				*Infliximab*			
Drug cost	99	308	604	Drug cost	1,037	5,279	16,504
Drug administration	18	56	110	Drug administration	189	962	3,007
TB testing	1	3	5	TB testing	9	48	150
Monitoring	1	3	6	Monitoring	10	50	155
TB treatment	0	0	0	TB treatment	1	4	13
AE treatment	0	1	3	AE treatment	5	24	74
AS costs	0	–1	–2	AS costs	–4	–22	–68
Total extra cost	118	370	726	*Total extra cost*	1,247	6,345	19,836

- The higher costs of infliximab may be very important in terms of affordability at a national level.
- The large volume of existing patients wanting treatment may cause a serious short-term financing problem, and long-term continuing therapy costs are likely to be substantial.

Sequential use

These estimates are based on the theoretical assumption that each drug is treated in isolation, and patients will only be offered one of the anti-TNF-α agents in their lifetime. If it is considered more likely that patients will be offered all three drugs in sequence until one is found that works, then it may be estimated that in a steady-state scenario an average patient is likely to try about two drugs before achieving a response (or, for some, finding that none of them works), and twice as many patients will need to be maintained on continuous treatment.

This means that the estimates shown in *Table 42* are almost certainly too low, and could reasonably be doubled in a real-life context.

TABLE 41 *Estimated average treatment costs in each year after the first*

Each subsequent year	Estimate (£ 000)		
	Lower	Central	Upper
England			
Long-term responders	352	1793	5605
Adalimumab/etanercept			
Drug cost	£3,274	£16,663	£52,095
Monitoring	£35	£179	£560
TB treatment	£5	£24	£74
AE treatment	£17	£85	£267
AS costs	–£8	–£41	–£129
Total extra cost	£3,323	£16,911	£52,868
Infliximab			
Drug cost	£4,794	£24,398	£76,274
Drug administration	£815	£4,148	£12,969
Monitoring	£35	£179	£560
TB treatment	£5	£24	£74
AE treatment	£17	£85	£267
AS costs	–£8	–£41	–£129
Total extra cost	£5,658	£28,793	£90,016
Wales			
Long-term responders	21	107	335
Adalimumab/etanercept			
Drug cost	£196	£996	£3,113
Monitoring	£2	£11	£33
TB treatment	£0	£1	£4
AE treatment	£1	£5	£16
AS costs	£0	–£2	–£8
Total extra cost	£199	£1,011	£3,159
Infliximab			
Drug cost	£286	£1,458	£4,558
Drug administration	£49	£248	£775
Monitoring	£2	£11	£33
TB treatment	£0	£1	£4
AE treatment	£1	£5	£16
AS costs	£0	–£2	–£8
Total extra cost	£338	£1,721	£5,379

Service implications

Two important problems should also be considered affecting the capacity of the NHS to manage anti-TNF-α therapy:

- Where infliximab is widely used, hospital units need the additional space, equipment and nursing staff to manage and monitor significant numbers of extra patients attending regularly for administration of intravenous infusions.
- The large volume of existing patients requiring assessment for eligibility, initiation onto trial treatment and the repeated review of response would pose considerable additional burdens on the current specialist services.

Summary

Although the numerical data on which to base estimates of additional costs and service demand are poor, it is still possible to demonstrate that approval of anti-TNF-α agents for general treatment of active AS is likely to lead to considerable financial consequences as well as large additional service demands.

Although the short-term aspects may be difficult to avoid, the long-term effects of continuing care would be much reduced if the implicit assumption made in all the company submissions of continuous use is not accepted. It could be argued that until additional credible evidence is available to demonstrate the need for patients to remain on treatment indefinitely, the existing evidence base only supports treatment to achieve short-term relief of severe symptoms and restore patients to a stable condition. If given episodically, the ongoing commitment of cost and hospital resources resulting from the use of anti-TNF-α agents may be reasonably contained, without undue disadvantage to many patients.

TABLE 42 *Combined incremental cost estimates assuming that initiation of prevalent cases is spread over 3 years*

	Programme year	Lower estimate (£ 000)				Central estimate (£ 000)				Upper estimate (£ 000)			
		1	2	3	4+	1	2	3	4+	1	2	3	4+
	Treatment year												
England													
Adalimumab/etanercept	Initial	4,272	4,272	4,272	957	19,858	19,858	19,858	2,986	58,611	58,611	58,611	5,863
	Others	0	1,108	2,215	3,323	0	5,637	11,274	16,911	0	17,623	35,245	52,868
	Total	4,272	5,380	6,487	4,280	19,858	25,495	31,132	19,897	58,611	76,234	93,856	58,731
Infliximab	Initial	8,961	8,961	8,961	2,007	41,657	41,657	41,657	6,264	122,948	122,948	122,948	12,299
	Others	0	1,886	3,772	5,658	0	9,598	19,195	28,793	0	30,005	60,011	90,016
	Total	8,961	10,847	12,733	7,664	41,657	51,255	60,852	35,057	122,948	152,953	182,959	102,316
Wales													
Adalimumab/etanercept	Initial	255	255	255	56	1,184	1,184	1,184	176	3,498	3,498	3,498	346
	Others	0	66	132	199	0	337	674	1,011	0	1,053	2,106	3,159
	Total	255	321	387	255	1,184	1,521	1,858	1,187	3,498	4,551	5,604	3,505
Infliximab	Initial	534	534	534	118	2,485	2,485	2,485	370	7,338	7,338	7,338	726
	Others	0	113	225	338	0	574	1,147	1,721	0	1,793	3,586	5,379
	Total	534	647	759	456	2,485	3,058	3,632	2,090	7,338	9,131	10,924	6,105

Chapter 9
Conclusions

The conclusions of this review need to be considered within the context of two key factors. The first is that there are currently no known effective treatments for AS. The second is that it is not clear from the identified trials or company submissions related to two of the three drugs (etanercept and infliximab) whether participants in the trials met conditions required within the treatment licence (e.g. failure of previous treatment).

The review has been limited in a number of areas. In the first instance, the results are limited by the currently available epidemiological and clinical data. The clinical review has been limited to exploration of AS-specific outcomes. No attempt has been made to consider other outcomes such as those on other affected joints (e.g. hips) or systems (e.g. eyes and gastrointestinal system). The economic analysis was limited to a consideration of direct costs. Therefore, consideration of indirect or social costs has not been included, and these are believed to be considerable.

The review of clinical data related to each of the three anti-TNF-α agents (including conventional treatment) compared with conventional treatment plus placebo indicates that in the short term (12 and 24 weeks) the three treatments demonstrate statistical differences and clinical effectiveness in relation to assessment of ASAS, BASDAI and BASFI. No studies providing head-to-head comparisons of the treatments were identified. Preliminary indirect comparisons indicate that with current limited data it is not possible to determine whether there are any significant differences in effectiveness between the three agents.

Longer term open-label studies provide published data that are primarily related to subgroups of patients and are therefore of limited value in assessing longer term outcomes for the overall population of AS patients. Registry data being collected within the BSRBR may, in the future, provide comparisons such as distribution of BASDAI and BASFI, change in these scores over time, relationship of these changes to quality of life and possibly comparisons of responses for differing treatments.

The limitations of the clinical outcome data imposed restrictions on the economic assessment of cost-effectiveness. The only period for which direct RCT evidence is available is in the short term. In addition, at present BASDAI and BASFI are the best tools available, but concern only intermediate outcomes. These tools were not designed for use in economic evaluation and it is important to be cognisant of potential difficulties, including enhanced scope for variability, inherent non-linearity of the scales, and the influence of the assumptions involved in linking index scores to utilities and costs.

The three submitted company models, although different in structure and methods, share a common set of assumptions governing how the anti-TNF-α agents should be assessed for cost-effectiveness. In each submission the initial treatment phase is followed by a long period of progressive chronic disease in which the original treatment remains the only option.

All three models were disappointing in the quality of execution, particularly in terms of quality control and transparency. After the correction of serious errors and unusual parameter values, the cost-effectiveness of the two self-administered anti-TNF-α agents (adalimumab and etanercept) appears to be closely comparable. By contrast, infliximab (administered by infusion) seems to be a far less attractive investment, with high long-term ICERs (£40,000–50,000 per QALY) and is even less appealing results over shorter periods.

An examination of IPD[51] (n = 397) to explore the nature and dynamics of the response to treatment was carried out and highlighted a number of issues critical to the development of an economic model. These included variability in BASDAI measures, non-linearity of outcome gains and spontaneous resolution without anti-TNF-α treatment. Subsequent short- and long-term modelling was carried out using key parameters identified within the submitted models. The rationale for the range of data used to populate these models is provided and sensitivity analysis is reported.

The short-term model developed by the assessment group confirmed the large front-loading of costs

with incremental cost per QALY gained varying between £57,000 and £120,000. It is also apparent that infliximab has much higher costs than the self-injected drugs, and therefore yields much poorer economic results. Although age and gender do not appear to be important factors, it is noticeable that the initial severity of symptoms may be a significant influence on effectiveness and cost-effectiveness.

The assumptions of the short-term model were used to explore the cost-effectiveness of the use of anti-TNF-α agents in the long term. It is acknowledged that this model is far more speculative than the first, since trends and parameter values must be projected far beyond the available evidence, with consequent loss of precision.

It is not possible to make a definitive assessment of economic performance in the face of the wide-ranging uncertainties; however, three clear conclusions can be drawn:

- Assuming clinical equivalence, the higher costs associated with infliximab (even if given less frequently) make it a much less favourable option than either adalimumab or etanercept.
- It is unlikely that extending the period of continuous treatment over decades will automatically improve cost-effectiveness.
- Without proven criteria by which to identify those patients most likely to benefit, the sequential trial and error approach to finding an effective agent for a patient will lead to less attractive economic results than those provided in the single treatment model.

Implications for the NHS

In terms of budget impact, uncertainties in the basic epidemiology of AS and the eligibility of patients to be offered anti-TNF-α agents lead to an extremely wide range of potential additional costs to the NHS. However, these analyses indicate that the approval of anti-TNF-α agents for the general treatment of active AS is likely to have considerable financial consequences and lead to large additional service demands.

Recommendations for further research

There is an absence of evidence concerning a number of limiting factors related to patients suffering from AS, the disease itself and its treatment.

Patient factors

- What are the current incidence and prevalence rates for AS?
- What patient variables are appropriate to predict disease progression?
- If a patient does not respond to one anti-TNF-α agent will they respond to another?
- What criteria should be used in the decision to discontinue treatment?
- Should the same criteria be applied to patients restarting treatment after previous treatment failure?

Disease factors

- What is standard disease progression?
- Could alternative disease measurements be developed to inform economic modelling more adequately?
- Is disease progression halted/slowed in patients treated with anti-TNF-α agents?

Treatment factors

- Do patients require treatment with anti-TNF-α agents continuously?
- Can anti-TNF-α treatment be titrated down or withdrawn over time?
- Can anti-TNF-α treatments be of use to manage disease flares rather than continuously?
- Is there dose creep that requires drug dosages to increase over time?
- What are the issues related to sequencing of treatments?
  - Which treatment should be considered first line?
  - If one treatment fails should a second/third be tried?
  - If one treatment works initially and then fails should a second/third be tried?
  - If the second/third treatment fails should the first be tried again?
- What role does conventional treatment (NSAIDs) play when an anti-TNF-α agent is prescribed?

In order to obtain robust estimates of the longer term clinical effectiveness and cost-effectiveness of anti-TNF-α agents for AS, clinical trials that aim to address these limiting factors need to be conducted.

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Contribution of authors

Adrian Bagust (Professor of Health Economics) was responsible for the development and writing of evaluation of the submitted economic models, economic modelling and evaluation, and the budget impact. Angela Boland (Research Fellow) carried out the study selection and contributed to the background, economic review and the evaluation of submitted economic models. Pierre Dagenais (Rheumatologist and Research Fellow) contributed to the background. Rumona Dickson (Director of the Liverpool Reviews and Implementation Group) was responsible for the project management, study selection and input into all aspects of the clinical component of the review, and contributed to writing the report. Yenal Dundar (Research Fellow) developed the search strategy and worked on the study selection and had input into aspects of the clinical component of the review. Ruaraidh Hill (Research Fellow) was responsible for the management and input into all aspects of the clinical component of the clinical review, study selection, data management and meta-analysis, and contributed to the protocol and writing the report. Ashley Jones (Medical Statistician) was the statistical expert, and advised on and conducted the clinical data analysis. Claire McLeod (Research Fellow) was the lead reviewer responsible for writing the protocol, background and economic review, contributed to the evaluation of submitted economic models and budget impact, and aided in study selection. She was also responsible for coordinating the final report. Ruben Mujica Mota (Research Fellow) contributed to the evaluation of the submitted economic models. Tom Walley (Professor of Clinical Pharmacology) carried out data assessment and interpretation of the clinical and economic data. All authors took part in the editing and production of this report.

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Appendix 1

Search strategy: clinical evidence

TABLE 43 *Search strategy and results for medical electronic databases (clinical review)*

Database	Years	Search strategy	References identified
MEDLINE (Ovid interface)	1966 to week 3, November 2005 (i.e. week 14 to 20 November 2005)	1 exp spondylitis, ankylosing/ 2 (bekhterev or bechterew or marie strumpell or ankylo$ spondyl$ or rheumatoid spondylitis or spondylarthiritis).tw. 3 (adalimumab or humira or etanercept or enbrel or infliximab or remicade).af. 4 1 or 2 5 3 and 4	189
EMBASE (Ovid interface)	1980 to week 49 2005 (i.e. week 28 November to 4 December 2005)	1 exp Ankylosing Spondylitis/ 2 exp Spondyloarthropathy/ 3 (bekhterev or bechterew or marie strumpell or ankylo$ spondyl$ or rheumatoid spondylitis or spondylarthiritis).tw. 4 (adalimumab or humira or etanercept or enbrel or infliximab or remicade).af. 5 or/1–3 6 4 and 5	499
Science Citation Index/ISI Web of Knowledge	1980 to 2005	TS=((adalimumab or humira or etanercept or enbrel or infliximab or remicade) and (ankylo* spondyl* or bekhtere* or bechterew or marie strumpell))	411
Science Citation Index/ ISI Proceedings	1980 to 2005	TS=((adalimumab or humira or etanercept or enbrel or infliximab or remicade) and (ankylo* spondyl* or bekhtere* or bechterew or marie strumpell))	119
Cochrane Library	2005, Issue 4	"(ankylo* spondyl* or bekhtere* or bechterew or marie strumpell) **and** (adalimumab or humira or etanercept or enbrel or infliximab or remicade)	
CENTRAL (formerly Cochrane Controlled Trials Register)		As above	26
CDSR		As above	4
DARE		As above	0
HTA		As above	5
NHS EED		As above	1
	Total references identified		**1254**
	Duplicates		**526**
	Total		**728**

TABLE 44 *Record selection from medical electronic database searching (clinical review)*

Inclusion/exclusion	Description	No. of records
Screened	**Selected for level 1 screening**	728
Excluded[a]	Does not include adalimumab/etanercept/infliximab	97 (97)
	Non-investigational, no interest, not relevant (i.e. exclude)	322 (412)
	Non-investigational, but potentially relevant to economics/costs	6 (9)
	Non-investigational, but of background interest	51 (184)
	Systematic review or meta-analysis	1 (7)
	Duplicate (identified at screening stage)	0 (3)
Included	**Passed level 1 screening**	251
	RCT or open-label study	85
	Non-randomised study	108
	Other	23
	Undetermined (full text ordered) [not necessarily exclusively undetermined, may have been included by another reviewer]	71
	Other	21
	Unobtainable within timespan of TAR	21
Included	**Selected for categorisation (second level screen)**	216
	RCTs	36
	Open-label extension studies of RCTs (above)	21
Not considered further	Open-label studies not determined to be associated with identified RCTs	–
Excluded[b]	No outcomes of interest/subgroups only/other	–

[a] Numbers of records excluded are presented as primary reason for exclusion (and any exclusion screening form response).
[b] Owing to the detailed screening at level 1, few systematic reviews or background references remained to be excluded at this later level.

Appendix 2

Quality assessment: clinical and economics evidence

Quality assessment – clinical studies

RCTs of clinical effectiveness were assessed using the following criteria, based on CRD Report No. 4.[42]

- Was the method used to assign participants to the treatment groups really random? (Computer-generated random numbers and random number tables will be accepted as adequate, while inadequate approaches will include the use of alternation, case record numbers, birth dates or days of the week.)
- Was the allocation of treatment concealed? (Concealment will be deemed adequate where randomisation is centralised or pharmacy controlled, or where the following are used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes, even if opaque.)
- Was the number of participants who were randomised stated?
- Were details of baseline comparability presented in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Was baseline comparability achieved for treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Were the eligibility criteria for study entry specified?
- Were any co-interventions identified that may influence the outcomes for each group?
- Were the outcome assessors blinded to the treatment allocation?
- Were the individuals who were administered the intervention blinded to the treatment allocation?
- Were the participants who received the intervention blinded to the treatment allocation?
- Was the success of the blinding procedure assessed?
- Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?
- Were the reasons for any withdrawals stated?
- Was an intention-to-treat analysis included?

Items will be graded in terms of ✔ **yes**, item adequately addressed; ✖ **no**, item not adequately addressed; ✔/✖ *partially*, item partially addressed; **? unclear** or not enough information; **NA**, not applicable; or **NS**, not stated.

Quality assessment – economics studies

Studies of cost-effectiveness were assessed using the following criteria, which is an updated version of the checklist developed by Drummond and Jefferson.[43]

Study design

- The research question is stated.
- The economic importance of the research question is stated.
- The viewpoint(s) of the analysis are clearly stated and justified.
- The rationale for choosing the alternative programmes or interventions compared is stated.
- The alternatives being compared are clearly described.
- The form of economic evaluation used is stated.
- The choice of form of economic evaluation is justified in relation to the questions addressed.

Data collection

- The source(s) of effectiveness estimates used are stated.
- Details of the design and results of effectiveness study are given (if based on a single study).
- Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies).
- The primary outcome measure(s) for the economic evaluation are clearly stated.

- Methods to value health states and other benefits are stated.
- Details of the subjects from whom valuations were obtained are given.
- Productivity changes (if included) are reported separately.
- The relevance of productivity changes to the study question is discussed.
- Quantities of resources are reported separately from their unit costs.
- Methods for the estimation of quantities and unit costs are described.
- Currency and price data are recorded.
- Details of currency of price adjustments for inflation or currency conversion are given.
- Details of any model used are given.
- The choice of model used and the key parameters on which it is based are justified.

Analysis and interpretation of results

- Time-horizon of costs and benefits is stated.
- The discount rate(s) is stated.
- The choice of rate(s) is justified.
- An explanation is given if costs or benefits are not discounted.
- Details of statistical tests and confidence intervals are given for stochastic data.
- The approach to sensitivity analysis is given.
- The choice of variables for sensitivity analysis is justified.
- The ranges over which the variables are varied are stated.
- Relevant alternatives are compared.
- Incremental analysis is reported.
- Major outcomes are presented in a disaggregated as well as an aggregated form.
- The answer to the study question is given.
- Conclusions follow from the data reported.
- Conclusions are accompanied by the appropriate caveats.

All items will be graded as either ✔ **yes**, item adequately addressed; ✖ **no**, item not adequately addressed; **?** **unclear** or not enough information; **NA**, not appropriate; or **NS**, not stated.

Appendix 3

Indirect comparisons: formula and calculations

BOX 3 *Statistical indirect comparison: formula*

Indirect comparison formula applied for both binary and continuous data

Suppose T_{BA} is the result of direct comparison of intervention B versus A, and T_{CA} is the direct comparison of intervention C versus A.

Then the estimate of the indirect comparison of intervention B versus C (T'_{BC}) is calculated by

$$T'_{BC} = T_{BA} - T_{CA}$$

and its standard error is

$$SE(T'_{BC}) = \sqrt{(SE(T_{BA})^2 + SE(T_{CA})^2)}$$

where $SE(T_{BA})$ and $SE(T_{CA})$ are the standard errors of T_{BA} and T_{CA}, respectively.

Taken from Song and colleagues.[83] Application of method to continuous data confirmed by Song (Song F, Reader in Research Synthesis, University of East Anglia: personal communication, 24 April 2006).

TABLE 45 *Statistical indirect comparison of ASAS*

Outcome	Calculation of indirect comparisons		
ASAS 20: 12 weeks	Indirect comparison: adalimumab vs etanercept		0.072429838
	SE (AIC)	0.237772835	
	LL 95% CI	–0.393604919	
	UL 95% CI	0.538464595	
	RR of A vs E (95% CI)	**1.075117371**	(0.674621 to 1.713374)
	Indirect comparison: adalimumab vs infliximab		–0.441208727
	SE (AIC)	0.496381876	
	LL 95% CI	–1.414117204	
	UL 95% CI	0.531699749	
	RR of A vs I (95% CI)	**0.643258427**	(0.24314 to 1.701823)
	Indirect comparison: etanercept vs infliximab		–0.513638565
	SE (AIC)	0.46152689	
	LL 95% CI	–1.41823127	
	UL 95% CI	0.39095414	
	RR of E vs I (95% CI)	**0.598314607**	(0.242142 to 1.478391)
ASAS 20: 24 weeks	Indirect comparison: etanercept vs infliximab		–0.22866
	SE (AIC)	0.296622	
	LL 95% CI	–0.81004	
	UL 95% CI	0.352717	
	RR of E vs I (95% CI)	**0.795597**	(0.44484 to 1.422928)
ASAS 50: 12 weeks	Indirect comparison: adalimumab vs etanercept		–0.09844
	SE (AIC)	0.302763	
	LL 95% CI	–0.69186	
	UL 95% CI	0.494976	
	RR of A vs E (95% CI)	**0.90625**	(0.500646 to 1.640459)
	Indirect comparison: adalimumab vs infliximab		–0.94898
	SE (AIC)	0.751447	
	LL 95% CI	–2.42182	
	UL 95% CI	0.523857	
	RR of A vs I (95% CI)	**0.387136**	(0.08876 to 1.688528)

continued

TABLE 45 *Statistical indirect comparison of ASAS (cont'd)*

Outcome	Calculation of indirect comparisons		
	Indirect comparison: etanercept vs infliximab		–0.85054
	SE (AIC)	0.731409	
	LL 95% CI	–2.2841	
	UL 95% CI	0.583022	
	RR of E vs I (95% CI)	**0.427184**	(0.101866 to 1.791444)
ASAS 70: 12 weeks	Indirect comparison: adalimumab vs etanercept		0.484366
	SE (AIC)	0.481889	
	LL 95% CI	–0.46014	
	UL 95% CI	1.428868	
	RR of A vs E (95% CI)	**1.623145**	(0.631198 to 4.17397)

A, adalimumab; AIC, adjusted indirect comparison; E, etanercept; I, infliximab; LL, lower limit; UL, upper limit.

TABLE 46 *Statistical indirect comparison of BASDAI and BASFI*

Outcome	Calculation of indirect comparisons						
BASDAI: 12 weeks	*Treatment*	*Control*	*Effect estimate*	*Value*	*LL*	*UL*	*SE*
	Adalimumab	Placebo	WMD (random)	[**Commercial-in-confidence information removed**]			
	Etanercept	Placebo	WMD (random)	–1.67	–2.1	–1.24	0.219388
	Infliximab	Placebo	WMD (random)	[**Commercial-in-confidence information removed**]			
	Indirect comparison: adalimumab vs etanercept			[**Commercial-in-confidence information removed**]			
	SE (AIC)			[**Commercial-in-confidence information removed**]			
	LL 95% CI			[**Commercial-in-confidence information removed**]			
	UL 95% CI			[**Commercial-in-confidence information removed**]			
	Indirect comparison: adalimumab vs Infliximab			[**Commercial-in-confidence information removed**]			
	SE (AIC)			[**Commercial-in-confidence information removed**]			
	LL 95% CI			[**Commercial-in-confidence information removed**]			
	UL 95% CI			[**Commercial-in-confidence information removed**]			
	Indirect comparison: etanercept vs infliximab			[**Commercial-in-confidence information removed**]			
	SE (AIC)			[**Commercial-in-confidence information removed**]			
	LL 95% CI			[**Commercial-in-confidence information removed**]			
	UL 95% CI			[**Commercial-in-confidence information removed**]			
BASDAI: 24 weeks	*Treatment*	*Control*	*Effect estimate*	*Value*	*LL*	*UL*	*SE*
	Etanercept	Placebo	WMD (random)	[**Commercial-in-confidence information removed**]			
	Infliximab	Placebo	WMD (random)	[**Commercial-in-confidence information removed**]			
	Indirect comparison: etanercept vs infliximab			–	0.3		
	SE (AIC)			[**Commercial-in-confidence information removed**]			
	LL 95% CI			[**Commercial-in-confidence information removed**]			
	UL 95% CI			[**Commercial-in-confidence information removed**]			
BASFI: 12 weeks	*Treatment*	*Control*	*Effect estimate*	*Value*	*LL*	*UL*	*SE*
	Adalimumab	Placebo	WMD (random)	[**Commercial-in-confidence information removed**]			
	Etanercept	Placebo	WMD (random)	–1.48	–1.83	–1.13	0.178571
	Infliximab	Placebo	WMD (random)	[**Commercial-in-confidence information removed**]			
	Indirect comparison: adalimumab vs etanercept			[**Commercial-in-confidence information removed**]			
	SE (AIC)			[**Commercial-in-confidence information removed**]			
	LL 95% CI			[**Commercial-in-confidence information removed**]			
	UL 95% CI			[**Commercial-in-confidence information removed**]			

continued

TABLE 46 *Statistical indirect comparison of BASDAI and BASFI (cont'd)*

Outcome	Calculation of indirect comparisons						
	Indirect comparison: adalimumab vs infliximab			[**Commercial-in-confidence information removed**]			
	SE (AIC)			[**Commercial-in-confidence information removed**]			
	LL 95% CI			[**Commercial-in-confidence information removed**]			
	UL 95% CI			[**Commercial-in-confidence information removed**]			
	Indirect comparison: etanercept vs infliximab			[**Commercial-in-confidence information removed**]			
	SE (AIC)			[**Commercial-in-confidence information removed**]			
	LL 95% CI			[**Commercial-in-confidence information removed**]			
	UL 95% CI			[**Commercial-in-confidence information removed**]			
BASFI: 24 weeks	*Treatment*	*Control*	*Effect estimate*	*Value*	*LL*	*UL*	*SE*
	Etanercept	Placebo	WMD (random)	–1.42	–1.89	–0.95	0.239796
	Infliximab	Placebo	WMD (random)	[**Commercial-in-confidence information removed**]			
	Indirect comparison: etanercept vs infliximab			[**Commercial-in-confidence information removed**]			
	SE (AIC)			[**Commercial-in-confidence information removed**]			
	LL 95% CI			[**Commercial-in-confidence information removed**]			
	UL 95% CI			[**Commercial-in-confidence information removed**]			

Appendix 4

Currency conversion and inflation of Kobelt and Ward studies

To inflate costs from Kobelt[85] to 2006 prices, the ratio of the UK CPI in January 2006[88] (100.5) and the UK CPI in January 2002[88] (94.4) was calculated (1.065) and multiplied by the cost requiring inflation.

To uplift the Ward costs,[86] the currency first needed to be changed to UK pounds. This was achieved using PPPs. The ratio of the PPP in the UK in 1999[87] (0.644) to the PPP of the USA in 1999[87] (1) was calculated (0.644) and multiplied by the cost requiring currency conversion. To inflate to 2006, the ratio of the UK CPI in January 2006[88] (100.5) and the UK CPI in January 1999[88] (91.4) was calculated (1.1) and multiplied by the product of the previous calculation.

TABLE 47 *Currency conversion and inflation of costs*

	Kobelt[85] (£ 2002)	Kobelt[85] (£ 2006)	Ward[86] ($ 1999)	Ward[86] ($ 1999)	Ward[86] (£ 2006)
Hospital care	£962.00	£1,024.16			
Community care	£604.00	£643.03			
Medication	£176.00	£187.37			
Direct costs	£1,742.00	£1,854.57	$1,545.00	£994.98	£1,094.04
Direct non-healthcare	£1,111.00	£1,182.79	$230.00	£148.12	£162.87
All direct	£2,853.00	£3,037.36	$1,775.00	£1,143.10	£1,256.91
Indirect	£3,913.00	£4,165.85	$4,945.00	£3,184.58	£3,501.64
Total	£6,766.00	£7,203.21	$6,720.00	£4,327.68	£4,758.55

Currency and price year are in parentheses.

Appendix 5

Exploratory analysis of patient subgroups identified from individual patient data

The modelled estimates of cost-effectiveness included in the main body of the Technology Assessment Report (TAR) suggest that treatment of ankylosing spondylitis patients with any of the anti-TNF-α drugs is unlikely to be cost-effective, where patients are selected solely on the basis of the current BSR treatment guidelines. However, detailed analysis of IPD from the two adalimumab RCTs reported in the TAR (section 7.2) makes clear that a minority of patients will respond rapidly and dramatically to anti-TNF-α therapy. This observation has been borne out by the personal experience of some patients, who report startling and enduring improvements in their condition. Unfortunately, there are no known predisposing patient characteristics that could be used to predict such a response with any reliability.

The approach adopted in the BSR guidelines is that of a 'test of efficacy' period for all suitable patients of about 12 weeks, by which time a modest improvement of at least 2 points on the BASDAI should be achieved to warrant treatment continuation. Unfortunately, this method involves a very high initial cost for all eligible patients, regardless of how many subsequently show benefit, so that over the group as a whole cost-effectiveness is hard to establish.

Additional analysis of the available IPD was requested by NICE on behalf of the assessment committee to explore the scope for identification of possible patient subgroups using different selection criteria, which may show more advantageous economic results.

This appendix describes the methods used and results obtained from this further analysis.

Objectives of subgroup analysis

In order to improve the cost-effectiveness of anti-TNF-α treatment, two questions need to be addressed:

- *Question 1*: can the initial cost of treatment during the 'treatment trial' be reduced by identifying patients unlikely to benefit as early as possible (i.e. in some cases before 12 weeks)?
- *Question 2*: can the proportion of patients allowed to continue on treatment beyond the trial period be reduced so that those remaining have a significantly better mean quality of life (estimated via the BASDAI and BASFI scores) than that achieved using the BSR criteria?

Success in answering question 1 would result in a reduction in the cost of treatment costs during the first year, but has no implications for costs thereafter, and has no impact on the quality of life of patients selected for continuing treatment.

By contrast, any smaller subgroup of patients continuing on treatment inevitably incurs reduced treatment costs in all subsequent periods. By retaining only those patients on treatment who show the best response, the quality gains that would normally accrue to the newly deselected patients are forgone. However, the balance of incremental costs and benefits is improved for those remaining on treatment in all subsequent periods, so that over time cost-effectiveness ratios should steadily reduce.

Defining subgroups

Utility gain in the submitted models, as well as in the LRiG model, is determined by changes in BASDAI and BASFI scores. In this group's previous IPD analysis (section 7.2.4 of the TAR) it was shown that the change in BASFI scores is the least reliable predictor of response, compared to changes in either BASDAI or the VAS pain scores. However, since the pain measure is not used by any of the models for estimating utility, it could not easily be adopted as a defining criterion to determine response to treatment. Thus, by elimination potential subgroups must be constructed in terms of the change in BASDAI score from baseline. In some cases this has implications for the allowable range of baseline BASDAI scores (e.g. requiring a minimum reduction of 5 points implies that the baseline value must be at least 5). This approach is

compatible with the BSR guidelines, which require a reduction of at least 2 points in BASDAI for treatment to continue.

The available IPD record values of BASDAI at baseline and at 2, 4, 8 and 12 weeks for virtually all patients. Visual examination of the time profiles of patients showing a clear strong response to treatment suggested that only a minority of such patients showed a strong response within 2 weeks of initiation. Therefore, attention was restricted to possible additional criteria for change in BASDAI score at 4 and 8 weeks, with a view to early termination of trial treatment to reduce initial costs (see question 1, above). In practice, it seems that formal assessment of BASDAI at 4 and 8 weeks could be reasonably included within normal clinical contacts during the current 12-week trial period.

The definition of selection criteria in terms of values at three separate time-points can potentially lead to a very large number of possible combinations. To limit the analytical burden, the restricted scheme of options shown in *Table 48* was adopted based on integer values of the required reduction in BASDAI from baseline.

If it is further assumed that the requirement at each assessment is at least as strict as earlier requirements, then there is a total of 110 possible scenarios on which to base the selection of subgroups with good response to treatment, while simultaneously reducing initial treatment costs. These include the BSR guideline recommendation as scenario 1, which is the basis of the model results previously reported.

Model amendments and limitations

The basic principle adopted for this exercise is to maintain the integrity of the existing LRiG model and the assumptions and relationships on which it is based. This allows direct comparison with results previously reported. Thus, the only changes made to the model logic were those necessary to allow the selection of IPD-derived subgroups and estimation of their expected effects.

Subgroup selection

The main mechanism used is to subdivide the patients on treatment at each time-point in the original model between those selected for continuing treatment by the selection scenario and those deemed to fail the change requirements and be withdrawn from treatment. Analysis of the IPD relating to those patients who met the BSR inclusion criteria and were randomised to receive adalimumab in the clinical trials was carried out to estimate the proportion of these patients remaining on therapy at the following time-points: 4, 8, 12, 20, 24, 30, 36, 42 and 48 weeks. In addition, the proportion at 52 weeks was estimated by linear regression, since only very small numbers of observations are available for this time-point. For the long-term model (post 12 months), it is assumed that the proportion of patients selected for treatment remains constant indefinitely.

Treatment-related costs

The re-estimation of treatment-related costs throughout the first 12 months is then straightforward from the time of discontinuation of each patient. An additional complication is introduced for those scenarios that involve a 12-week requirement for a reduction in BASDAI of more than 4 points (i.e. 5 or 6). In these cases, it would be illogical to initiate trial treatment for any patients with a baseline BASDAI score of less than the 12-week requirement, despite their passing the BSR criteria. In effect, under these circumstances an additional baseline screen would apply to prevent such patients receiving any anti-TNF-α treatment. The proportion of cases likely to fail such a screen has been estimated for each scenario from the IPD, and an adjustment to initial treatment costs incorporated into the model.

TABLE 48 *Selection criteria: values at three time-points*

Time on treatment	Required reduction in BASDAI score	Notes
4 weeks	None, 0, 1, 2, 3, 4, 5, 6	None = no assessment
8 weeks	None, 0, 1, 2, 3, 4, 5, 6	0 = not worse than baseline
12 weeks	2, 3, 4, 5, 6	2 = BSR guidelines

Outcome estimation

However, adjusting outcomes for the discontinuation of treatment is more complex and less certain. Most of those patients who would not be selected for continued treatment under one of the new scenarios did continue to receive treatment in the trial. There is no direct or indirect way to estimate what would have happened to their BASDAI and BASFI scores following a premature termination of active treatment. Both IPD-available trials included an early escape option, which allowed many patients in the control arm to switch to active treatment at any time from 12 weeks onwards. This therefore precludes indirect inferences from being drawn from the experience of placebo patients. Many possible modelling assumptions are conceivable, including:

(a) Patients revert to their baseline values.
(b) Patients maintain the scores at the time of discontinuation.
(c) Patients continue to enjoy the same pattern of changes recorded on treatment.

Assumption (a) appears to be unreasonably harsh, since the earlier IPD analysis showed clear evidence of a downward drift in scores over time for those patients who neither showed a very obvious immediate response nor experienced steady very high BASDAI and BASFI scores. Assumption (c) in effect reflects a situation where anti-TNF-α therapy makes no difference to the outcome gains experienced by any patient whose treatment in terminated; that is, all the gains that are recorded in their IPD would have happened without any active treatment. This also seems to be unreasonable and at variance with the previous findings. By default, therefore, in the absence of an obvious alternative and because it is easily modelled, the revised model was based on assumption (b). It is recognised that this is far from being a well-founded position, and therefore a sensitivity analysis was carried out to illustrate how results might change if only a proportion of these outcome losses occurred in practice.

Analysis of IPD for patients not selected under each scenario yielded estimates for mean BASDAI and BASFI scores at each time-point from week 12 onwards. These are used to calculate an adjusted cohort mean score every week throughout the first year. Beyond week 52, it is assumed that the mean BASDAI and BASFI scores for patients not selected remain constant indefinitely.

Additional considerations

In the specification document relating to the scope of additional work to be undertaken by the review group, mention was made of a possible analysis of the correlations between responses to different measures of patient outcome (specifically BASDAI, BASFI and spinal pain VAS). On reflection, the authors came to the view that such an analysis would add little to the understanding of the decision problem. In particular, it could not provide a basis for designing alternative bases for setting trial treatment response criteria, since there is no objective measure of efficacy beyond those already set by the BSR guidelines. The analysis reported previously was based on examination of choices made by a subset of patients as a proxy for dissatisfaction with response to treatment, and was designed to be indicative of a possible threshold for later discontinuation of treatment no longer found to be effective. This is unlikely to be a reliable basis for the initial decision to allow treatment.

Therefore, no additional IPD analysis of the suggested type has been carried out. However, it was considered potentially valuable to examine the response profiles over time for selected subgroups shown to be cost-effective, to assess the extent to which good response to treatment may or may not be sustainable at the individual level. This may be helpful in informing recommendations concerning the frequency and nature of patient reviews for patients receiving long-term anti-TNF-α therapy.

Main cost-effectiveness results

Table 49 shows the results obtained from the modified LRiG model in terms of the estimated incremental cost per QALY gained, for each of the 110 selection scenarios at 12 months and 20 years, and for both adalimumab/etanercept and infliximab.

The first group of five scenarios involves different values of the 12-week selection threshold, but without any prior testing: scenario 1 is the same as the original model, reflecting BSR guidelines. Thereafter, scenarios are grouped according to the value of the 12-week selection threshold.

Table 50 explores the impact of relaxing assumption (b) on outcome assessment to count only 50% of the calculated loss of benefit, when treatment is with either adalimumab or etanercept.

TABLE 49 *Cost-effectiveness ratios for 110 subgroup selection scenarios*

Scenario	Required BASDAI reduction			Proportion selected	Cost per QALY gained			
					Adalimumab/ etanercept		Infliximab	
	At 4 weeks	At 8 weeks	At 12 weeks		12 months	20 years	12 months	20 years
1	None	None	2		£55,246	£92,598	£124,183	£176,322
2	None	None	3		£53,638	£92,265	£121,218	£175,698
3	None	None	4		£46,373	£92,589	£109,872	£176,784
4	None	None	5		£35,369	£91,025	£90,465	£175,807
5	None	None	6		£22,171	£74,834	£65,049	£147,434
6	None	0	2		£55,164	£92,583	£124,172	£176,326
7	None	1	2		£54,469	£92,404	£123,081	£176,046
8	None	2	2		£53,310	£92,082	£121,184	£175,529
9	0	0	2		£53,278	£92,288	£122,462	£176,137
10	0	1	2		£52,484	£92,146	£121,937	£176,077
11	1	1	2		£50,489	£91,780	£118,267	£175,352
12	0	2	2		£50,834	£91,738	£120,092	£175,618
13	1	2	2		£49,342	£91,534	£117,112	£175,114
14	2	2	2		£43,598	£92,384	£108,723	£176,979
15	None	0	3		£53,359	£92,140	£120,637	£175,470
16	None	1	3		£52,558	£91,860	£119,139	£174,977
17	None	2	3		£51,701	£91,593	£117,634	£174,523
18	None	3	3		£47,382	£91,166	£112,052	£174,622
19	0	0	3		£52,002	£92,143	£120,316	£175,865
20	0	1	3		£51,365	£92,071	£120,137	£175,933
21	1	1	3		£49,185	£92,295	£116,766	£176,365
22	0	2	3		£49,657	£91,660	£118,287	£175,484
23	1	2	3	[**Commercial-**	£47,806	£91,957	£115,281	£175,979
24	2	2	3	**in-confidence**	£43,077	£92,462	£108,058	£177,130
25	0	3	3	**information**	£45,072	£93,295	£113,482	£179,495
26	1	3	3	**removed**]	£43,748	£93,971	£111,339	£180,587
27	2	3	3		£40,754	£96,563	£106,263	£185,664
28	3	3	3		£35,942	£104,292	£98,667	£201,585
29	None	0	4		£43,855	£89,717	£104,463	£171,549
30	None	1	4		£40,956	£86,278	£98,238	£165,281
31	None	2	4		£38,926	£84,058	£94,050	£161,263
32	None	3	4		£37,032	£80,786	£91,165	£155,838
33	None	4	4		£33,741	£78,230	£86,122	£151,713
34	0	0	4		£45,613	£93,437	£111,470	£178,839
35	0	1	4		£45,450	£93,630	£112,377	£179,434
36	1	1	4		£43,888	£94,184	£110,185	£180,409
37	0	2	4		£43,877	£93,020	£110,814	£178,652
38	1	2	4		£42,631	£93,731	£108,925	£179,839
39	2	2	4		£39,379	£93,838	£103,569	£180,039
40	0	3	4		£41,253	£94,236	£108,443	£181,808
41	1	3	4		£40,147	£95,470	£106,779	£183,920
42	2	3	4		£38,104	£96,384	£102,808	£185,398
43	3	3	4		£33,804	£102,794	£95,748	£198,856
44	0	4	4		£36,165	£95,097	£101,650	£184,563
45	1	4	4		£35,308	£96,489	£100,328	£186,948
46	2	4	4		£34,026	£98,995	£97,843	£191,283
47	3	4	4		£30,986	£103,535	£92,438	£200,571
48	4	4	4		£23,626	£106,755	£79,468	£207,871
49	None	0	5		£32,624	£74,359	£84,255	£145,358
50	None	1	5		£28,778	£60,180	£75,615	£119,339
51	None	2	5		£26,529	£52,996	£70,562	£106,161
52	None	3	5		£23,986	£39,177	£65,773	£81,432
53	None	4	5		£22,034	£36,704	£61,568	£76,306
54	None	5	5		£22,728	£46,172	£64,497	£93,789

continued

TABLE 49 *Cost-effectiveness ratios for 110 subgroup selection scenarios (cont'd)*

Scenario	Required BASDAI reduction			Proportion selected	Cost per QALY gained			
					Adalimumab/ etanercept		Infliximab	
	At 4 weeks	At 8 weeks	At 12 weeks		12 months	20 years	12 months	20 years
55	0	0	5		£37,409	£96,327	£98,425	£186,926
56	0	1	5		£37,318	£97,621	£99,597	£189,734
57	1	1	5		£36,119	£101,370	£98,188	£196,599
58	0	2	5		£36,013	£96,198	£98,485	£187,618
59	1	2	5		£35,109	£100,529	£97,337	£195,483
60	2	2	5		£32,227	£106,020	£92,702	£205,605
61	0	3	5		£33,593	£102,601	£96,500	£201,771
62	1	3	5		£32,738	£110,025	£95,372	£215,429
63	2	3	5		£30,769	£121,423	£91,720	£236,291
64	3	3	5		£27,686	£118,962	£85,431	£231,456
65	0	4	5		£30,722	£100,947	£92,506	£199,208
66	1	4	5		£29,730	£106,986	£91,019	£210,305
67	2	4	5		£28,398	£120,890	£88,542	£235,868
68	3	4	5		£26,384	£123,632	£84,090	£240,592
69	4	4	5		£20,302	£131,261	£72,508	£258,123
70	0	5	5		£26,767	£96,002	£86,405	£190,569
71	1	5	5		£25,910	£102,806	£85,123	£203,080
72	2	5	5		£24,886	£114,862	£83,029	£225,248
73	3	5	5		£23,193	£117,957	£79,109	£230,654
74	4	5	5		£18,645	£128,531	£70,050	£253,594
75	5	5	5		£13,828	£153,864	£61,720	£309,739
76	None	0	6		£19,650	£48,096	£58,872	£98,184
77	None	1	6	[**Commercial-**	£17,244	£32,598	£52,977	£69,605
78	None	2	6	**in-confidence**	£15,622	£25,877	£49,046	£57,171
79	None	3	6	**information**	£13,642	£21,801	£44,644	£49,662
80	None	4	6	**removed**]	£12,096	£19,010	£40,845	£43,935
81	None	5	6		£10,580	£16,861	£37,321	£39,617
82	None	6	6		£11,077	£16,748	£42,121	£42,961
83	0	0	6		£24,617	£83,816	£73,427	£166,152
84	0	1	6		£25,263	£86,697	£76,142	£172,261
85	1	1	6		£25,962	£95,661	£79,470	£189,479
86	0	2	6		£24,514	£84,437	£75,959	£168,744
87	1	2	6		£24,961	£94,134	£78,440	£187,247
88	2	2	6		£23,049	£108,042	£75,830	£213,434
89	0	3	6		£22,961	£90,201	£74,449	£180,024
90	1	3	6		£23,473	£100,815	£77,189	£200,402
91	2	3	6		£22,487	£117,159	£75,723	£230,849
92	3	3	6		£19,720	£116,232	£69,571	£228,532
93	0	4	6		£20,894	£88,399	£71,096	£176,728
94	1	4	6		£21,267	£96,955	£73,615	£193,346
95	2	4	6		£20,843	£116,325	£73,272	£229,615
96	3	4	6		£18,806	£121,040	£68,514	£237,809
97	4	4	6		£13,786	£113,568	£57,576	£223,187
98	0	5	6		£18,557	£84,317	£66,894	£169,155
99	1	5	6		£19,103	£93,798	£69,788	£187,522
100	2	5	6		£18,636	£111,286	£69,338	£220,375
101	3	5	6		£16,881	£116,200	£65,030	£229,005
102	4	5	6		£13,196	£113,346	£56,458	£222,912
103	5	5	6		£9,428	£130,822	£49,070	£261,213
104	0	6	6		£14,455	£74,703	£60,168	£155,043
105	1	6	6		£15,483	£86,502	£64,017	£178,649
106	2	6	6		£15,032	£117,105	£63,853	£237,974
107	3	6	6		£13,623	£129,993	£60,027	£261,787
108	4	6	6		£10,528	£125,839	£52,181	£252,339
109	5	6	6		£8,500	£126,107	£47,321	£252,063
110	6	6	6		£5,699	£129,014	£41,538	£272,128

TABLE 50 *Cost-effectiveness ratios for 110 subgroup selection scenarios when adalimumab/etanercept is used, showing outcome gain sensitivity analysis*

Scenario	Required BASDAI reduction			Proportion selected	Cost per QALY gained			
					100% loss of benefit		50% loss of benefit	
	At 4 weeks	At 8 weeks	At 12 weeks		12 months	20 years	12 months	20 years
1	None	None	2		£55,246	£92,598	£55,246	£92,598
2	None	None	3		£53,638	£92,265	£53,528	£92,177
3	None	None	4		£46,373	£92,589	£44,132	£88,455
4	None	None	5		£35,369	£91,025	£32,418	£69,069
5	None	None	6		£22,171	£74,834	£19,666	£44,505
6	None	0	2		£55,164	£92,583	£55,146	£92,576
7	None	1	2		£54,469	£92,404	£54,486	£92,410
8	None	2	2		£53,310	£92,082	£53,456	£92,139
9	0	0	2		£53,278	£92,288	£52,753	£92,076
10	0	1	2		£52,484	£92,146	£51,817	£91,874
11	1	1	2		£50,489	£91,780	£49,511	£91,373
12	0	2	2		£50,834	£91,738	£50,229	£91,483
13	1	2	2		£49,342	£91,534	£48,319	£91,099
14	2	2	2		£43,598	£92,384	£40,681	£89,175
15	None	0	3		£53,359	£92,140	£53,389	£92,114
16	None	1	3		£52,558	£91,860	£52,790	£91,926
17	None	2	3		£51,701	£91,593	£52,075	£91,723
18	None	3	3		£47,382	£91,166	£46,577	£88,276
19	0	0	3		£52,002	£92,143	£51,099	£91,725
20	0	1	3		£51,365	£92,071	£50,239	£91,557
21	1	1	3		£49,185	£92,295	£47,158	£90,842
22	0	2	3		£49,657	£91,660	£48,575	£91,154
23	1	2	3	[**Commercial-**	£47,806	£91,957	£45,772	£90,504
24	2	2	3	**in-confidence**	£43,077	£92,462	£39,856	£89,074
25	0	3	3	**information**	£45,072	£93,295	£42,525	£88,530
26	1	3	3	**removed**]	£43,748	£93,971	£40,193	£88,415
27	2	3	3		£40,754	£96,563	£36,454	£86,816
28	3	3	3		£35,942	£104,292	£31,343	£80,456
29	None	0	4		£43,855	£89,717	£42,945	£87,114
30	None	1	4		£40,956	£86,278	£41,504	£85,453
31	None	2	4		£38,926	£84,058	£40,298	£84,311
32	None	3	4		£37,032	£80,786	£38,377	£80,600
33	None	4	4		£33,741	£78,230	£34,393	£76,102
34	0	0	4		£45,613	£93,437	£42,007	£88,413
35	0	1	4		£45,450	£93,630	£41,595	£88,420
36	1	1	4		£43,888	£94,184	£39,123	£88,247
37	0	2	4		£43,877	£93,020	£40,264	£87,991
38	1	2	4		£42,631	£93,731	£38,063	£87,922
39	2	2	4		£39,379	£93,838	£34,524	£87,466
40	0	3	4		£41,253	£94,236	£37,463	£86,041
41	1	3	4		£40,147	£95,470	£35,383	£86,165
42	2	3	4		£38,104	£96,384	£32,975	£86,162
43	3	3	4		£33,804	£102,794	£28,789	£79,497
44	0	4	4		£36,165	£95,097	£32,195	£82,467
45	1	4	4		£35,308	£96,489	£30,550	£82,665
46	2	4	4		£34,026	£98,995	£28,565	£83,219
47	3	4	4		£30,986	£103,535	£25,599	£79,125
48	4	4	4		£23,626	£106,755	£19,055	£70,486
49	None	0	5		£32,624	£74,359	£31,653	£63,515
50	None	1	5		£28,778	£60,180	£29,674	£57,539
51	None	2	5		£26,529	£52,996	£28,408	£54,007
52	None	3	5		£23,986	£39,177	£26,234	£41,345
53	None	4	5		£22,034	£36,704	£24,486	£39,790
54	None	5	5		£22,728	£46,172	£23,761	£44,422

continued

TABLE 50 *Cost-effectiveness ratios for 110 subgroup selection scenarios when adalimumab/etanercept is used, showing outcome gain sensitivity analysis (cont'd)*

Scenario	Required BASDAI reduction			Proportion selected	Cost per QALY gained			
					100% loss of benefit		50% loss of benefit	
	At 4 weeks	At 8 weeks	At 12 weeks		12 months	20 years	12 months	20 years
55	0	0	5		£37,409	£96,327	£32,830	£70,454
56	0	1	5		£37,318	£97,621	£32,426	£70,697
57	1	1	5		£36,119	£101,370	£30,347	£71,223
58	0	2	5		£36,013	£96,198	£31,374	£70,123
59	1	2	5		£35,109	£100,529	£29,558	£70,863
60	2	2	5		£32,227	£106,020	£26,342	£71,610
61	0	3	5		£33,593	£102,601	£28,853	£61,902
62	1	3	5		£32,738	£110,025	£27,123	£62,821
63	2	3	5		£30,769	£121,423	£24,687	£64,143
64	3	3	5		£27,686	£118,962	£22,240	£63,257
65	0	4	5		£30,722	£100,947	£26,414	£61,099
66	1	4	5		£29,730	£106,986	£24,677	£61,780
67	2	4	5		£28,398	£120,890	£22,626	£63,595
68	3	4	5		£26,384	£123,632	£20,900	£63,650
69	4	4	5		£20,302	£131,261	£15,860	£50,968
70	0	5	5		£26,767	£96,002	£22,991	£59,382
71	1	5	5		£25,910	£102,806	£21,461	£60,331
72	2	5	5		£24,886	£114,862	£19,818	£62,021
73	3	5	5		£23,193	£117,957	£18,294	£62,182
74	4	5	5		£18,645	£128,531	£14,412	£50,286
75	5	5	5		£13,828	£153,864	£10,136	£35,860
76	None	0	6		£19,650	£48,096	£19,005	£37,577
77	None	1	6	[**Commercial-**	£17,244	£32,598	£18,191	£31,494
78	None	2	6	**in-confidence**	£15,622	£25,877	£17,402	£28,051
79	None	3	6	**information**	£13,642	£21,801	£15,871	£25,553
80	None	4	6	**removed**]	£12,096	£19,010	£14,569	£23,617
81	None	5	6		£10,580	£16,861	£13,175	£21,987
82	None	6	6		£11,077	£16,748	£12,267	£17,450
83	0	0	6		£24,617	£83,816	£20,697	£46,115
84	0	1	6		£25,263	£86,697	£20,976	£46,604
85	1	1	6		£25,962	£95,661	£20,645	£47,817
86	0	2	6		£24,514	£84,437	£20,386	£46,072
87	1	2	6		£24,961	£94,134	£19,853	£47,387
88	2	2	6		£23,049	£108,042	£17,565	£48,663
89	0	3	6		£22,961	£90,201	£18,830	£46,685
90	1	3	6		£23,473	£100,815	£18,405	£48,004
91	2	3	6		£22,487	£117,159	£16,918	£49,560
92	3	3	6		£19,720	£116,232	£14,765	£48,981
93	0	4	6		£20,894	£88,399	£17,193	£46,098
94	1	4	6		£21,267	£96,955	£16,776	£47,164
95	2	4	6		£20,843	£116,325	£15,651	£49,189
96	3	4	6		£18,806	£121,040	£13,907	£49,269
97	4	4	6		£13,786	£113,568	£9,959	£47,526
98	0	5	6		£18,557	£84,317	£15,383	£45,082
99	1	5	6		£19,103	£93,798	£15,203	£46,427
100	2	5	6		£18,636	£111,286	£14,120	£48,321
101	3	5	6		£16,881	£116,200	£12,564	£48,474
102	4	5	6		£13,196	£113,346	£9,565	£47,414
103	5	5	6		£9,428	£130,822	£6,379	£33,640
104	0	6	6		£14,455	£74,703	£11,688	£31,143
105	1	6	6		£15,483	£86,502	£12,053	£32,369
106	2	6	6		£15,032	£117,105	£10,994	£34,252
107	3	6	6		£13,623	£129,993	£9,743	£34,606
108	4	6	6		£10,528	£125,839	£7,276	£33,676
109	5	6	6		£8,500	£126,107	£5,633	£33,217
110	6	6	6		£5,699	£129,014	£3,376	£15,893

Observations

When infliximab is used, in all scenarios the ICER at both 12 months and 20 years exceeds £30,000, in many cases very substantially. The best result is obtained for scenario 81, for which [**Commercial-in-confidence information removed**] of patients are selected for treatment at week 12, yielding ICERs of £37,300 per QALY at 12 months and £39,600 at 20 years.

For adalimumab/etanercept, there are no scenarios with ICERs below £30,000 per QALY when the required week 12 BASDAI reductions are 2 or 3. Only one scenario (number 48) with a week 12 threshold of 4 yields an ICER less than £30,000 per QALY over 12 months, but it shows a very high ICER at 20 years. Two scenarios (52 and 53) with a week 12 threshold of 5 show good ICERs at 12 months (£24,000 and £22,000) and could also be considered acceptable at 20 years (less than £40,000 per QALY).

Five scenarios yield consistently good results at both 12 months and 20 years and are characterised by using adalimumab/etanercept, a week 12 threshold of 6 points BASDAI reduction, using an additional threshold at week 8 (but not at week 4) and selecting between [**Commercial-in-confidence information removed**] of BSR-eligible patients for continued treatment.

Although there are some changes in results as a consequence of relaxing the outcomes assumption (especially for long-term ICERs) this does not materially alter the nature of the scenarios that may be considered cost-effective.

Influence of selection thresholds on cost-effectiveness

The key indicator of the effect of subgroup selection scenarios is the extent to which they restrict the number of patients allowed to continue treatment beyond 12 weeks. *Figure 18* illustrates the dominant effect of this value on the cost-effectiveness results (regardless of the assumption made about outcome loss) by plotting the 12-month ICER for each of the 110 scenarios against the proportion of patients selected. The original result obtained by the LRiG model

[**Commercial-in-confidence information removed**]

FIGURE 18 *Relationship between the proportion of patients selected for continued treatment at 12 weeks and the 12-month ICER (adalimumab/etanercept)*

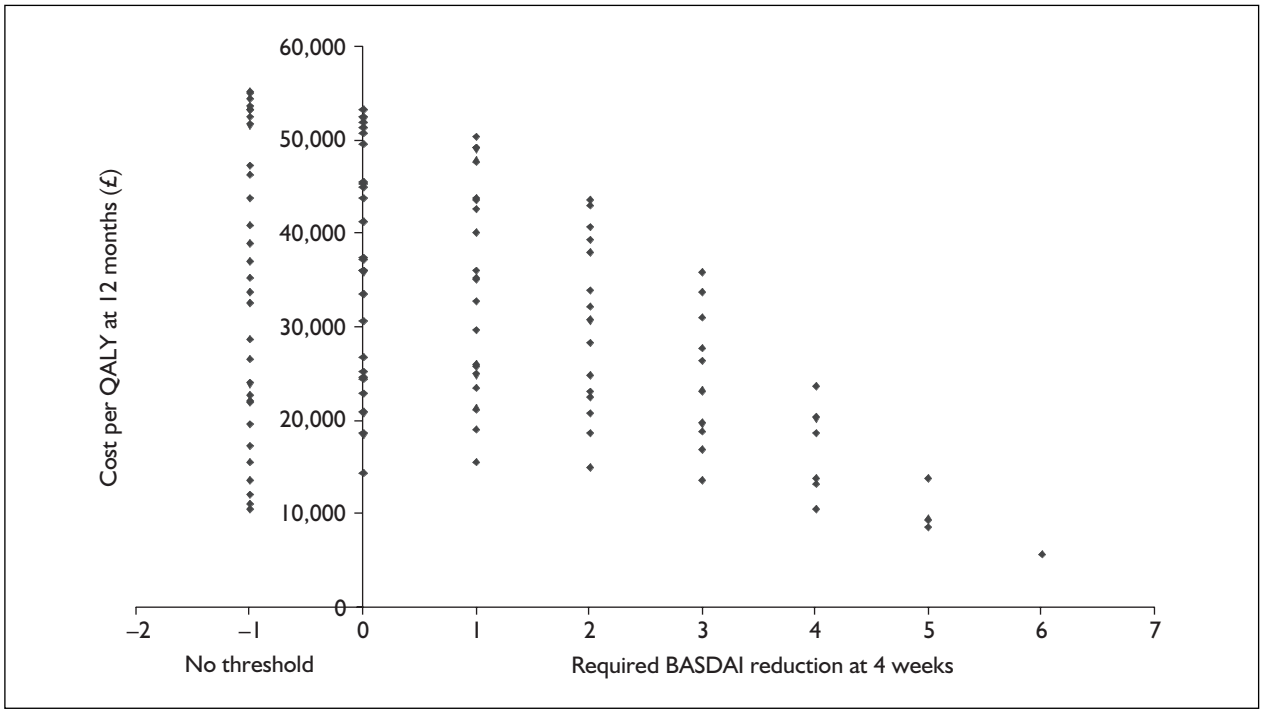

FIGURE 19 *Relationship between the 4-week threshold reduction in BASDAI and the 12-month ICER (adalimumab/etanercept)*

(scenario 1 with 57% of patients selected) is at the far right of the plot. It appears that an ICER of less than £30,000 per QALY is guaranteed only for scenarios restricting treatment to less than 20% of patients.

In *Figures 19–21*, 12-month ICERs are compared between scenarios involving different values for thresholds at 4, 8 and 12 weeks, illustrating how the 4- and 8-week thresholds are less influential on cost-effectiveness than the crucial 12-week criterion.

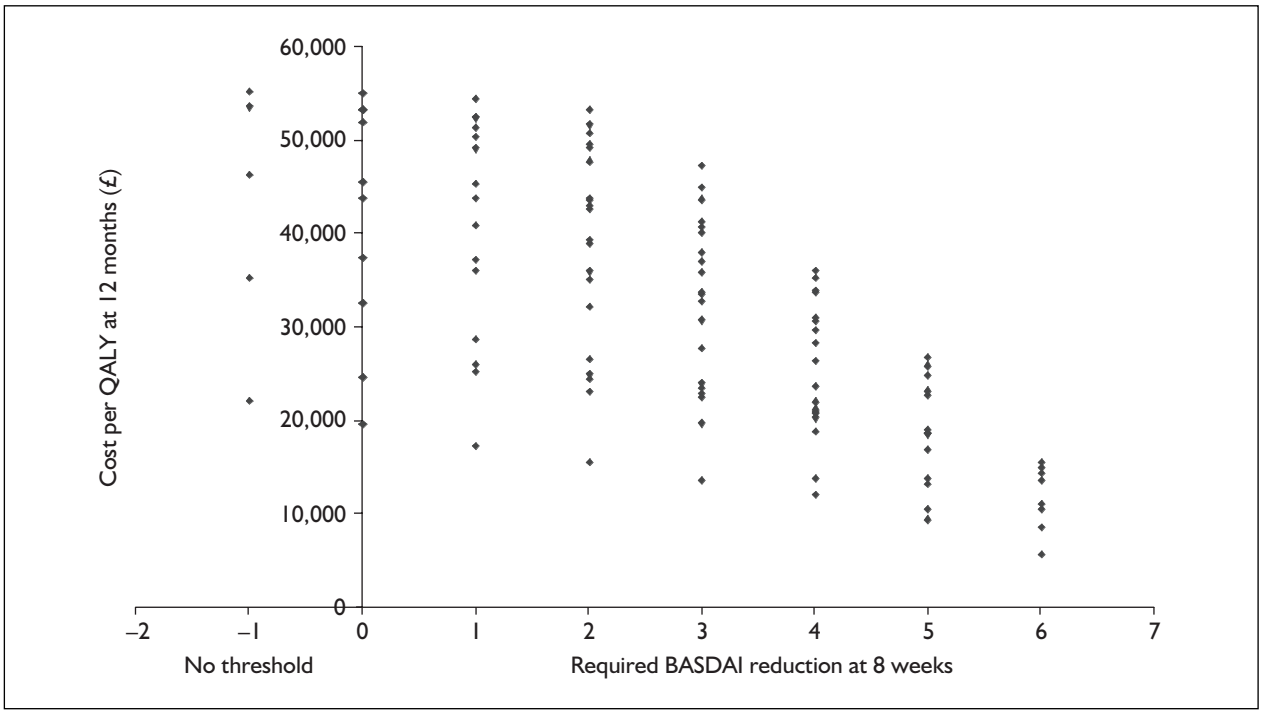

FIGURE 20 *Relationship between the 8-week threshold reduction in BASDAI and the 12-month ICER (adalimumab/etanercept)*

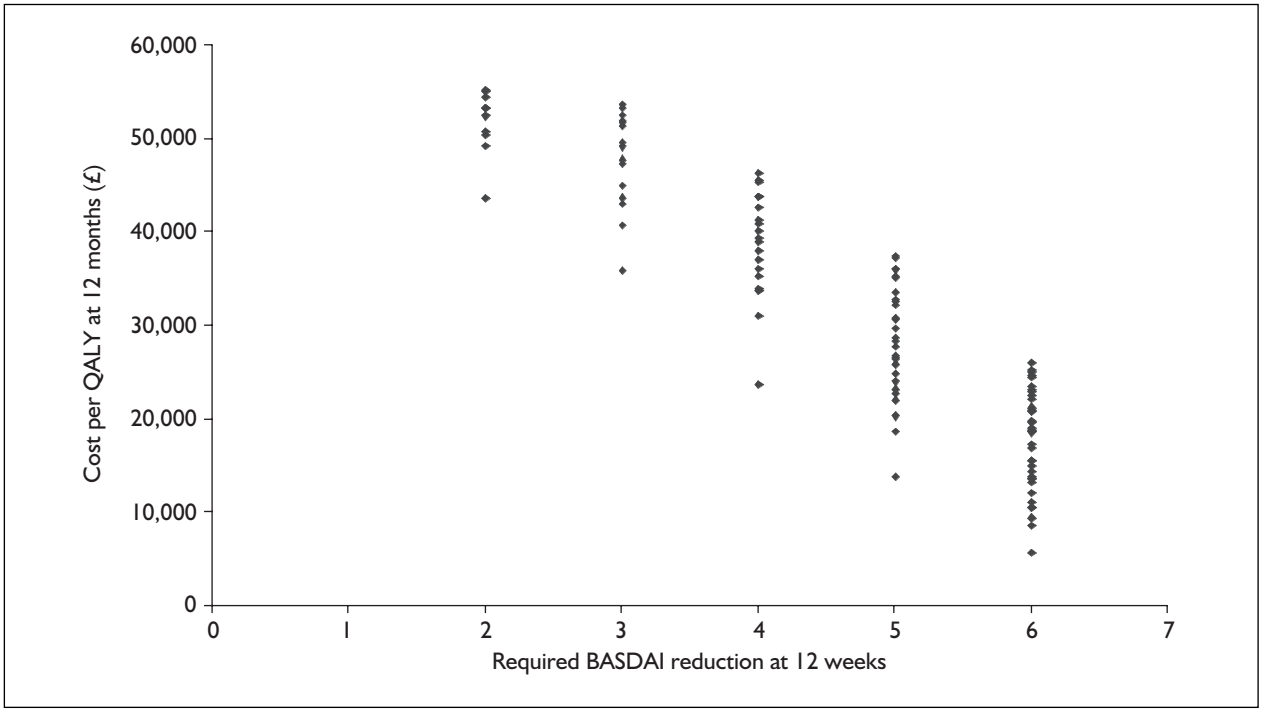

FIGURE 21 *Relationship between the 12-week threshold reduction in BASDAI and the 12-month ICER (adalimumab/etanercept)*

Sensitivity analysis on key model variables

Table 51 shows a full set of sensitivity analyses covering the main variables identified in the TAR as influential on long-term cost-effectiveness results. The tables have been prepared on the basis of treatment with adalimumab or etanercept.

Despite the most favourable combination of model assumptions, it is clear that the findings already described remain broadly unchanged:

- scenarios requiring only 2-, 3- or 4-point reductions in BASDAI scores at 12 weeks fail to show cost-effectiveness at both 12 months and 20 years.
- some scenarios requiring a 5- or 6-point reduction at 12 weeks could be cost-effective under certain sets of assumptions.
- scenarios based on thresholds at 8 and 12 weeks (but not 4 weeks) generally perform better than other scenarios.

Durability of outcome gains

In addition to the extent of the initial response to anti-TNF-α treatment, it is important to consider the likelihood that a patient will sustain the benefit seen at 12 weeks at later times. The IPD allow the experience of single patients to be explored for up to 52 weeks. In particular, one can consider whether the subgroups identified by more exacting thresholds lead to more or less long-term stability in the various outcome measures available.

In *Figures 22–25* these data are displayed for patients belonging to three subgroups which differ only in the level of the final 12-week threshold:

- subgroup 79 (6-point reduction in BASDAI)
- subgroup 52 (5-point reduction in BASDAI)
- subgroup 32 (4-point reduction in BASDAI).

These three groups are nested, since all members of subgroup 79 are also members of 52, which in turn is fully included within subgroup 32. For clarity, the three charts for each outcome are restricted to those patients not included in a smaller subgroup.

In *Figure 22* it appears that low BASDAI scores are sustained by all but [**Commercial-in-confidence information removed**] with the higher reduction thresholds (5 and 6), whereas with a threshold of 4 BASDAI scores show more variability, with several patients experiencing some episodes with higher levels of disease activity. The charts for the spinal pain VAS scores (*Figure 23*) show a similar pattern, but with much larger and more frequent short-term fluctuations.

Figure 24 relates to the BASFI score patterns and again shows evidence of much greater variability when a lower threshold is used. Of particular note [**Commercial-in-confidence information removed**] experienced a steady and unusually high BASFI score throughout, largely independent of important improvements in disease activity and pain.

Finally, *Figure 25* illustrates patient careers through use of the indicative combination of BASDAI and pain VAS scores suggested in the TAR (section 7.2) as a possible basis for withdrawal of treatment for loss of efficacy. The results are quite similar to those obtained with BASDAI, but are considerably more stable than the pain VAS score.

[**Commercial-in-confidence information removed**] shows clear evidence of a serious loss of efficacy

[**Commercial-in-confidence information removed**]

FIGURE 22 *Patient profiles of BASDAI scores for three nested subgroups*

[**Commercial-in-confidence information removed**]

FIGURE 23 *Patient profiles of pain VAS scores for three nested subgroups*

[**Commercial-in-confidence information removed**]

FIGURE 24 *Patient profiles of BASFI scores for three nested subgroups*

[**Commercial-in-confidence information removed**]

FIGURE 25 *Patient profiles of (BASDAI + pain VAS/10) scores for three nested subgroups*

TABLE 51 *Sensitivity analyses for 110 subgroup selection scenarios (treatment by adalimumab/etanercept) using options in* Figure 17 *on p. 96*

Scenario	Required BASDAI reduction			Proportion selected	Cost per QALY gained											
					A: baseline		B: no progression on treatment		C: 7% p.a. withdrawal rate		D: no spontaneous recovery without Tx		E: 0.05 p.a. long-term progression		B, C and D	
	At 4 weeks	At 8 weeks	At 12 weeks		12 months	20 years	12 months	20 years	12 months	20 years	12 months	20 years	12 months	20 years	12 months	20 years
1	None	None	2	[Commercial-in-confidence information removed]	£55,246	£92,598	£55,144	£83,221	£55,246	£68,952	£49,100	£56,745	£55,251	£92,725	£48,985	£41,787
2	None	None	3		£53,638	£92,265	£53,538	£82,900	£53,638	£68,712	£47,628	£56,346	£53,643	£92,393	£47,515	£41,552
3	None	None	4		£46,373	£92,589	£46,275	£82,494	£46,373	£67,574	£40,677	£54,178	£46,378	£92,722	£40,566	£39,329
4	None	None	5		£35,369	£91,025	£35,283	£77,261	£35,369	£56,441	£30,582	£46,507	£35,374	£91,099	£30,485	**£29,920**
5	None	None	6		**£22,171**	£74,834	**£22,102**	£59,367	**£22,171**	£38,523	**£18,710**	£34,967	**£22,175**	£74,796	**£18,633**	**£17,687**
6	None	0	2		£55,164	£92,583	£55,063	£83,206	£55,164	£68,940	£49,023	£56,725	£55,169	£92,711	£48,908	£41,775
7	None	1	2		£54,469	£92,404	£54,369	£83,043	£54,469	£68,826	£48,401	£56,552	£54,474	£92,531	£48,286	£41,682
8	None	2	2		£53,310	£92,082	£53,211	£82,755	£53,310	£68,630	£47,373	£56,261	£53,315	£92,209	£47,261	£41,531
9	0	0	2		£53,278	£92,288	£53,177	£82,898	£53,278	£68,681	£47,221	£56,269	£53,283	£92,417	£47,107	£41,490
10	0	1	2		£52,484	£92,146	£52,384	£82,756	£52,484	£68,569	£46,477	£56,080	£52,490	£92,275	£46,363	£41,376
11	1	1	2		£50,489	£91,780	£50,390	£82,396	£50,489	£68,287	£44,615	£55,607	£50,494	£91,909	£44,504	£41,096
12	0	2	2		£50,834	£91,738	£50,736	£82,383	£50,834	£68,306	£44,993	£55,675	£50,839	£91,867	£44,882	£41,158
13	1	2	2		£49,342	£91,534	£49,245	£82,163	£49,342	£68,116	£43,568	£55,333	£49,348	£91,662	£43,458	£40,942
14	2	2	2		£43,598	£92,384	£43,501	£82,460	£43,598	£68,206	£38,010	£54,136	£43,603	£92,518	£37,901	£39,803
15	None	0	3		£53,359	£92,140	£53,260	£82,795	£53,359	£68,642	£47,400	£56,268	£53,364	£92,267	£47,288	£41,517
16	None	1	3		£52,558	£91,860	£52,461	£82,553	£52,558	£68,475	£46,710	£56,054	£52,563	£91,988	£46,599	£41,410
17	None	2	3		£51,701	£91,593	£51,606	£82,318	£51,701	£68,313	£45,958	£55,830	£51,706	£91,721	£45,849	£41,295
18	None	3	3		£47,382	£91,166	£47,288	£81,384	£47,382	£66,285	£41,821	£53,924	£47,387	£91,298	£41,714	£39,103
19	0	0	3		£52,002	£92,143	£51,902	£82,728	£52,002	£68,530	£45,999	£55,971	£52,007	£92,271	£45,885	£41,292
20	0	1	3		£51,365	£92,071	£51,265	£82,645	£51,365	£68,455	£45,381	£55,826	£51,370	£92,200	£45,268	£41,198
21	1	1	3		£49,185	£92,295	£49,084	£82,689	£49,185	£68,439	£43,243	£55,359	£49,190	£92,425	£43,130	£40,780
22	0	2	3		£49,657	£91,660	£49,559	£82,268	£49,657	£68,185	£43,842	£55,412	£49,662	£91,788	£43,731	£40,971
23	1	2	3		£47,806	£91,957	£47,707	£82,377	£47,806	£68,190	£41,991	£55,022	£47,811	£92,087	£41,880	£40,586
24	2	2	3		£43,077	£92,462	£42,979	£82,499	£43,077	£68,231	£37,479	£54,065	£43,082	£92,597	£37,370	£39,747
25	0	3	3		£45,072	£93,295	£44,975	£83,021	£45,072	£68,286	£39,420	£54,159	£45,077	£93,430	£39,311	£39,371
26	1	3	3		£43,748	£93,971	£43,649	£83,496	£43,748	£68,769	£38,024	£54,102	£43,753	£94,108	£37,913	£39,318
27	2	3	3		£40,754	£96,563	£40,655	£85,085	£40,754	£69,939	£35,157	£53,525	£40,759	£96,703	£35,047	£38,380
28	3	3	3		£35,942	£104,292	£35,847	£89,157	£35,942	£70,898	£30,732	£51,434	£35,947	£104,415	£30,627	£35,009
29	None	0	4		£43,855	£89,717	£43,765	£80,120	£43,855	£65,156	£38,639	£52,891	£43,860	£89,848	£38,537	£38,503
30	None	1	4		£40,956	£86,278	£40,875	£77,261	£40,956	£62,277	£36,269	£51,321	£40,960	£86,405	£36,177	£37,487
31	None	2	4		£38,926	£84,058	£38,852	£75,400	£38,926	£60,434	£34,570	£50,250	£38,931	£84,184	£34,483	£36,791
32	None	3	4		£37,032	£80,786	£36,959	£72,300	£37,032	£56,081	£32,838	£48,187	£37,037	£80,913	£32,754	£34,590
33	None	4	4		£33,741	£78,230	£33,670	£69,613	£33,741	£52,079	**£29,757**	£46,002	£33,746	£78,357	**£29,676**	£32,227

continued

TABLE 51 *Sensitivity analyses for 110 subgroup selection scenarios (treatment by adalimumab/etanercept) using options in* Figure 17 *on p. 96*

Scenario	Required BASDAI reduction			Proportion selected	Cost per QALY gained											
					A: baseline		B: no progression on treatment		C: 7% p.a. withdrawal rate		D: no spontaneous recovery without Tx		E: 0.05 p.a. long-term progression		B, C and D	
	At 4 weeks	At 8 weeks	At 12 weeks		12 months	20 years	12 months	20 years	12 months	20 years	12 months	20 years	12 months	20 years	12 months	20 years
34	0	0	4	[Commercial-in-confidence information removed]	£45,613	£93,437	£45,510	£83,104	£45,613	£68,060	£39,707	£54,229	£45,617	£93,573	£39,593	£39,288
35	0	1	4		£45,450	£93,630	£45,346	£83,247	£45,450	£68,191	£39,507	£54,248	£45,454	£93,766	£39,393	£39,290
36	1	1	4		£43,888	£94,184	£43,784	£83,622	£43,888	£68,591	£37,910	£54,129	£43,893	£94,321	£37,794	£39,207
37	0	2	4		£43,877	£93,020	£43,777	£82,716	£43,877	£67,721	£38,128	£53,811	£43,882	£93,156	£38,017	£39,037
38	1	2	4		£42,631	£93,731	£42,528	£83,226	£42,631	£68,240	£36,806	£53,794	£42,635	£93,869	£36,693	£39,012
39	2	2	4		£39,379	£93,838	£39,279	£83,217	£39,379	£68,428	£33,795	£53,315	£39,384	£93,976	£33,684	£38,771
40	0	3	4		£41,253	£94,236	£41,156	£83,241	£41,253	£67,671	£35,717	£52,948	£41,258	£94,373	£35,608	£37,896
41	1	3	4		£40,147	£95,470	£40,047	£84,162	£40,147	£68,647	£34,513	£53,088	£40,152	£95,609	£34,402	£37,979
42	2	3	4		£38,104	£96,384	£38,005	£84,825	£38,104	£69,549	£32,579	£53,016	£38,109	£96,525	£32,469	£38,000
43	3	3	4		£33,804	£102,794	£33,710	£87,891	£33,804	£69,359	**£28,702**	£50,736	£33,809	£102,917	**£28,598**	£34,477
44	0	4	4		£36,165	£95,097	£36,073	£83,144	£36,165	£66,478	£31,072	£51,148	£36,170	£95,234	£30,969	£35,885
45	1	4	4		£35,308	£96,489	£35,213	£84,179	£35,308	£67,537	£30,126	£51,349	£35,313	£96,627	£30,022	£35,994
46	2	4	4		£34,026	£98,995	£33,929	£86,081	£34,026	£69,757	**£28,805**	£51,768	£34,031	£99,135	**£28,699**	£36,319
47	3	4	4		£30,986	£103,535	£30,893	£88,302	£30,986	£69,756	**£26,060**	£50,378	£30,991	£103,661	**£25,958**	£34,241
48	4	4	4		**£23,626**	£106,755	**£23,544**	£88,072	**£23,626**	£65,224	**£19,548**	£46,802	**£23,630**	£106,823	**£19,459**	£30,306
49	None	0	5		£32,624	£74,359	£32,549	£64,325	£32,624	£45,766	**£28,466**	£42,483	£32,628	£74,454	**£28,381**	**£27,100**
50	None	1	5		**£28,778**	£60,180	**£28,715**	£52,880	**£28,778**	£36,576	**£25,311**	£38,102	**£28,783**	£60,293	**£25,239**	**£24,061**
51	None	2	5		**£26,529**	£52,996	**£26,473**	£46,932	**£26,529**	£31,881	**£23,438**	£35,526	**£26,534**	£53,118	**£23,372**	**£22,267**
52	None	3	5		**£23,986**	£39,177	**£23,934**	£34,415	**£23,986**	**£22,872**	**£21,191**	**£29,450**	**£23,991**	£39,307	**£21,131**	**£16,415**
53	None	4	5		**£22,034**	£36,704	**£21,986**	£32,365	**£22,034**	**£21,548**	**£19,481**	**£28,242**	**£22,038**	£36,825	**£19,425**	**£15,773**
54	None	5	5		**£22,728**	£46,172	**£22,674**	£40,182	**£22,728**	**£27,267**	**£19,882**	£31,589	**£22,732**	£46,269	**£19,820**	**£18,078**
55	0	0	5		£37,409	£96,327	£37,312	£81,169	£37,409	£59,213	£32,073	£47,769	£37,413	£96,408	£31,966	£30,525
56	0	1	5		£37,318	£97,621	£37,221	£82,096	£37,318	£59,907	£31,921	£47,956	£37,323	£97,703	£31,813	£30,624
57	1	1	5		£36,119	£101,370	£36,018	£84,750	£36,119	£61,985	£30,643	£48,340	£36,123	£101,448	£30,533	£30,864
58	0	2	5		£36,013	£96,198	£35,918	£80,974	£36,013	£58,983	£30,786	£47,445	£36,018	£96,282	£30,681	£30,303
59	1	2	5		£35,109	£100,529	£35,011	£84,077	£35,109	£61,426	**£29,768**	£47,995	£35,114	£100,610	**£29,661**	£30,650
60	2	2	5		£32,227	£106,020	£32,130	£87,921	£32,227	£64,678	**£27,071**	£48,331	£32,232	£106,094	**£26,965**	£30,977
61	0	3	5		£33,593	£102,601	£33,500	£82,646	£33,593	£56,844	**£28,570**	£44,998	£33,597	£102,606	**£28,468**	**£26,599**
62	1	3	5		£32,738	£110,025	£32,642	£87,558	£32,738	£59,996	**£27,599**	£45,724	£32,743	£110,016	**£27,494**	**£27,019**
63	2	3	5		£30,769	£121,423	£30,672	£94,929	£30,769	£64,904	**£25,698**	£46,589	£30,773	£121,388	**£25,593**	**£27,633**
64	3	3	5		**£27,686**	£118,962	**£27,596**	£93,126	**£27,686**	£63,750	**£23,041**	£45,691	**£27,690**	£118,926	**£22,943**	**£27,165**
65	0	4	5		£30,722	£100,947	£30,634	£81,348	£30,722	£55,999	**£26,061**	£44,187	£30,726	£100,950	**£25,964**	**£26,176**
66	1	4	5		**£29,730**	£106,986	**£29,640**	£85,322	**£29,730**	£58,501	**£24,993**	£44,734	**£29,734**	£106,979	**£24,894**	**£26,471**

continued

TABLE 51 *Sensitivity analyses for 110 subgroup selection scenarios (treatment by adalimumab/etanercept) using options in* Figure 17 *on p. 96*

Scenario	Required BASDAI reduction			Proportion selected	Cost per QALY gained											
					A: baseline		B: no progression on treatment		C: 7% p.a. withdrawal rate		D: no spontaneous recovery without Tx		E: 0.05 p.a. long-term progression		B, C and D	
	At 4 weeks	At 8 weeks	At 12 weeks		12 months	20 years	12 months	20 years	12 months	20 years	12 months	20 years	12 months	20 years	12 months	20 years
67	2	4	5	[Commercial-in-confidence information removed]	**£28,398**	£120,890	**£28,306**	£94,384	**£28,398**	£64,492	**£23,613**	£46,026	**£28,403**	£120,855	**£23,512**	**£27,319**
68	3	4	5		**£26,384**	£123,632	**£26,294**	£96,028	**£26,384**	£65,657	**£21,848**	£45,890	**£26,388**	£123,587	**£21,751**	**£27,325**
69	4	4	5		**£20,302**	£131,261	**£20,224**	£93,800	**£20,302**	£57,190	**£16,549**	£40,299	**£20,306**	£131,052	**£16,464**	**£20,713**
70	0	5	5		**£26,767**	£96,002	**£26,687**	£77,648	**£26,767**	£53,391	**£22,588**	£42,668	**£26,772**	£96,014	**£22,498**	**£25,260**
71	1	5	5		**£25,910**	£102,806	**£25,827**	£82,219	**£25,910**	£56,353	**£21,659**	£43,407	**£25,914**	£102,805	**£21,568**	**£25,696**
72	2	5	5		**£24,886**	£114,862	**£24,800**	£90,160	**£24,886**	£61,593	**£20,580**	£44,626	**£24,890**	£114,839	**£20,487**	**£26,479**
73	3	5	5		**£23,193**	£117,957	**£23,110**	£92,062	**£23,193**	£62,882	**£19,078**	£44,605	**£23,197**	£117,926	**£18,987**	**£26,528**
74	4	5	5		**£18,645**	£128,531	**£18,569**	£91,968	**£18,645**	£56,029	**£15,086**	£39,681	**£18,649**	£128,335	**£15,004**	**£20,312**
75	5	5	5		**£13,828**	£153,864	**£13,760**	£91,573	**£13,828**	£46,224	**£10,825**	£32,571	**£13,832**	£153,287	**£10,751**	**£12,234**
76	None	0	6		**£19,650**	£48,096	**£19,593**	£39,913	**£19,650**	**£26,232**	**£16,781**	**£29,230**	**£19,655**	£48,153	**£16,716**	**£14,170**
77	None	1	6		**£17,244**	£32,598	**£17,197**	**£27,717**	**£17,244**	**£18,025**	**£14,882**	**£24,231**	**£17,248**	£32,710	**£14,827**	**£11,093**
78	None	2	6		**£15,622**	**£25,877**	**£15,582**	**£22,196**	**£15,622**	**£14,178**	**£13,552**	**£21,409**	**£15,627**	**£26,013**	**£13,504**	**£9,358**
79	None	3	6		**£13,642**	**£21,801**	**£13,606**	**£18,751**	**£13,642**	**£11,717**	**£11,828**	**£19,320**	**£13,647**	**£21,952**	**£11,784**	**£8,070**
80	None	4	6		**£12,096**	**£19,010**	**£12,064**	**£16,414**	**£12,096**	**£10,170**	**£10,487**	**£17,748**	**£12,101**	**£19,157**	**£10,448**	**£7,249**
81	None	5	6		**£10,580**	**£16,861**	**£10,551**	**£14,582**	**£10,580**	**£8,922**	**£9,147**	**£16,409**	**£10,585**	**£17,007**	**£9,111**	**£6,526**
82	None	6	6		**£11,077**	**£16,748**	**£11,039**	**£13,266**	**£11,077**	**£7,322**	**£9,283**	**£14,518**	**£11,082**	**£16,922**	**£9,239**	**£2,830**
83	0	0	6		**£24,617**	£83,816	**£24,538**	£65,298	**£24,617**	£41,553	**£20,598**	£36,639	**£24,622**	£83,780	**£20,511**	**£18,339**
84	0	1	6		**£25,263**	£86,697	**£25,181**	£67,181	**£25,263**	£42,547	**£21,098**	£37,122	**£25,267**	£86,659	**£21,009**	**£18,556**
85	1	1	6		**£25,962**	£95,661	**£25,875**	£72,922	**£25,962**	£45,642	**£21,502**	£38,335	**£25,967**	£95,597	**£21,407**	**£19,169**
86	0	2	6		**£24,514**	£84,437	**£24,434**	£65,602	**£24,514**	£41,561	**£20,448**	£36,648	**£24,519**	£84,410	**£20,360**	**£18,253**
87	1	2	6		**£24,961**	£94,134	**£24,875**	£71,822	**£24,961**	£44,928	**£20,632**	£37,918	**£24,966**	£94,080	**£20,539**	**£18,902**
88	2	2	6		**£23,049**	£108,042	**£22,963**	£80,214	**£23,049**	£49,382	**£18,797**	£38,955	**£23,053**	£107,942	**£18,705**	**£19,505**
89	0	3	6		**£22,961**	£90,201	**£22,882**	£69,266	**£22,961**	£43,664	**£19,038**	£37,055	**£22,965**	£90,150	**£18,952**	**£18,551**
90	1	3	6		**£23,473**	£100,815	**£23,389**	£75,906	**£23,473**	£47,180	**£19,287**	£38,338	**£23,478**	£100,735	**£19,195**	**£19,195**
91	2	3	6		**£22,487**	£117,159	**£22,401**	£85,596	**£22,487**	£52,274	**£18,264**	£39,659	**£22,492**	£117,026	**£18,171**	**£19,958**
92	3	3	6		**£19,720**	£116,232	**£19,640**	£84,818	**£19,720**	£51,852	**£15,891**	£38,991	**£19,724**	£116,092	**£15,805**	**£19,649**
93	0	4	6		**£20,894**	£88,399	**£20,820**	£68,006	**£20,894**	£43,006	**£17,262**	£36,426	**£20,899**	£88,342	**£17,180**	**£18,271**
94	1	4	6		**£21,267**	£96,955	**£21,188**	£73,375	**£21,267**	£45,826	**£17,416**	£37,485	**£21,271**	£96,877	**£17,330**	**£18,779**
95	2	4	6		**£20,843**	£116,325	**£20,760**	£84,969	**£20,843**	£51,937	**£16,857**	£39,239	**£20,847**	£116,188	**£16,768**	**£19,761**
96	3	4	6		**£18,806**	£121,040	**£18,727**	£87,502	**£18,806**	£53,232	**£15,072**	£39,186	**£18,810**	£120,881	**£14,987**	**£19,785**
97	4	4	6		**£13,786**	£113,568	**£13,717**	£82,614	**£13,786**	£50,464	**£10,752**	£37,440	**£13,790**	£113,427	**£10,677**	**£18,824**
98	0	5	6		**£18,557**	£84,317	**£18,489**	£65,207	**£18,557**	£41,421	**£15,259**	£35,422	**£18,562**	£84,265	**£15,183**	**£17,754**
99	1	5	6		**£19,103**	£93,798	**£19,030**	£71,279	**£19,103**	£44,732	**£15,589**	£36,690	**£19,107**	£93,720	**£15,509**	**£18,414**

continued

TABLE 51 *Sensitivity analyses for 110 subgroup selection scenarios (treatment by adalimumab/etanercept) using options in* Figure 17 *on p. 96*

Scenario	Required BASDAI reduction			Proportion selected	Cost per QALY gained											
					A: baseline		B: no progression on treatment		C: 7% p.a. withdrawal rate		D: no spontaneous recovery without Tx		E: 0.05 p.a. long-term progression		B, C and D	
	At 4 weeks	At 8 weeks	At 12 weeks		12 months	20 years	12 months	20 years	12 months	20 years	12 months	20 years	12 months	20 years	12 months	20 years
100	2	5	6	[Commercial-in-confidence information removed]	**£18,636**	£111,286	**£18,559**	£81,846	**£18,636**	£50,328	**£15,011**	£38,324	**£18,640**	£111,157	**£14,927**	**£19,314**
101	3	5	6		**£16,881**	£116,200	**£16,807**	£84,535	**£16,881**	£51,685	**£13,458**	£38,353	**£16,885**	£116,051	**£13,377**	**£19,360**
102	4	5	6		**£13,196**	£113,346	**£13,129**	£82,429	**£13,196**	£50,380	**£10,260**	£37,268	**£13,201**	£113,204	**£10,186**	**£18,752**
103	5	5	6		**£9,428**	£130,822	**£9,368**	£80,553	**£9,428**	£41,430	**£6,965**	£30,423	**£9,432**	£130,359	**£6,899**	**£11,006**
104	0	6	6		**£14,455**	£74,703	**£14,393**	£53,309	**£14,455**	£30,605	**£11,626**	**£27,809**	**£14,459**	£74,533	**£11,557**	**£9,986**
105	1	6	6		**£15,483**	£86,502	**£15,416**	£60,030	**£15,483**	£33,630	**£12,407**	**£29,182**	**£15,487**	£86,280	**£12,333**	**£10,575**
106	2	6	6		**£15,032**	£117,105	**£14,961**	£75,463	**£15,032**	£39,937	**£11,843**	£31,200	**£15,036**	£116,735	**£11,766**	**£11,442**
107	3	6	6		**£13,623**	£129,993	**£13,554**	£81,154	**£13,623**	£42,072	**£10,596**	£31,521	**£13,627**	£129,548	**£10,521**	**£11,597**
108	4	6	6		**£10,528**	£125,839	**£10,465**	£78,625	**£10,528**	£40,824	**£7,923**	£30,502	**£10,532**	£125,402	**£7,854**	**£11,066**
109	5	6	6		**£8,500**	£126,107	**£8,442**	£78,324	**£8,500**	£40,548	**£6,167**	**£29,981**	**£8,504**	£125,659	**£6,103**	**£10,799**
110	6	6	6		**£5,699**	£129,014	**£5,646**	£58,021	**£5,699**	**£23,124**	**£3,744**	**£17,969**	**£5,703**	£127,895	**£3,685**	**£856**

ICERs ⩽£30,000 per QALY gained are shown in bold.
Tx, treatment.

after an initial good response, indicating the need for periodic patient reviews. However, for other patients occasional minor excursions away from the efficacy zone are generally resolved by the next 4- or 6-weekly observation. This suggests that it would be wiser to require, for instance, two further confirmatory poor observations of BASDAI or the BASDAI/pain compound score as the signal for withdrawal of treatment.

Summary

The additional data analysis and modelling undertaken demonstrated that it is possible to define sets of response criteria that identify subgroups of patients who respond strongly to anti-TNF-α therapy, and for whom use can be considered cost-effective. In these particular scenarios it is necessary to apply much more exacting thresholds of required reductions in the BASDAI score as the basis for continuing with treatment beyond a test period of 12 weeks.

The use of infliximab has not been shown to be cost-effective for any subgroup of treated patients, in accordance with the conclusions reported in the TAR.

When either adalimumab or etanercept is used, it is necessary to require a reduction in BASDAI score after 12 weeks treatment of at least 5 points and preferably 6 points. In addition, an early assessment should be made after 8 weeks of treatment, requiring achievement of a minimum reduction of between 2 and 6 points. No assessment is appropriate at 4 weeks, since it appears that either it has no influence on patient selection, or in other cases it prematurely discontinues treatment for some patients who would otherwise respond well (the effect on ICERs being variable depending on the balance between the extra cost saving and the extra benefit forgone). The proportion of patients who can be expected to continue on treatment in the long term varies between [**Commercial-in-confidence information removed**] and [**Commercial-in-confidence information removed**]%, depending on the chosen threshold values.

It appears that subgroups defined by either a 5- or 6-point reduction in BASDAI at 12 weeks benefit from generally stable outcome gains, at least for the first 12 months of treatment, although the experience of pain is subject to more short-term fluctuations than the BASDAI. The BASFI generally mirrors the other measures, but is not suitable for defining an efficacy standard, since it is possible for patients with very poor BASFI to benefit from good general response to treatment. It is important to monitor the effect of treatment regularly and to consider withdrawal when BASDAI scores (with or without pain VAS) remain high for at least 12 weeks.

Finally, it must be reiterated that these cost-effectiveness findings only relate to circumstances where patients undergo a single efficacy test period of treatment. In the event that patients routinely start a second or third test treatment on failure of the first, the probability that treatment is cost-effective will be markedly reduced in all cases.

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We look forward to hearing from you.

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