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A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness

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Abstract

A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness

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Objectives: This report reviews the clinical effectiveness and cost-effectiveness of adalimumab, etanercept and infliximab, agents that inhibit tumour necrosis factor-α (TNF-α), when used in the treatment of rheumatoid arthritis (RA) in adults.

Data sources: Electronic databases were searched up to February 2005.

Review methods: Systematic reviews of the literature on effectiveness and cost-effectiveness were undertaken and industry submissions to the National Institute for Health and Clinical Excellence (NICE) were reviewed. Meta-analyses of effectiveness data were also undertaken for each agent. The Birmingham Rheumatoid Arthritis Model (BRAM), a simulation model, was further developed and used to produce an incremental cost-effectiveness analysis.

Results: Twenty-nine randomised controlled trials (RCTs), most of high quality, were included. The only head-to-head comparisons were against methotrexate. For patients with short disease duration (≤ 3 years) who were naïve to methotrexate, adalimumab was marginally less and etanercept was marginally more effective than methotrexate in reducing symptoms of RA. Etanercept was better tolerated than methotrexate. Both adalimumab and etanercept were more effective than methotrexate in slowing radiographic joint damage. Etanercept was also marginally more effective and better tolerated than methotrexate in patients with longer disease durations who had not failed methotrexate treatment. Infliximab is only licensed for use with methotrexate. All three agents, either alone (where so licensed) or in combination with ongoing disease-modifying antirheumatic drugs (DMARDs), were effective in reducing the symptoms and signs of RA in patients with established disease. At the licensed dose, the numbers needed to treat (NNTs) (95% CI) required to produce an American College for Rheumatology (ACR) response compared with placebo were: ACR20: adalimumab 3.6 (3.1 to 4.2), etanercept 2.1 (1.9 to 2.4), infliximab 3.2 (2.7 to 4.0); ACR50: adalimumab 4.2 (3.7 to 5.0), etanercept 3.1 (2.7 to 3.6), infliximab 5.0 (3.8 to 6.7); and ACR70: adalimumab 7.7 (5.9 to 11.1), etanercept 7.7 (6.3 to 10.0), infliximab 11.1 (7.7 to 20.0). In patients who were naïve to methotrexate, or who had not previously failed methotrexate treatment, a TNF inhibitor combined with methotrexate was significantly more effective than methotrexate alone. Infliximab combined with methotrexate had an increased risk of serious infections. All ten published economic evaluations met standard criteria for quality, but the incremental cost-effectiveness ratios (ICERs) ranged from being within established thresholds to being very high because of varying assumptions and parameters. All three sponsors who submitted economic models made assumptions favourable to their product. BRAM incorporates improvements in quality of life and mortality, but assumes no effect of TNF inhibitors on joint replacement. For use in accordance with current NICE guidance as the third DMARD in a sequence of DMARDs, the base-case ICER was around £30,000 per quality-adjusted life-year (QALY) in early RA and

£50,000 per QALY in late RA. Sensitivity analyses showed that the results were sensitive to the estimates of Health Assessment Questionnaire (HAQ) progression while on TNF inhibitors and the effectiveness of DMARDs, but not to changes in mortality ratios per unit HAQ. TNF inhibitors are most cost-effective when used last. The ICER for etanercept used last is £24,000 per QALY, substantially lower than for adalimumab (£30,000 per QALY) or infliximab (£38,000 per QALY). First line use as monotherapy generates ICERs around £50,000 per QALY for adalimumab and etanercept. Using the combination of methotrexate and a TNF inhibitor as first line treatment generates much higher ICERs, as it precludes subsequent use of methotrexate, which is cheap. The ICERs for sequential use are of the same order as using the TNF inhibitor alone.

Conclusions: Adalimumab, etanercept and infliximab are effective treatments compared with placebo for RA patients who are not well controlled by conventional DMARDs, improving control of symptoms, improving physical function, and slowing radiographic changes in joints. The combination of a TNF inhibitor with methotrexate was more effective than methotrexate alone in early RA, although the clinical relevance of this additional benefit is yet to be established, particularly in view of the well-established effectiveness of MTX alone. An increased risk of serious infection cannot be ruled out for the combination of methotrexate with adalimumab or infliximab. The results of the economic evaluation based on BRAM are consistent with the observations from the review of clinical effectiveness, including the ranking of treatments. TNF inhibitors are most cost-effective when used as last active therapy. In this analysis, other things being equal, etanercept may be the TNF inhibitor of choice, although this may also depend on patient preference as to route of administration. The next most cost-effective use of TNF inhibitors is third line, as recommended in the 2002 NICE guidance. Direct comparative RCTs of TNF inhibitors against each other and against other DMARDs, and sequential use in patients who have failed a previous TNF inhibitor, are needed. Longer term studies of the quality of life in patients with RA and the impact of DMARDs on this are needed, as are longer studies that directly assess effects on joint replacement, other morbidity and mortality.

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

ACR20 A 20% improvement in the counts of the number of tender and swollen joints and at least three items from the following: observer evaluation of overall disease activity, patient evaluation of overall disease activity, patient evaluation of pain, a score of physical disability, and improvements in blood acute-phase responses.

ACR50 A 50% improvement in the parameters described above.

ACR70 A 70% improvement in the parameters described above.

ACR-N A single number that describes the percentage of improvement from baseline that a patient experiences; it is derived from the same clinical parameters as the ACR response. Details are provided in Appendix 1.

Anti-TNFs Biological agents that block tumour necrosis factor activity.

Cytokines Small peptides that mediate signals between cells, primarily in a localised environment.

Health Assessment Questionnaire (HAQ) Designed to assess the physical function of patients. Scores range from 0 (no functional impairment) to 3 (most impaired). Details are provided in Appendix 1.

Disease Activity Score (DAS) Calculated using a formula that includes counts for tender (53 joints) and swollen joints (44 joints), an evaluation by the patient of general health and blood acute-phase responses. Scale 0 (best) to 10 (most active disease).

DAS28 Disease Activity Score 28, similar to DAS above but using only 28 joints for assessment. Scale 0 (best) to 10 (most active disease).

List of abbreviations

ACR	American College for Rheumatology
Adal	adalimumab
ADORE	Add Enbrel or Replace Methotrexate (study)
ARAMIS	Arthritis, Rheumatism and Aging Medical Information System
ARMADA	Anti-Tumor Necrosis Factor Research Study Program of the Monoclonal Antibody Adalimumab (D2E7) in Rheumatoid Arthritis
ASPIRE	Active-controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset
ATTRACT	Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy
AUC	area under the curve
AZA	azathioprine
BCP	biochemical profile
BeSt	Behandel–Strategieën study
BRAM	Birmingham Rheumatoid Arthritis Model
BSR	British Society for Rheumatology
BSRBR	British Society for Rheumatology Biologics Register
CHEC	Consensus on Health Economic Criteria
CI	Confidence interval
CRP	C-reactive protein
CXR	chest X-ray
CyA	ciclosporin
DAS	Disease Activity Score
DMARD	disease-modifying antirheumatic drug
DPen	penicillamine
EMEA	European Medicines Agency
EQ-5D	EuroQol 5 Dimensions
ERA	Early Rheumatoid Arthritis study
ESR	erythrocyte sedimentation rate
Etan	etanercept
EULAR	European League Against Rheumatism
FBC	full blood count
FDA	Food and Drug Administration
GPRD	General Practice Research Database
GST	injectable gold
HAQ	Health Assessment Questionnaire
HCQ	hydroxychloroquine
HLA	human leucocyte antigen
i.m.	intramuscular
i.v.	intravenous
ICER	incremental cost-effectiveness ratio
IgG	immunoglobulin G
IL-1	interleukin-1
IL-2	interleukin-2
IL-6	interleukin-6
Infl	infliximab
IQR	interquartile range
ITT	intention-to-treat
LEF	leflunomide

continued

List of abbreviations *continued*

MCP	metacarpophalangeal joint
MHAQ	Modified Health Assessment Questionnaire
MRI	magnetic resonance imaging
MTX	methotrexate
NA	not applicable
NICE	National Institute for Health and Clinical Excellence
NNH	number needed to harm
NNT	number needed to treat
NR	not reported
NSAID	non-steroidal anti-inflammatory drug
Pall	palliation
PCT	primary care trust
PREMIER	A prospective, randomised trial (DE013) comparing adalimumab, methotrexate, and the combination of both over 2 years in patients with early rheumatoid arthritis
PSS	Personal and Social Services
QoL	quality of life
QALY	quality-adjusted life-year
QSE	quasi-standard error
TNF-R	tumour necrosis factor receptor
RA	rheumatoid arthritis
RCT	randomised controlled trial
RD	risk difference
RR	relative risk
s.c.	subcutaneous
SAE	serious adverse event
SD	standard deviation
SDD	smallest detectable difference
SEER	Surveillance Epidemiology and End Results
SEM	standard error of the mean
SF-36	Short Form 36
SJC	swollen joint count
SLE	systemic lupus erythematosus
SMD	standardised mean difference
SSZ	sulfasalazine
STAR	Safety Trial of Adalimumab in Rheumatoid Arthritis
START	Safety Trial for Rheumatoid Arthritis with Remicade Therapy
sTNFR	soluble tumour necrosis factor receptor
TACE	tumour necrosis factor-α converting enzyme
TEMPO	Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes
TJC	tender joint count
TNF	tumour necrosis factor
TNF-α	tumour necrosis factor-α
VAS	visual analogue scale
WMD	weighted mean difference
WR	weighted response

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

Rheumatoid arthritis (RA) is a chronic illness characterised by inflammation of the synovial tissue in joints, which can lead to joint destruction. Treatment aims to control pain and inflammation, reduce joint damage and disability, and maintain or improve physical function and quality of life.

Description of technology

Drugs that inhibit joint destruction are known as disease-modifying antirheumatic drugs (DMARDs). There are around eight DMARDs, which are not biologics, in common use in the UK. These drugs are not always effective, may lose effectiveness with time or may cause adverse effects. Alternative DMARDs are therefore needed and tumour necrosis factor (TNF) inhibitors are one class of new agents that has been developed.

Tumour necrosis factor-α (TNF-α) is a cytokine that plays an important role in joint inflammation. TNF inhibitors have been designed to inhibit its actions. Three are currently licensed for use in the UK:

- *adalimumab*: given by subcutaneous injections (40 mg) every other week, but the dose may be increased to weekly if the disease is poorly controlled
- *etanercept*: given by a once-weekly subcutaneous injection (50 mg) or twice weekly (25 mg each)
- *infliximab*: given by intravenous infusion (3 mg kg^{-1}) at 0, 2 and 6 weeks and at 8-weekly intervals thereafter. It is only licensed for use concomitantly with methotrexate.

Current recommendations and service provision

National Institute for Health and Clinical Excellence (NICE) 2002 guidance for the use of TNF inhibitors recommended that:

- etanercept and infliximab be used in patients with clinically active disease that has not responded adequately to at least two DMARDs including methotrexate (unless contraindicated)
- details of patients and their treatment should be recorded in a registry.

There is variable implementation of the guidance, with limited access to these agents in some areas. Where used, these drugs have tended to be used after people have failed two or more DMARDs (as recommended), but they are also being used sequentially, after patients fail on a TNF inhibitor (not recommended). There are currently around 10,000 patients (about 2% of the RA population) on these drugs in the UK, with an estimated annual cost to the NHS of around £100 million. These figures are rising.

Since 2002 more evidence has become available and a new agent, adalimumab, has been licensed for use in the UK. In addition, all three agents have been licensed for use in early disease.

Objective to the report

This report reviews the clinical and cost-effectiveness of adalimumab, etanercept and infliximab when used in the treatment of RA in adults.

Methods

Systematic reviews of the literature on effectiveness and cost-effectiveness were undertaken. A wide range of databases was searched and information sought from researchers and industry. Industry submissions to NICE were reviewed. Meta-analyses of effectiveness data were undertaken for each agent.

The Birmingham Rheumatoid Arthritis Model (BRAM), a simulation model, was further developed and used to produce an incremental cost-effectiveness analysis.

Results

Number and quality of studies

Twenty-nine randomised controlled trails (RCTs), most of high quality, were included: nine on

adalimumab, 11 on etanercept and nine on infliximab. There were 14 economic evaluations: three from industry submissions, one from the British Society for Rheumatology and ten from published literature.

Direction of evidence and size of treatment effect

Direct comparison with standard treatments

The only head-to-head comparisons were against methotrexate. For patients with short disease duration (≤ 3 years) who were naïve to methotrexate:

- adalimumab was marginally less and etanercept was marginally more effective than methotrexate in reducing symptoms of RA; etanercept was better tolerated than methotrexate
- both adalimumab and etanercept were more effective than methotrexate in slowing radiographic joint damage.

Etanercept was also marginally more effective and better tolerated than methotrexate in patients with longer disease durations who had not failed methotrexate treatment. Infliximab is only licensed for use with methotrexate.

TNF inhibitors versus placebo

All the three agents, either alone (where so licensed) or in combination with ongoing DMARDs, were effective in reducing the symptoms and signs of RA in patients with established disease. At the licensed dose the numbers needed to treat (95% CI) required to produce an American Colleague for Rheumatology (ACR) response compared with placebo were: ACR20: adalimumab 3.6 (3.1 to 4.2), etanercept 2.1 (1.9 to 2.4), infliximab 3.2 (2.7 to 4.0); ACR50: adalimumab 4.2 (3.7 to 5.0), etanercept 3.1 (2.7 to 3.6), infliximab 5.0 (3.8 to 6.7); ACR70: adalimumab 7.7 (5.9 to 11.1), etanercept 7.7 (6.3, to 10.0), infliximab 11.1 (7.7 to 20.0).

Combination (TNF inhibitor plus methotrexate) versus methotrexate

In patients who were naïve to methotrexate, or who had not previously failed methotrexate treatment, a TNF inhibitor combined with methotrexate was significantly more effective than methotrexate alone. Infliximab combined with methotrexate had an increased risk of serious infections (relative risk 2.74, 95% CI 1.12 to 6.70; number needed to harm 25, 95% CI 16.7 to 100).

Existing economic evaluations

All ten published economic evaluations met standard criteria for quality, but the incremental cost-effectiveness ratios (ICERs) ranged from being within established thresholds to being very high because of varying assumptions and parameters. All three sponsors submitted economic models. All made assumptions favourable to their product (e.g. assuming that 'responders' can be separated from 'non-responders' and choosing the most favourable trial data for effectiveness).

Cost-effectiveness

BRAM incorporates improvements in quality of life and mortality, but assumes no effect of TNF inhibitors on joint replacement. For use in accordance with current NICE guidance as the third DMARD in a sequence of DMARDs, the base-case ICER was around £30,000 per quality-adjusted life-year (QALY) in early RA and £50,000 per QALY in late RA. Sensitivity analyses showed that the results were sensitive to the estimates of Health Assessment Questionnaire (HAQ) progression while on TNF inhibitors and the effectiveness of DMARDs, but not to changes in mortality ratios per unit HAQ.

TNF inhibitors are most cost-effective when used last. The ICER for etanercept used last is £24,000 per QALY, substantially lower than for adalimumab (£30,000 per QALY) or infliximab (£38,000 per QALY). First line use as monotherapy generates ICERs around £50,000 per QALY for adalimumab and etanercept. Using the combination of methotrexate and a TNF inhibitor as first line treatment generates much higher ICERs, as it precludes subsequent use of methotrexate, which is cheap. The ICERs for sequential use are of the same order as using the TNF inhibitor alone.

Conclusions

Adalimumab, etanercept and infliximab are effective treatments compared with placebo for RA patients who are not well controlled by conventional DMARDs, improving control of symptoms, improving physical function and slowing radiographic changes in joints. When used alone, adalimumab is marginally less effective and etanercept is marginally more effective than methotrexate, in methotrexate-naïve patients. The combination of a TNF inhibitor with methotrexate was more effective than methotrexate alone in early RA, although the clinical relevance of this additional benefit is yet to be established, particularly in view of the well-established effectiveness of MTX alone. In addition, an

increased risk of serious infection cannot be ruled out for the combination of methotrexate with adalimumab or infliximab.

Results of published economic evaluations vary: some analyses suggest that the use of TNF inhibitors may fall within the usual acceptable cost-effectiveness ranges, whereas others report very high ICERs. Although most are of high quality, none of them uses all the appropriate parameters, effectiveness data, perspective and comparators required to make their results generalisable to the NHS context. The societal perspective generates more favourable ICERs. All economic evaluations submitted by the manufacturers report ICERs that fall within the currently accepted thresholds of cost-effectiveness. However, in the authors' opinion, these models make assumptions and use data that favour the TNF inhibitor being evaluated, the appropriateness of which can be questioned.

The results of the economic evaluation based on BRAM are consistent with the observations from the review of clinical effectiveness, including the ranking of treatments. TNF inhibitors are most cost-effective when used as last active therapy, with the ICER for etanercept (£24,000 per QALY) being significantly lower than the ICER for adalimumab (£30,000 per QALY) or infliximab (£38,000 per QALY). Other things being equal, etanercept would be, therefore, the TNF inhibitor of choice based on this evidence. However, the most appropriate choice of TNF inhibitor may also depend on patient preference as to route of administration.

The next most cost-effective use of TNF inhibitors is third line, as recommended in the 2002 NICE guidance, which gives ICERs around £30,000 per QALY using early RA effectiveness data. Using data for late RA, however, gives an ICER of around £50,000 per QALY for etanercept, with higher figures for adalimumab and infliximab. First-line use gives ICERs around £50,000 per QALY for adalimumab and etanercept as monotherapies with much higher figures for combinations with methotrexate.

Sequential use of TNF inhibitors was modelled, with the TNF inhibitors starting as third line therapy and using the 'late RA' values for the TNF inhibitors. The results are similar to those using the given TNF inhibitor as the sole TNF inhibitor in third place, except that the two other TNF inhibitors are somewhat less cost-effective if used after etanercept.

Recommendations for further research

Direct comparative RCTs of TNF inhibitors against each other and against other DMARDs, and sequential use in patients who have failed a previous TNF inhibitor, are needed. Longer term studies of the quality of life in patients with RA and the impact of DMARDs on this are needed, as are longer studies that directly assess effects on joint replacement, other morbidity and mortality.

Chapter 1

Aims of the review

The aims of this review were:

- To provide a background on rheumatoid arthritis (RA), including epidemiology, current therapeutic options, and impact of disease on individuals and health services.
- To update[1] and undertake a systematic review and meta-analysis of the clinical benefits and adverse effects of adalimumab, etanercept and infliximab for RA.
- To review published cost-effectiveness and cost–utility studies of these agents and economic evaluations included in manufacturers' submissions.
- To adapt the Birmingham Rheumatoid Arthritis Model (BRAM)[2,3] to evaluate the cost-effectiveness of these agents compared with other treatment options.

Chapter 2
Background

Summary

RA is a common, chronic, inflammatory condition causing systemic illness and pain, swelling and destruction of the joints. The cause is not known. Treatment aims to control pain and inflammation, reduce joint damage and disability, and maintain or improve physical function and quality of life.

Although there are a number of disease-modifying drugs for this condition these are of limited efficacy and are often withdrawn because of toxicity or loss of effectiveness. New treatments are needed. Tumour necrosis factor (TNF) inhibitors are new biological agents that have been designed to interrupt the inflammatory pathway. Three are licensed for use in the UK: adalimumab, etanercept and infliximab.

National Institute for Health and Clinical Excellence (NICE) guidance for the use of TNF inhibitors was produced in 2002. Guidance recommends that etanercept and infliximab should only be used in patients who have tried and failed conventional agents and that details of patients and their treatment should be recorded in a registry. There is variable implementation of the guidance with limited access to these agents in some areas. Where the drugs are used they tend to be used after people have failed two or more disease-modifying antirheumatic drugs (DMARDs), as recommended, but they are also used sequentially when patients fail on a previous TNF inhibitor (not recommended). There are currently around 10,000 patients on these drugs in the UK, with an annual cost to the NHS of £100 million. These figures are rising.

Since this guidance more evidence has become available and a new agent, adalimumab, has been licensed for use in the UK. All three agents have also now been licensed for use early in the disease.

This report reviews evidence about the effectiveness and cost-effectiveness of all three agents when used both early and later in the disease.

Description of underlying health problem

Clinical features of RA

RA is a systemic inflammatory disorder that most often begins between the ages of 40 and 70 years. It is more common in women than in men and is characterised, pathologically, by an inflammatory reaction and increased cellularity of the lining layer of synovial joints. RA causes pain, swelling and stiffness of affected joints: these symptoms are often worse in the morning and after periods of inactivity. Other organ systems, occasionally with potentially life-threatening complications, may also be affected. Patients commonly experience fatigue and blood abnormalities such as anaemia and a raised platelet count. Weight loss, lymph-node enlargement, lung diseases (such as pleurisy, pleural fluid and alveolitis), pericarditis, vascular inflammation (vasculitis), skin nodules and eye diseases (reduced tear production or inflammation) may also occur.

The severity of disease, its clinical course and individual responses to treatment vary greatly. For example, in a community cohort nearly one in five patients were in 'remission off treatment' after 3 years of follow-up. By contrast, half of the patients attending hospital clinics were at least moderately disabled, as rated by a Health Assessment Questionnaire (HAQ) of greater than 1.0 (see Appendix 1).[4] Symptoms of RA may develop within days or evolve over many weeks and months.[5] Several distinct patterns of joint disease are recognised, including predominantly small or medium joint disease, predominantly large joint disease, flitting or transient attacks of joint pain (palindromic rheumatism), pain and stiffness of the shoulder and pelvic girdles (polymyalgic disease), and disease associated with weight loss and fever (systemic onset), or any combination of these. Pain and disability, in early RA, are linked to disease severity and to measures of psychological distress.[4] Disease progression can be relentless, or punctuated by partial or complete remissions, of variable and unpredictable intervals.

Diagnosis of RA

RA is diagnosed from a constellation of clinical, laboratory and radiographic abnormalities.

Diagnosis may be obvious or may need specialist assessment or a period of clinical observation. Internationally agreed classification criteria for RA are used widely in contemporary research studies. The most recent criteria require patients to fulfil four of the following: morning stiffness in joints exceeding 1 hour, physician observed arthritis of three or more areas with soft-tissue swelling, arthritis involving hand joints, symmetrical arthritis, rheumatoid skin nodules, a positive blood test for rheumatoid factor and radiographic changes typical of rheumatoid disease.[6] Such criteria have limited utility in routine practice and most clinicians diagnose RA without reference to them. Indeed, many patients do not meet formal disease classification criteria, at least early in their disease.[7,8]

Radiographic features of RA

Conventional radiographs may be normal or may show soft-tissue swelling and reduced bone density around affected joints, in early RA. Later, there may be diffuse joint damage, indicated by narrowing of the joint space, or focal loss of bone and cartilage at the joint margin, called erosions. Joint damage is assessed in clinical trials using scores of both joint space narrowing and joint erosions. Joint deformity or instability may occur as damage progresses and in advanced disease bony fusion occurs. More sensitive imaging, for example with magnetic resonance imaging (MRI), shows detailed anatomical and pathological change. Some studies indicate that erosions are seen on MRI up to 2 years before they become visible on radiographs;[9] however, only a quarter of erosions seen on MRI are eventually also seen on X-rays. The clinical importance of some MRI changes is debated but MRI remains, potentially, an important and sensitive outcome measure.[10]

Epidemiology

RA affects around 0.5–1% of the population, three times as many women as men, and has a peak age of onset between the ages of 40 and 70 years. Prevalence of the disease at the age of 65 is six times that at the age of 25 years. Recent estimates from England and Wales show an annual incidence of 31 per 100,000 women and 13 per 100,000 men, suggesting a decline in recent decades and a prevalence of 1.2% in women and 0.4% in men.[11] There are approximately 426,800 patients with RA in England and Wales (population 52,793,000).[12] A primary care trust (PCT) with a population of half a million, for example, has around 4000 patients with RA.

Aetiology

A specific cause for RA has not been identified; it appears to have many contributory factors including genetic and environmental influences. Genetic influence is estimated at 50–60%.[13] The occurrence of RA in both of a pair of monozygotic twins is 12–15% and a family history of RA gives an individual a risk ratio of 1.6, compared with the expected population rate.[14] The human leucocyte antigen HLA-DRB1 of chromosome 6 has been most clearly linked to RA, although this accounts for less than half of the overall genetic susceptibility of RA.[15] HLA plays a key role in immune function and regulation. The only known function of DR is in presentation of peptides to T-cells for mounting an immune response to particular antigens. Rheumatoid factor, an autoantibody produced by B lymphocytes and directed against immunoglobulin G (IgG), is also an important feature of a proportion of patients with RA and is implicated in disease.[16]

Infectious agents have been suspected, but no consistent relationship with an infective agent has been shown. Sex hormones have also been suspected because of the higher prevalence of RA in women and a tendency for disease to improve in pregnancy. However, a precise relationship has not been identified. A causal link with lifestyle factors such as diet, occupation or smoking has not been shown.

Pathology

Synovial joints occur where the ends of two bones, covered with hyaline cartilage, meet in a region where free movement is desirable. This joint space is encapsulated by a fibrous capsule lined, on the inside, by a synovial membrane; which functions to secrete fluid to lubricate and nourish hyaline cartilage. The synovial layer of affected joints becomes enlarged owing to increased cellularity, or hyperplasia, infiltration by white blood cells and formation of new blood vessels. This is accompanied by increased fluid in the joint cavity, which contains white blood cells and a high level of protein (an exudate) contributing to the joint swelling. Bony erosions of cartilage and bone occur where synovial tissue meets cartilage and bone. This occurs through the combined actions of synovial tissue (pannus) and resident cartilage and bone cells. Erosions, and loss of cartilage, are rarely reversible. Such damage therefore compromises the structure and function of a normal joint.

Role of TNF

TNF-α and other cytokines such as interferon-γ, interferon-β, interleukin-1 (IL-1), interleukin-2

(IL-2) and interleukin-6 (IL-6), produced by macrophages and activated lymphocytes, promote inflammation. In early RA TNF-α is expressed in abundance in synovial tissues and, locally, promotes growth of new blood vessels, orchestrates inflammation and other cytokine production, and induces migration of white blood cells into the joint, which release potentially harmful enzymes. Systemically, TNF-α is an important mediator of cachexia, fever, bone resorption and cardiovascular collapse (as in septic or endotoxic shock).

TNF-α has a half-life of a few minutes and its production can comprise as much as 1–2% of protein released by activated macrophages. Newly produced TNF-α spans the cell membrane and may be active in this membrane-bound form, especially in T lymphocytes. More usually, TNF-α is released as a soluble molecule by cleavage of the intracellular tail by an enzyme known as TNF-α-converting enzyme (TACE).[17] Three soluble molecules combine together, forming a trimer, and signal to cells by binding to one of two possible cell receptors: a 55-kDa (TNF-R1) or a 75-kDa TNF (TNF-R2) receptor. Receptor binding induces a pair of receptors to combine and triggers biological activity. TNF-α has a greater affinity for TNF-R1 than for TNF-R2; the latter appears to capture TNF-α and pass it on to TNF-R1. Mice lacking TNF-R1 have poorly developed lymphoid organs, are highly susceptible to infection by mycobacteria and *Listeria monocytogenes*, and are particularly prone to chronic inflammation and to endotoxic shock induced by TNF-α. Expression of TNF-R2 is restricted to endothelial cells (lining cells in blood vessels) and white blood cells. TNF-R1 is expressed by virtually all cell types.[18]

The extracellular sections of TNF receptors on cells are shed by proteolysis and these soluble TNF receptors (sTNFRs) are natural inhibitors of TNF and a means of regulating TNF-α activity,[19] although it has also been suggested that sTNFRs stabilise circulating TNF-α and function as TNF agonists. Levels of sTNFR are raised in RA and other conditions causing inflammation. Defective shedding of the TNF-R1 can be caused by rare autosomal recessive gene defects; known as familial periodic syndromes or TNF-receptor-associated periodic syndromes (TRAPs). People with these conditions experience episodic fever, inflammation and deposition of amyloid but may also have a survival advantage in terms of a more effective host defence against certain bacterial infections.[20,21]

Goals of management

Physicians treating RA aim to control symptoms of joint pain and stiffness and to minimise loss of function and improve the quality of life of their patients. Reducing the risk of disability associated with joint damage and deformity and treating any extra-articular manifestations are also key objectives. Since RA is a heterogeneous disease, which may vary over time, a long-term plan with regular clinical evaluation to assess disease status, co-morbidity, patient preferences and psychosocial factors is essential, and is aided by well-informed and satisfied patients and carers.[22,23]

Current drug therapy for RA

Non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics are commonly used for symptom relief in RA. These drugs do not modify the disease process and, in severe disease, are often insufficiently effective for symptom control. Corticosteroids may produce dramatic and rapid improvements in RA symptoms, including systemic features such as fatigue and weight loss, and may be given by mouth, as intramuscular injections, intravenously or as joint injections. Steroid injections provide only short-term benefits, but oral steroids may provide prolonged benefits. In clinical practice a significant proportion of patients take steroids for years and experience difficulty when therapy is withdrawn.

Some RA patients are managed solely with oral steroids, NSAIDs and analgesics, in varying combinations. Corticosteroids are also commonly used for short-term management of acute symptoms, or as bridge therapy, to allow rapid control of disease while awaiting the effects of slower acting drugs such as DMARDs, which reduce the risk of joint damage. Drugs used commonly in the UK and regarded as DMARDs include azathioprine, etanercept, ciclosporin A, hydroxychloroquine, infliximab, leflunomide, sulfasalazine, methotrexate and injectable gold.[24–26]

Glucocorticoids may be regarded as DMARDs, as their use appears to reduce the risk of joint damage.[27] Steroids were not included in the baseline clinical pathway of the economic model in this review, for the following reasons. First, glucocorticoids are used widely as an adjunct to other antirheumatic therapy whether that therapy includes conventional DMARDs or TNF inhibitors. For example, in clinical trials in established RA 50% or more of adalimumab- or placebo-treated patients were on glucocorticoids. Secondly, practice with regard to steroid use varies

greatly, such that some physicians prefer high-dose oral therapy while initiating a DMARD,[28] others prefer intramuscular[29] or even intravenous steroids, others low oral prednisolone given for prolonged periods[27] (with or without DMARDs) and yet others may rely on intra-articular therapy wherever possible. Thirdly, patients with established RA also differ in their preferences for how glucocorticoids are used and many, particularly those experiencing adverse effects such as weight gain or osteoporosis, prefer to avoid them altogether.

DMARDs rarely induce complete disease remission, although effective disease control can be achieved and may also lead to other benefits such as reduced cardiovascular mortality.[30] The mode of action of most DMARDs is incompletely understood. It is recommended that patients with active RA should be treated soon after diagnosis with DMARDs, since delayed use appears to lead to worse clinical outcomes.[31] This has led to the concept of a 'window of opportunity' in the treatment of RA; that is, delayed use of DMARDs reduces the prospect of benefits in the future. Appropriate concerns have been expressed about data supporting this idea.[32] Indeed, the 'window of opportunity' concept risks creating a therapeutic imperative for DMARD use when clinicians and patients face newly diagnosed inflammatory polyarthritis: this may be misplaced since early inflammatory polyarthritis commonly remits. Thus, careful evaluation and appropriate clinical judgements are needed in choosing therapies.[33]

Effective disease control with DMARDs commonly leads to successful withdrawal of NSAIDs, analgesics and corticosteroids. Some DMARDs, such as azathioprine and hydroxychloroquine, are probably less effective than other agents, such as methotrexate, sulfasalazine and leflunomide. Toxicity of DMARDs also differs, and each drug has a specific dosing and monitoring schedule. Unfortunately, discontinuation of therapy is common with these agents; for example, the proportion of people still taking gold after 5 years is 20%, sulfasalazine 35% and methotrexate 57%.[34] Such data highlight the limitations of the available agents; that is, relatively short-term drug 'survival' for a disease with a lifelong course.

DMARDs may be discontinued because of toxicity, inadequate disease control, disease relapse, patient or physician preferences, complicating co-morbidity or a combination of these. Toxicity varies from relatively minor reactions to life-threatening events such as bone-marrow suppression.[35] Hydroxychloroquine and methotrexate appear to have the most favourable risk–benefit profile.[36] Methotrexate is widely regarded as the standard against which other drugs should be judged, and treatment is more likely to be sustained with this drug.

DMARDs are used in a variety of ways: several agents, often with corticosteroids added, may be combined early in disease (combination therapy[18,37]), which may then be continued or some drugs gradually withdrawn (step-down treatment[28]); DMARDs may be used singly and agents added (step-up); or withdrawn and replaced (sequential monotherapy), if disease control is judged to be inadequate.[31,38] In the UK monotherapy with sulfasalazine or methotrexate, in newly diagnosed patients, is currently the preferred initial strategy. Preferred DMARD combinations include methotrexate and sulfasalazine given together, or ciclosporin A or hydroxychloroquine given with methotrexate.[25] It appears that as successive DMARDs are tried to control disease the likelihood of sustained drug use declines, regardless of the choice of initial DMARD; that is, the second DMARD tried is likely to be used for a shorter time than the first and the third shorter than the second, and so on.[26] Patients achieving good disease control, or remission, with a DMARD are at risk of relapse if treatment is discontinued, and current guidelines advocate sustained long-term therapy.[23] Nearly a quarter of patients on long-term therapy, however, are consistently non-compliant with DMARDs.[39]

Non-drug treatments

With advanced joint damage surgical intervention such as joint replacement arthroplasty, joint fusion or osteotomy may be necessary. Long-term observations show that around a quarter of patients with RA undergo a total joint arthroplasty.[40] It cannot, of course, be assumed that all such surgery is directly attributable to RA, especially as osteoarthritis is the most prevalent form of arthritis. Other surgical interventions, such as removal of synovial tissues and rheumatoid nodules, peripheral nerve decompression (such as in carpal tunnel syndrome), or soft-tissue procedures such as tendon release or repair may be necessary at any stage of disease. Patients often also need advice and support from a multidisciplinary team, including specialist nurses, podiatrists, physiotherapists and occupational therapists in contemporary rheumatology practice.

Assessment of response to DMARDs

Remission is not usually achieved in RA, but very effective disease control is often possible. Modern clinical trials rely on composite end-points such as the American College for Rheumatology (ACR) definition of improvement, preferred in US trials, and the Disease Activity Score (DAS), preferred in European studies. The ACR response, for example, requires an improvement in counts of the number of tender and swollen joints (using designated joints) and at least three items from the following: observer evaluation of overall disease activity, patient evaluation of overall disease activity, patient evaluation of pain, a score of physical disability; and improvements in blood acute-phase responses [e.g. erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)]. Response is defined as ACR20, ACR50 or ACR70, where the figures refer to percentage improvement of these clinical measures. This creates a dichotomous outcome of responders and non-responders. Achieving an ACR20 response has been regarded as a low hurdle, but in clinical practice patients who achieve this hurdle often gain a worthwhile clinical improvement, especially in early RA.

The DAS is calculated using a formula that includes counts for tender and swollen joints, an evaluation by the patient of general health (on a scale of 0–100), and blood acute-phase responses (usually ESR, but more recently using CRP). Originally the DAS was based on an assessment of 53 joints for tenderness and 44 joints for swelling. More recently DAS28, based on an evaluation of 28 joints, has been developed and proposed for use in routine clinical practice. DAS28, like DAS, is a continuous scale with a theoretical range from 0 to 10. Thresholds have been suggested for the scale, such that a score greater than 5.1 is regarded as indicating high disease activity, a score of less than 3.2 low disease activity and a score of less than 2.6 remission (for DAS28).[41,42] It is of interest that these thresholds were originally derived from actual decisions by physicians in practice[43] and are now being proposed as instruments for decision-making in practice. Details of both scoring systems are provided in Appendix 1.

Radiographic outcomes are believed by many to be the most important outcome measure in RA. It is acknowledged, however, that variation in joint inflammation has a more profound and immediate impact on disability compared with the slow and cumulative effect of radiographic damage on disability.[44] The most commonly used tools for assessing joint damage are the Sharp and Larsen methods and their modifications, which rely on evaluations of plain radiographs (Appendix 1). As indicated above, plain radiographs are rather insensitive to change, but are cheap and widely available. A majority of patients show only mild or no progression on plain radiographs over periods of 1–2 years, highlighting one of their limitations in modern clinical trials.[45]

Prognosis

The impact of RA on an individual can be viewed from a variety of perspectives, including employment status, economic costs to the individual or society, quality of life, physical disability, life expectancy, and medical complications such as extra-articular disease and joint deformity, radiographic damage or the need for surgery. In general, persistent disease activity is associated with poorer outcomes, although in the first 5 years of disease physical function is especially labile. Greater physical disability at presentation is associated with greater disability later in disease. Other factors linked with poorer function include older age at presentation, the presence of rheumatoid nodules, female gender, psychological distress and degree of joint tenderness.[46,47]

Continued employment is related to type of work and other aspects of the workplace, such as pace of work, physical environment, physical function, education and psychological status; work disability is not necessarily linked to measures of disease activity.[48,49] Radiographic damage in RA joints is also influenced by rheumatoid factor status, age, disease duration, extent of disease, and perhaps genetic factors. Life expectancy in RA is reduced and is related to age, disability, disease severity, co-morbidity and rheumatoid factor status, in particular.[50–53] For example, a 50-year-old woman with RA is expected to live for 4 years less than one without RA.[54] This appears to be due, principally, to increased cardiovascular disease, particularly in those who are rheumatoid factor positive.

Burden of illness

Early in disease indirect costs exceed costs due to healthcare utilisation and medication (direct costs), by two-fold.[55] It is also clear that informal caregivers shoulder a considerable burden in terms of forgone paid employment, leisure activity and personal health.[56] Inevitably, in a disease characterised by lifelong pain, discomfort and physical impairment, the burden on individuals and families is increased. Recent studies show that

medication costs, especially in those treated with biological agents such as TNF inhibitors, account for a majority of the direct costs of RA.[57] Some drug intervention studies have shown reduced work absence with aggressive treatment strategies,[58] although only one-third of employed patients cease because of disease and, unsurprisingly, manual workers are much more likely to stop work.[59]

Current service provision

Most patients with RA are referred to hospital services for assessment, but up to one-quarter of those with early inflammatory arthritis (not necessarily RA) are managed in primary care. Most district general hospitals now have a department of rheumatology with varied support from clinical nurse specialists and other professionals allied to medicine. The majority of patients followed up in a hospital rheumatology department have RA or another type of inflammatory arthritis or connective-tissue disease. A proportion of such patients may also require inpatient treatment, although there are considerable variations in inpatient facilities and hospitalisation rates for RA. The Arthritis and Musculoskeletal Alliance (ARMA) has recently proposed standards of care for patients with inflammatory arthritis. The principal motive for these standards[60] is to improve service provision and delivery and to reduce regional variations in access to services.[61–63] For example, access to TNF inhibitors varies depending on local funding arrangements, such that some districts operate waiting lists for patients to begin treatment despite wide drug availability. A recent survey, commissioned by ARMA and the British Society for Rheumatology (BSR), with support from Schering-Plough, indicated that around one-third of 148 rheumatologists, mainly from England and Wales, were unable to prescribe TNF inhibitors.[64] Principal barriers to prescribing were identified as difficulties with local funding arrangements or problems of infrastructure such as the availability of day-case facilities or nursing support. Variable implementation of guidance on the use of TNF inhibitors was also confirmed by a survey of 196 hospitals and PCTs undertaken by the Audit Commission, which found that 'the biggest perceived barrier to implementation among NHS bodies, for both clinical guidelines and technology appraisals, was lack of money. We found that 85 per cent of respondents identified that the funds available to implement technology appraisals were insufficient, particularly in relation to high-cost appraisals, such as … etanercept and infliximab for rheumatoid arthritis.'[60] Access to adalimumab has caused particular difficulties in some areas because this drug has not yet been evaluated by NICE.

However, some services have managed to secure additional funding for drugs and junior medical and nursing staff to enable NICE guidance to be implemented.[65]

Description of the technology

Adalimumab (Humira®; Abbott Laboratories)

Adalimumab is a recombinant monoclonal antibody, made from human peptide sequences, which binds specifically to TNF and neutralises its biological functions by blocking interactions with the p55 and p75 cell-surface TNF receptors. Treatment is currently recommended for use in people with moderate or severe RA who have not responded to one or more DMARDs, including methotrexate. An application to extend the licence of adalimumab for use in severe, active, progressive RA in adults not previously treated with methotrexate was submitted by Abbott Laboratories in December 2004[66] and approved in June 2005.[67] Concomitant treatment with methotrexate is recommended for optimum efficacy, but adalimumab may be used alone where methotrexate is not tolerated or is contraindicated. Clearance of adalimumab from the body is decreased with age and by concomitant methotrexate administration, whereas adalimumab increases methotrexate clearance.[68] Patients normally self-administer adalimumab by subcutaneous injections, after training, at a standard dose of 40 mg every other week; but the dose may be increased to 40 mg weekly if disease is poorly controlled.[69]

Etanercept (Enbrel®; Wyeth Laboratories)

Etanercept is a combination protein consisting of the extracellular portion of two of the 75-kDa TNF receptors (TNF-R2) for TNF combined with a human Fc portion of human IgG class 1 (IgG_1). Etanercept binds soluble and cell-bound TNF-α with high affinity and does this by competing with TNF receptors. Etanercept is administered as a twice-weekly subcutaneous injection of 25 mg or a once-weekly injection of 50 mg. Patients or caregivers normally administer etanercept, after suitable training. No dose changes are necessary for patients with renal or hepatic failure or in elderly subjects. Etanercept may be used in

combination with methotrexate or alone for the treatment of active RA in adults when the response to DMARDs, including methotrexate (unless contraindicated), has been inadequate, and for the treatment of severe, active and progressive RA not previously treated with methotrexate. Etanercept is also licensed for use in juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis and severe psoriasis.

Infliximab (Remicade®; Schering-Plough)

Infliximab is a recombinant chimeric human–murine monoclonal antibody that binds soluble and membrane-bound TNF-α. Stable complexes are formed, binding of TNF-α is prevented and TNF-α already bound to TNF receptors may be dissociated. The TNF-α binding region is of mouse origin and comprises 30% of the amino acid sequence of infliximab. The remainder is a human IgG_1 heavy-chain and kappa-chain constant region.

Infliximab is licensed for use in RA with methotrexate, although in clinical practice it is used without methotrexate or with other DMARDs if patients are intolerant of methotrexate.[70] The recommended dose of infliximab for RA is 3 mg kg^{-1} body weight given as an intravenous infusion, followed by further infusion, at the same dose, 2 and 6 weeks later. Thereafter, infusions are given at 8-week intervals. An interval between infusions of greater than 16 weeks is not recommended because of an increased risk of hypersensitivity reactions, although infusions after longer gaps have been administered safely.[62,71,72] Freshly reconstituted infliximab is diluted to a volume of 250 ml using 0.9% sodium chloride and the infusion is administered intravenously over at least 2 hours using a low-protein-binding filter. Treated patients should be observed for 1–2 hours post infusion. Recent studies indicate that patients who tolerate infusions well and are established on therapy may receive infusions over 1 hour or less.[73]

Infliximab is also licensed for use in severe Crohn's disease (5 mg kg^{-1}), including disease complicated by fistulae, ankylosing spondylitis (5 mg kg^{-1}) and psoriatic arthritis (5 mg kg^{-1}). Use of higher doses of infliximab in trials has encouraged use of higher doses or a shorter interval between infusions in RA.[74]

Special precautions for use of TNF inhibitors

TNF inhibitors may cause a variety of adverse effects.[1] Reactivation of *Mycobacterium tuberculosi*s organisms lying dormant in walled granuloma, in individuals previously infected with tuberculosis, is a particular concern. Such 'latent' tuberculosis, thought to be highly prevalent in the world's population, rarely causes disease. TNF-α is a key component of host defence against *M. tuberculosis*, especially in the formation of granulomas.[75] Inhibition of TNF-α appears to increase the risk of *M. tuberculosis* and other agents causing granulomatous diseases, such as *Listeria monocytogenes* (a bacterium associated with foodborne diseases) and *Histoplasma capsulatum* (a fungus which, in endemic areas, causes lung disease in people with a compromised immune system). The risk appears to be significantly greater with infliximab (53 patients per 100,000 treated cases) than with etanercept (28 per 100,000).[76] Data for adalimumab are limited, but an increased risk has also been shown. The summary of product characteristics (SPC) for adalimumab and infliximab and guidance including proposed guidance from the BSR, British Thoracic Society and the British Society for Gastroenterology recommend screening patients before treatment.[77] In RA this is currently done by taking a personal and family history of tuberculosis and a pretreatment chest X-ray, but the addition of skin tests using tuberculin has been proposed. Skin testing before the use of TNF inhibitors poses problems in the UK because of the use of bacille Calmette-Guérin (BCG) vaccination for tuberculosis prevention in childhood. In addition, many patients with RA are poorly responsive to tuberculin, perhaps as a result of previous or current immunosuppressive therapy, but also due to the disease.[78] Preventive antituberculous drug treatment in latent tuberculosis is also associated with a risk of drug-induced hepatitis, which needs to be considered in deciding about prophylactic therapy.

Routine blood monitoring is not necessary for patients taking TNF inhibitors, but may be needed for concomitantly used DMARDs such as methotrexate. TNF inhibitors can induce antinuclear and anti-double-stranded DNA antibodies in the blood of some patients treated with TNF inhibitors. These antibodies are associated with systemic lupus erythematosus (SLE), a potentially serious rheumatic disease. Cases of drug-induced SLE have been reported with TNF inhibitors, but are rare.[79]

Choosing between TNF inhibitors and patient preferences

Physicians may prefer one TNF inhibitor to another for clinical reasons; for example, etanercept or adalimumab may be preferred to

infliximab if a patient has had an adverse effect to methotrexate, since the licence for infliximab stipulates combined therapy with methotrexate. Physicians also favour drugs with which they are familiar – etanercept and infliximab have been around longer than adalimumab – and also based on their personal experiences, or perceived efficacy, in individual circumstances. Often a choice is made for practical reasons such as convenience of self-administered injections against a need to attend hospital for intravenous infusions[80] or the availability of resources to deliver timely infusions. Preliminary data for infliximab administered as subcutaneous injections compared with intravenous infusions have recently been presented.[81]

Patients starting DMARDs are most concerned about drug toxicity[82] and commonly have a fear of giving their own injections; but clinical experience shows that a majority, even those with markedly impaired hand dexterity, cope very well. Patients may prefer adalimumab to etanercept, as fewer injections are needed, and also because adalimumab is available as a prefilled syringe, whereas etanercept needs to be prepared from a powdered formulation. However, a prefilled syringe of etanercept was approved in the USA late in 2004, but at the time of writing is not available in Europe. Personal experience also suggests that some elderly patients prefer to receive intravenous infusions rather than contemplate administrating their own injections.

Current NICE guidance for use of TNF inhibitors

Treatment of RA with etanercept and infliximab was considered in a previous NICE appraisal and the guidance published in 2002[83] mirrors that proposed earlier by a committee of the BSR.[84] A brief commentary on aspects of this guidance is given below.

A key feature of the guidance is a requirement to register treated patients, with their consent, in a national register, the BSR Biologics Register (BSRBR). The aim of the BSRBR is to establish the long-term safety of a variety of biological agents (including TNF inhibitors) in adult patients with RA and other rheumatic diseases. In particular, the BSRBR is interested in mortality, malignancy and serious adverse events (SAEs) and its sample size was based on being able to detect a two-fold increase in risk of lymphoma over 5 years. There are two cohorts: a group of patients with rheumatic disorders newly exposed to biological agents, mainly TNF inhibitors, and a comparison group with similar disease characteristics being treated with other non-biological DMARDs. It is proposed that patients are monitored for 5 years or more.[85] The target for recruiting patients treated with etanercept was met recently and clinicians are no longer required to register patients being treated with this drug. Clinicians have described their difficulties finding funding for TNF inhibitors and also meeting the demands of current guidance in terms of BSRBR registration and patient evaluations.[63]

It is recommended that neither etanercept nor infliximab is used unless a patient has failed to respond to two DMARDs, including methotrexate. Other eligibility criteria, dose ranges and desired duration of previously tried therapies were as proposed by the BSR. Since 2002 evidence of the use of TNF inhibitors before other DMARDs has accumulated and this is considered in this review. The BSR, in their updated guidance, state that circumstances leading to first line use of TNF inhibitors would be rare.[86] Data from the BSRBR show that the median number of previous DMARDs used by registered patients was four, indicating conservative use of these new drugs.[87]

The BSR, endorsed by NICE in 2002, recommended that patients should only be eligible for TNF inhibitors if they fulfil the 1987 American Rheumatism Association (ARA) criteria for the classification of RA.[88] As indicated earlier, clinicians rarely apply criteria for diagnosis in practice. Around 10% of patients in the BSRBR with a clinical diagnosis of RA appeared not to meet disease classification criteria.[85] The criteria, especially the list version, have important limitations.[89] Moreover, patients may take several years after disease onset to fulfil these criteria,[7] and it is possible that, as TNF inhibitors are used earlier in disease, some patients suitable for TNF inhibitors do not meet formal classification criteria.

Current guidance stipulates that patients should have active disease determined by a DAS28 of greater than 5.1 and that disease activity should be assessed at two time-points 1 month apart, before therapy. Funding agreements between some hospital trusts and PCTs require that these thresholds must be met before funding is agreed. Inevitably, this influences the DAS scores recorded in busy clinics. Some argue that it is unreasonable for patients to have to continue with active disease for a month, having already tolerated active

disease between clinic appointments, before being eligible for therapy. A majority of patients (94%) registered in the BSRBR are recorded as having met this standard, although the veracity of recorded data is unclear – it is not audited and there is an incentive for clinicians, who judge that thresholds inappropriately control access to therapy, to state that patients have met the criteria.

Guidance also recommends that, in order to continue therapy with TNF inhibitors, disease activity needs to decrease by a DAS28 of 1.2, or be at or below 3.2 after 3 months of treatment. The BSR submission to NICE indicates that this may have been a typing error as a good DAS response is defined as a change of greater than 1.2 *and* a score below 3.2.[85] DAS28 thresholds scores were derived originally from actual decisions taken in practice[43] and their principal role is as outcome measures in clinical trials. Although these may be useful hurdles and good instruments for monitoring therapy, it has been argued that unthinking application of such thresholds devalues clinical judgements, especially since the DAS28 has some properties that undermine confidence in its value for individual decision-making.[90–93] In the BSRBR 41% of patients classified as non-responders on DAS thresholds continued with TNF inhibitors, indicating that clinicians and patients clearly felt that the modest improvement in DAS (mean improvement 0.3) and other health gains[85] were sufficient to warrant continued drug use.

Sequential use of TNF inhibitors, where patients fail to respond or experience an adverse reaction to one agent, was not recommended in previous guidance on the basis that there was no evidence supporting this practice. Since then, many practising clinicians have noted benefits for patients when switching agents. Some experiences have been published and demonstrate potential benefits for patients switching from any one of the three agents to another of these agents.[94,95] BSR guidance (2005) cites some of this evidence without making any specific recommendations. Data from the BSRBR indicate that this practice is prevalent, despite current guidance.

Updated BSR guidance considers, briefly, the use of dose changes and increased frequency of dosing for infliximab and adalimumab. A significant proportion of patients receiving infliximab experience increased disease activity after an initial good response. Clinicians have responded, in some cases, by reducing the interval between infusions such that patients are given 3 mg kg^{-1} of infliximab every 6 weeks instead of every 8 weeks, or by increasing the dose of infliximab to 5 mg kg^{-1} at 8-week intervals.[96,97] Published observations indicate effective disease control by doing this, but at significantly increased drug costs. A large series from Belgium, for example, showed that nearly one-quarter of treated patients had dose increases,[74] whereas a US study showed that over 60% of patients had dose increases.[98] In addition, the licence for adalimumab allows for increasing the dose from 40 mg every other week to once a week, effectively doubling the cost of therapy. It is unclear how commonly this is done in practice. By contrast, increasing etanercept beyond a total of 50 mg per week (as one or two injections) does not appear to improve efficacy.[99]

Degree of diffusion and anticipated costs

By the end of 2004, 8455 patients with RA and 1081 with other rheumatic diseases were treated with TNF inhibitors and were registered with the BSRBR. New patients were being added to the registry at a rate of 450 per month, in early 2004.[62,85] If one estimates that currently around 8000–10,000 patients with RA are being treated with TNF inhibitors, at approximately £10,000 per annum each, then the annual national costs of TNF inhibitors for RA is in the region of £80–100 million. These figures are rising and, given that only around 2% of patients with RA are currently on TNF inhibitors, there is the potential for future increases to be substantial.

Chapter 3

Effectiveness

Summary

A comprehensive search for randomised controlled trials (RCTs) was undertaken. Studies were selected, and assessed for quality, and data were extracted by two reviewers independently.

Twenty-nine trials met the inclusion criteria. One trial, the Behandel–Strategieën (BeSt), did not meet the inclusion criteria but is reported in detail as it is relevant to informing the decision on the most appropriate use of TNF inhibitors. Most trials were of good quality and compared one of the TNF inhibitors with placebo. Only three trials looked at a head-to-head comparison between a TNF inhibitor and methotrexate. No trial compared TNF inhibitors with each other.

When used alone, adalimumab was slightly less effective and etanercept was slightly more effective than methotrexate in patients who had not been treated with methotrexate or who had not previously failed methotrexate treatment.

All three TNF inhibitors, used either alone (where licensed) or in combination with ongoing conventional DMARDs, were effective in controlling the signs and symptoms of RA compared with placebo in patients who had had an inadequate response to conventional DMARDs.

Combination of a TNF inhibitor plus methotrexate was more effective than methotrexate alone in patients who had not been treated with methotrexate or who had not previously failed methotrexate treatment. The combination involving infliximab, however, was associated with an increased risk of serious infection.

Patients' previous experience with the therapy has to be taken into account when interpreting treatment effects observed in trials, particularly when combination therapy is involved. No clear relationship between disease duration and treatment effects was observed among the limited evidence from trials.

Methods for reviewing effectiveness

Search strategy

Clinical effectiveness

The following resources were used to identify relevant studies:

- Searches of bibliographic databases:
  - Cochrane Library 2005 Issue 1
  - MEDLINE (Ovid) 1966 to February 2005, EMBASE (Ovid) 1980 to week 8 2005
  - Science Citation Index (ISI Web of Science) 1981–2005
- National Research Register 2005 Issue 1
- Internet sites of the Food and Drug Administration (FDA) and EMEA
- manufacturers' submissions to NICE 2005 appraisal process
- citation lists
- contact with experts and researchers.

Searches used index and text words encompassing rheumatoid arthritis, tumour necrosis factor, tumour necrosis factor receptors, anti-tumour necrosis factor, adalimumab, etanercept and infliximab. Search filters were used in MEDLINE and EMBASE to identify RCTs. Searches for adalimumab were not limited by date; searches for etanercept and infliximab started from 2001 as the previous report had covered the earlier period.[1] There were no restrictions by language. Full details of strategies are contained in Appendix 2.

Inclusion and exclusion criteria

Clinical effectiveness: efficacy outcomes

Inclusion criteria

- RCTs that compared adalimumab, etanercept or infliximab with any other agent including placebo in adult RA patients.
- Trial reports were only included if the recruitment of patients was complete.
- A trial had to be fully published as a paper or be available as a complete trial report to be included. Trial reports were requested on all major trials from the manufacturers.

Exclusion criteria

- Trials of adalimumab, etanercept or infliximab

in juvenile arthritis, Crohn's disease, psoriatic arthritis and other forms of spondyloarthritis.
- Trials of adalimumab, etanercept or infliximab comparing different doses or routes of administration without including another active or a placebo control group were only assessed for safety outcomes.
- Studies reporting solely on laboratory measures aimed at investigating disease or treatment mechanisms and which did not report relevant clinical outcomes.
- Observational studies of TNF inhibitor therapies that did not include a control group, except for information on adverse events.
- Trials only available as abstracts.

Clinical effectiveness: safety outcomes

Inclusion criteria

- RCTs that met the inclusion criteria for the review on efficacy outcomes.
- In addition to RCTs, data from postmarketing surveillance, major observational studies and various registries including the BSRBR were used to inform the assessment of the safety of these three agents.

Based on the above inclusion and exclusion criteria, study selection was made independently by two reviewers. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary.

Data extraction strategy

Data included in the previous peer-reviewed, published, assessment report[1] were taken directly from the report and incorporated into updated analyses. Data for outcomes that were not assessed in the previous assessment report, and additional data from new trials not included in the previous report, were extracted independently by two reviewers using an agreed data extraction form. Results were extracted, where possible, for intention-to-treat (ITT) populations as raw numbers, plus any summary measures with standard deviations, confidence intervals and *p*-values. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary.

Quality assessment strategy

The quality of RCTs was judged by adequacy of randomisation, allocation concealment, blinding, differential withdrawal between treatment arms, and use of ITT analysis. Two reviewers independently examined trial quality. Discrepancies were resolved by discussion with involvement of a third reviewer when necessary. Results of quality assessment were tabulated.

Data analysis

Outcomes of interest

Meta-analyses were carried out on selected key outcomes listed below, as specified in the review protocol (http://www.pcpoh.bham.ac.uk/publichealth/wmhtac/pdf/protocols/Anti-TNF_2004_final_protocol%20.pdf).

Efficacy

- Proportions of patients meeting the ACR20, ACR50 and ACR70 response criteria. Where ACR response was not reported, Paulus20 and Paulus50 were assumed to be equivalent to ACR20 and ACR50, respectively, for the purposes of meta-analysis
- swollen joint count (SJC)
- patient's global assessment of disease activity
- Health Assessment Questionnaire (HAQ)
- Disease Activity Score (DAS or DAS28)
- accepted indices of joint damage (van der Heijde modified Sharp score).

Further descriptions of the ACR response criteria, HAQ, DAS and modified Sharp score can be found in Appendix 1.

Tolerability

- Withdrawals for lack of efficacy
- withdrawals due to adverse events
- withdrawals for any reason.

Safety

- Serious adverse events (SAEs)
- serious infections
- malignancy.

SAEs are defined as an adverse event that met any of the following criteria:

- fatal
- life-threatening
- results in an unplanned inpatient hospitalisation, or prolongs an existing hospitalisation
- significantly or permanently disabling
- a congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening or require hospitalisation may still be considered SAEs if, based on appropriate medical judgement, they require medical or surgical intervention to prevent one of the outcomes listed in the definition above.

Serious infections are defined as any infections that require hospitalisation or parenteral antimicrobial treatment. If the number of patients

experiencing these events was not reported, the number of patients who experienced infections that were classified as SAEs was used instead. Figures of serious infection reported by study investigators without a clear definition were also included if the above information was not available.

Additional exploratory analyses on death, any infections, non-melanoma skin cancer and all cancer excluding non-melanoma skin cancers were carried out.

Approach for meta-analysis

Each TNF inhibitor was meta-analysed separately. The primary analysis compared each TNF inhibitor at the licensed dose (or its equivalent) with placebo or other active comparators using the latest follow-up data available from the randomised, controlled period of each trial. The doses included in the primary analysis are:

- adalimumab: 40 mg every other week (may be increased to every week if response is inadequate) or 20 mg every week
- etanercept: 25 mg twice weekly, 50 mg once weekly or 16 mg m^{-2} twice weekly
- infliximab: 3 mg kg^{-1} at 0, 2 and 6 weeks, and then every 8 weeks.

Sensitivity analyses included TNF inhibitors at licensed doses and above, and at all doses including sublicensed doses. Studies in which single injections or infusions were administered are not included in the primary analysis, but are included in the all-dose sensitivity analyses. Duration of follow-up for each trial is displayed on the forest plots of primary analysis for comparison. Additional analyses of results at 1 month, 3, 6 and 12 months and beyond are also conducted for ACR20 response.

For each TNF inhibitor three comparisons were made:

1. TNF inhibitor versus conventional DMARD: this head-to-head comparison is most relevant for clinical practice. A fair head-to-head comparison requires that patients should not have previously tried any of the drugs being compared, or at least not be selected as responders/non-responders.
2. TNF inhibitor versus placebo (with or without concomitant, ongoing DMARDs): trials that were included in this comparison typically recruited patients whose disease had been inadequately controlled by conventional DMARDs. The DMARDs that the patients had been taking before study entry (if any) were either stopped or continued during the trial and a TNF inhibitor or placebo was given to patients. In both cases a TNF inhibitor is compared with placebo but the scenarios behind the comparisons are different. The former represents a comparison of stopping DMARDs versus replacing a DMARD with a TNF inhibitor. The latter represents a comparison of continuing a DMARD (which is, at best, partially effective) versus adding a TNF inhibitor to that DMARD.
   To explore whether treatment effects differ between these two scenarios, the primary analyses of trials are displayed in the forest plots according to concomitant DMARD treatment. Studies in which patients stopped all concomitant DMARDs are placed on top of the plots and are labelled with a (–) sign. These are followed by studies in which patients continued their existing DMARD treatment, which are labelled with a (+) sign. In a few studies the patients continued their ongoing antirheumatic therapy, which may have included DMARDs. These studies are labelled with a (±) sign.
3. Combination (TNF inhibitor plus newly initiated conventional DMARD) versus newly-initiated conventional DMARD alone: this analysis reports trials in which patients were naïve to, or had not previously failed treatment with the TNF inhibitor and the DMARD being compared. The only comparator DMARD used in such trials to date has been methotrexate. The effect size in these trials represents the additional treatment benefit (or harm) of the combination over the newly initiated methotrexate alone. In these trials there is a greater benefit to patients in the control arm than seen in trials where the comparator is an established ongoing DMARD. It is thus necessary to distinguish between this analysis and that in (2), above, and the authors feel that it is inappropriate to cite a summary statistic combining these two different types of comparisons. However, for illustrative purpose, the forest plots of the primary analyses give both comparisons (2) and (3) on the same plot to illustrate the overall heterogeneity between these two types of 'placebo versus TNF inhibitor' comparison.

Although most trials contributed data to only one of the three comparisons described above, a few trials contributed to more than one. For example, the PREMIER trial compared adalimumab alone, methotrexate alone, and the combination of

adalimumab plus methotrexate in patients naïve to both treatments. The study therefore allowed two comparisons: adalimumab versus methotrexate (comparison 1), and combination of adalimumab plus methotrexate versus methotrexate (comparison 3). No statistical adjustment was made for the multiple comparisons within a trial.

Although subgroup analyses according to disease duration (mean disease duration ≤ 3 years versus >3 years) were planned, on reviewing the data it was felt that they were insufficient to support this, as disease duration relates closely to patients' prior exposure to DMARD therapies, which was strongly associated with the type of trials that had been carried out. For example, trials that compared TNF inhibitors with placebo tended to recruit predominately RA patients with long disease duration and with prior exposure to multiple DMARDs, whereas trials that included genuine head-to-head comparison between TNF inhibitors and conventional DMARDs were predominantly carried out in patients with early RA.

Handling of data and presentation of results

For continuous outcomes, results are presented as a weighted mean difference (WMD). For binary outcomes, results are presented as relative risk (RR). Risk differences (RD) were also used to calculate numbers needed to treat (NNT).

For outcomes with continuous data, the decision about whether to use the change from baseline or the final result depended on whether data were available for a sufficient number of studies. Where possible, the standard deviation (SD) was taken directly from the reported results, or derived from the standard error of the mean (SEM) or confidence intervals (CIs). When only the baseline SD was available, it was used as the SD for the final results as well.[100] SDs for mean change from baseline, if not available, were imputed using baseline SD and final SD assuming an intercorrelation coefficient of 0.5.[101] When only the median and interquartile ranges (IQRs) were reported, the median was used as the mean, and the difference between the first and third quartiles was considered equivalent to 1.35 SD.[101] Where the SD could not be estimated from trial data using the above methods, an imputed SD was calculated from the baseline SD of other trials with the same intervention.

Many outcomes were meta-analysed; for brevity, only the summary results are presented. Forest plots of the primary analyses for the six key outcomes (ACR20, ACR50, ACR70, HAQ, SAEs and malignancies) are shown. A fixed effects model was used unless trials demonstrated statistical heterogeneity (test for heterogeneity $p < 0.10$), in which case a random effects model was also used. In such cases the most conservative result is presented.

Results for effectiveness review

Number and type of studies included

In total, 29 RCTs are included in this systematic review: nine on adalimumab, 11 on etanercept and nine on infliximab. One further trial (BeSt) is also described here.

The process of study selection is summarised in *Figure 1*. Thirty-six citations met inclusion criteria (kappa for two independent reviewers was 0.70, 95% CI 0.66 to 0.75): ten papers or conference abstracts describing further results from two trials [Early Rheumatoid Arthritis (ERA) and Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT)] included in the previous technology assessment report (TAR),[1] and 26 papers or conference abstracts describing results from 15 RCTs not included in the previous review. For more details of excluded studies see Appendix 3.

Seven new RCTs were identified through manufacturers' submissions and abstracts (not yet indexed in electronic databases) from conferences. Five met the inclusion criteria. Trial reports were obtained from the manufacturers for four of the trials [PREMIER,[102] Codreanu,[103] Baumgartner,[104] and Safety Trial for Rheumatoid Arthritis with Remicade Therapy (START)[105]] which are included in the systematic review. The study by Schattenkirchner and colleagues[106] (adalimumab DE004) could not be included because attempts to obtain the trial report from the manufacturer were unsuccessful. Two trials, Add Enbrel or Replace Methotrexate (ADORE)[107] and BeSt[108] did not meet the inclusion criteria as they had TNF inhibitors in all arms, thereby preventing appropriate comparisons between TNF inhibitors and other active comparators or placebo. However, although BeSt, which was a trial of DMARD sequences in RA, could not be included in meta-analyses, this study is described in detail in the section 'Infliximab' (p. 46), because it reports data that may inform the appropriate use of these agents.

The results of the PREMIER,[109] Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO; 2-year data),[110] START[111] and the BeSt[108] trials were published in full after the initial completion of this review, but before the publication of this report. In addition, a

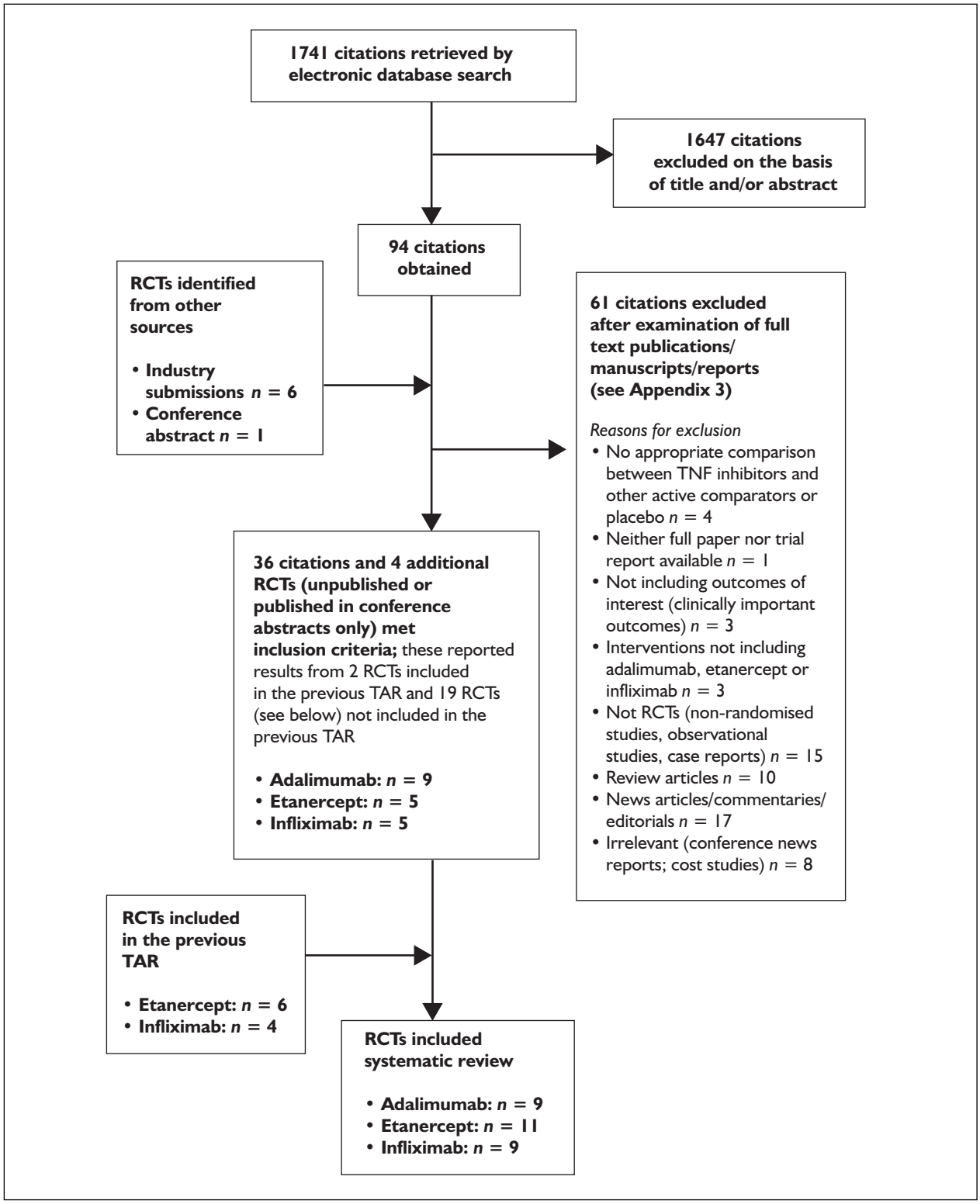

FIGURE 1 *Flowchart for study selection*

meta-analysis of serious infections and malignancies associated with adalimumab and infliximab treatment was published recently.[202] Related references were added to this report and relevant changes in the confidentiality status of data were made.

Adalimumab

Descriptions of individual adalimumab trials

Nine trials comprising a total of 3387 patients were included. Abbott Laboratories provided clinical study reports for five studies: Anti-Tumor Necrosis Factor Research Study Program of the

Monoclonal Antibody Adalimumab (D2E7) in Rheumatoid Arthritis (ARMADA; DE009),[112] van de Putte (DE011),[113] PREMIER (DE013),[102,109] Keystone (DE019)[114] and Safety Trial of Adalimumab in Rheumatoid Arthritis (STAR; DE031).[115] Data from these reports and additional trial data provided within the company submission are included. A list of these nine trials, the comparators and baseline patient characteristics are shown in *Table 1*. Trial quality, based on available data, is summarised in *Table 2*. In general, the trials were of high quality.

In most trials patients met agreed disease classification criteria and active RA was defined on the basis of tender and swollen joint counts, and other parameters including ESR, CRP or morning stiffness. Two early-phase trials[116,117] used DAS for inclusion. Stable doses of oral prednisolone (≤ 10 mg per day) and NSAIDs were allowed. Only one trial (PREMIER)[102,109] recruited exclusively early RA patients (disease duration <3 years).

Excluding PREMIER, five trials had a treatment arm with the licensed dose of adalimumab: DE007, DE009, DE011, DE019 and DE031. These trials are described below and key data from all trials are presented in the tables. Mean disease duration in these trials was around 10 years. In DE031 adalimumab-treated patients had a mean disease duration of 9 years compared with 12 years for the placebo group. Oral corticosteroids were used by 50% or more of patients in most treatment arms, except in PREMIER in which over 35% of patients with early RA were on steroids. The number of tender and swollen joints required for entry varied between trials recruiting from European centres compared with US trials. For example, ten swollen joints were required for entry into DE007 and DE011, compared with six in DE019 and DE031 (US studies). Baseline HAQ scores were also higher in the former studies, indicating more functional limitation.

van de Putte and colleagues, 2003 (DE007)[119]
This 12-week, double-blind, multicentre study compared weekly adalimumab 20, 40 or 80 mg s.c. with placebo without concomitant methotrexate. After 8 weeks in the trial, patients in any treatment arms with 'unbearable' disease were allowed to enter a rescue arm, during which other standard RA therapies were permitted but adalimumab was not permitted until week 12. After 12 weeks placebo-treated patients were given adalimumab 40 mg weekly for 40 weeks during a blinded continuation phase which is not included in this review. ACR20 response at week 12 was the primary end-point. Methods of randomisation, allocation concealment and blinding were not clearly described.

ARMADA, Weinblatt and colleagues, 2003 (DE009)[112]
This 24-week, double-blind, multicentre RCT compared adalimumab 20 mg every other week, 40 mg every other week, 80 mg every other week and placebo in patients receiving concomitant methotrexate. Treatment with methotrexate for at least 6 months before entry was required, with the dose stable at between 10 and 25 mg per week for more than 4 weeks. A minimum of six swollen joints and nine tender joints, and prior treatment failure with at least one DMARD besides methotrexate but no more than four DMARDs, were required. The primary end-point was ACR20 response at 24 weeks.

van de Putte and colleagues, 2004 (DE011)[113]
This 26-week, double-blind, multicentre RCT compared adalimumab monotherapy (s.c. 20 mg every other week, 20 mg every week, 40 mg every other week or 40 mg every week) with placebo in patients who had failed at least one DMARD. Patients with at least ten swollen joints and 12 tender joints were recruited. The primary end-point was ACR20 response.

PREMIER: Breedveld and colleagues, 2006 (DE013)[102,109]
This 2-year, double-blind, multicentre RCT compared treatment with methotrexate alone (started at 7.5 mg per week and escalated to up to 20 mg per week), adalimumab alone (40 mg s.c. every other week) or the combination of both in early RA patients (disease duration <3 years) who had not previously been treated with methotrexate. Patients with at least eight swollen joints and ten tender joints were recruited. Patients previously treated with more than two DMARDs were not eligible. Sixty-eight per cent of the randomised patients were DMARD naïve. Dose escalation of methotrexate had to be completed by week 26. After 16 weeks and the completion of methotrexate dose escalation, the dosing frequency for the parenteral study medication (adalimumab or placebo) was to be increased to every week for patients who failed to achieve or maintain an ACR20 response.

The primary end-points … **[Commercial-in-confidence information removed]** … to the comparison of ACR50 response at week 52 and

TABLE 1 *Description of included RCTs and baseline patient characteristics: adalimumab*

Study and description	Interventions[a]	No. of patients	Mean age (years)	Mean disease duration (years)	Mean no. of previous DMARDs	On steroids (%)	On NSAIDs (%)	Mean baseline HAQ score
DE001								
den Broeder *et al.*, 2002[116]	Placebo i.v. (one dose)	31	55	11.9	3.7	77	68	1.57
Netherlands and Germany, three centres, double-blind	Adalimumab 0.5 mg kg^{-1} i.v. (one dose)	17	54	11.0	3.6	53	94	1.57
	Adalimumab 1 mg kg^{-1} i.v. (one dose)	18	58	11.2	3.9	78	72	1.85
Adalimumab treatment: single injection	Adalimumab 3 mg kg^{-1} i.v. (one dose)	18	54	10.8	3.9	67	56	1.41
Duration of follow-up: 4 weeks to 3 months[b]	Adalimumab 5 mg kg^{-1} i.v. (one dose)	18	59	14.5	4.4	78	89	1.61
	Adalimumab 10 mg kg^{-1} i.v. (one dose)	18	53	8.9	3.9	67	72	1.93
DE005								
Weisman *et al.*, 2003[118]	Placebo i.v. (one dose) + MTX (12.5–25 mg per week, mean 17 mg per week)	15	51	15	NR	NR	NR	1.1
USA and Canada, six centres, double-blind								
Adalimumab treatment: single injection[c]	Adalimumab 0.25 mg kg^{-1} i.v. (one dose) + MTX (12.5–25 mg per week, mean 17 mg per week)	9	50	17				1.3
Duration of follow-up: 4 weeks[d]	Adalimumab 0.5 mg kg^{-1} i.v. (one dose) + MTX (12.5–25 mg per week, mean 13 mg per week)	9	56	13				0.9
	Adalimumab 1 mg kg^{-1} i.v. (one dose) + MTX (12.5–25 mg per week, mean 16 mg per week)	9	51	16				1.5
	Adalimumab 3 mg kg^{-1} i.v. (one dose) + MTX (12.5–25 mg per week, mean 15 mg per week)	9	56	15				1.0
	Adalimumab 5 mg kg^{-1} i.v. (one dose) + MTX (12.5–25 mg per week, mean 18 mg per week)	9	54	18				1.4
DE007								
van de Putte *et al.*, 2003[119]	Placebo s.c. weekly	70	50	9	3.5	77	80	1.63
Europe, 25 centres, double-blind	Adalimumab 20 mg s.c. weekly	72	54	10	4.1	76	76	1.79
Duration of treatment and follow-up: 12 weeks[c]	Adalimumab 40 mg s.c. weekly	70	53	10	3.7	70	81	1.74
	Adalimumab 80 mg s.c. weekly	72	53	10	3.7	75	78	1.66
DE009, ARMADA								
Weinblatt *et al.*, 2003[112]	Placebo s.c. every other week + MTX (12.5–25 mg per week, mean 17 mg per week)	62	56	11	3.0	58	NR	1.64
USA and Canada, 35 centres, double-blind								
Duration of treatment and follow-up: 24 weeks	Adalimumab 20 mg s.c. every other week + MTX (12.5–25 mg per week, mean 17 mg per week)	69	54	13	3.0			1.52
	Adalimumab 40 mg s.c. every other week + MTX (12.5–25 mg per week, mean 16 mg per week)	67	57	12	2.9	46		1.55
	Adalimumab 80 mg s.c. every other week + MTX (12.5–25 mg per week, mean 17 mg per week)	73	56	13 (n = 72)	3.1			1.55

continued

TABLE 1 *Description of included RCTs and baseline patient characteristics: adalimumab (cont'd)*

Study and description	Interventions[a]	No. of patients	Mean age (years)	Mean disease duration (years)	Mean no. of previous DMARDs	On steroids (%)	On NSAIDs (%)	Mean baseline HAQ score
DE010								
Rau *et al.*, 2004[117]	Placebo s.c. and i.v. (one dose) + MTX (7.5–25 mg per week, mean 14 mg per week)	18	54	12	3.5	72	94	1.38
Netherlands and Germany, four centres, double-blind	Adalimumab 1 mg kg^{-1} i.v. (one dose) + MTX (7.5–25 mg per week, mean 18 mg per week)	18	52	11	3.4	72	100	1.32
Duration of treatment and follow-up: 4 weeks[e]	Adalimumab 1 mg kg^{-1} s.c. (one dose) + MTX (7.5–25 mg per week, mean 16 mg per week)	18	53	11	3.3	83	89	1.33
DE011								
van de Putte *et al.*, 2004[113]	Placebo s.c. weekly	110	54	12	3.6	67	84	1.88
Europe, Canada and Australia, 52 centres, double-blind	Adalimumab 20 mg s.c. every other week	106	53	9	3.7	70	81	1.88
	Adalimumab 20 mg s.c. weekly	112	54	11	3.6	68	75	1.88
Duration of treatment and follow-up: 26 weeks[f]	Adalimumab 40 mg s.c. every other week	113	53	11	3.8	68	82	1.83
	Adalimumab 40 mg s.c. weekly	103	52	12	3.8	82	77	1.84
DE013, PREMIER								
Breedveld *et al.*, 2006[102,109]	MTX (7.5–20 mg per week) weekly[g]	257	52	0.8	0.4	35	NR	1.48
North America, Europe and Australia, multicentre, double-blind	Adalimumab 40 mg s.c. every other week[g]	274	52	0.7	0.4	37		1.63
Duration of treatment and follow-up: 2 years	Adalimumab 40 mg s.c. every other week + MTX (7.5–20 mg per week) weekly[g]	268	52	0.7	0.4	36		1.47
DE019								
Keystone *et al.*, 2004[114]								
USA and Canada, 89 centres, double-blind	Placebo s.c. + MTX (12.5–25 mg per week, mean 17 mg per week)	200	56	11	2.4	**[Commercial-in-confidence information removed]**	NR	1.48
Duration of treatment and follow-up: 52 weeks	Adalimumab 20 mg s.c. weekly + MTX (12.5–25 mg per week, mean 16 mg per week)	212	57	11	2.4			1.44
	Adalimumab 40 mg s.c. every other week + placebo s.c. on alternate weeks + MTX (12.5–25 mg per week, mean 17 mg per week)	207	56	11	2.4			1.45

continued

TABLE 1 *Description of included RCTs and baseline patient characteristics: adalimumab (cont'd)*

Study and description	Interventions[a]	No. of patients	Mean age (years)	Mean disease duration (years)	Mean no. of previous DMARDs	On steroids (%)	On NSAIDs (%)	Mean baseline HAQ score
DE 031, STAR								
Furst *et al.*, 2003[115]	Placebo s.c. + baseline standard antirheumatic therapy	318	56	12	≥ 2.0	54	64	1.43
USA and Canada, 69 centres, double-blind								
Duration of treatment and follow-up: 24 weeks	Adalimumab 40 mg s.c. every other week + baseline standard antirheumatic therapy	318	55	9	≥ 2.1	51	62	1.37

[a] Some of the groups receiving active treatment also received matching placebo (where necessary) to maintain blinding. These placebo injections are not listed.
[b] Open-label, continuation study (DE003) in which patients in the placebo group were switched to receive adalimumab is not included in current review.
[c] Patients in the placebo group were switched to adalimumab 40 mg at week 12. Subsequent blinded and open-label continuation studies without placebo control are not included in the current review.
[d] Patients received the first dose at baseline and the second dose after 4 weeks or on loss of response. Once the second dose was administered, the patient was considered to have completed the study and had the option to participate in a continuation study. This open-label continuation study (DE005X) in which the placebo group was switched to receive adalimumab is not included in the current review.
[e] A second double-blinded injection of randomised drug was given between 4 weeks and 3 months after the first injection according to the patient's response. Follow-up beyond 4 weeks and further 2.5-year open-label continuation study are not included in the current review.
[f] Further open-label extension is not included in the current review.
[g] Oral medication (MTX) started at 7.5 mg per week for 4 weeks. If any swollen joints remained, it could be escalated to a maximum of 20 mg per week by week 26. The dosing frequency of the parenteral medication (adalimumab) could be increased to every week on or after week 16, in patients who failed to respond or lost their response (ACR20) after escalating the oral medication.
MTX, methotrexate; NR, not reported.

TABLE 2 *Quality of included RCTs: adalimumab*

Study	Sample size	Truly random allocation/ remain on randomised treatment	Adequate allocation concealment	Blinding			Important differences in baseline characteristics between groups (item)	Important differences in completion rates between groups (% randomised patients completed)	Use of ITT analysis
				Participants	Investigators	Assessors			
DE001 den Broeder, 2002[116]	Placebo: 31 Adalimumab: 89	Unclear	Unclear	Yes	Yes	Unclear	No	No Placebo: 100% Adalimumab: 99%	Yes
DE005 Weisman, 2003[118]	Placebo: 15 Adalimumab: 45	Yes	Yes	Yes	Yes	Unclear	NA (sample size too small)	No Placebo: 100% Adalimumab: 100%	Yes
DE007 van de Putte, 2003[119]	Placebo: 70 Adalimumab: 214	Unclear	Unclear	Unclear	Unclear	Unclear	No	No Placebo: 97% Adalimumab: 95%	Yes
DE009 ARMADA: Weinblatt, 2003[112]	Placebo: 62 Adalimumab: 209	Yes	Yes	Yes	Yes	Yes	No	**[Commercial-in-confidence information removed]**	Yes
DE010 Rau, 2004[117]	Placebo: 18 Adalimumab: 36	Unclear	Unclear	Yes	Yes	Unclear	No	No Placebo: 100% Adalimumab: 97%	Yes
DE011 van de Putte, 2004[113]	Placebo: 110 Adalimumab: 434	Yes	Yes	Yes	Yes	Yes	No	Yes Placebo: 44% Adalimumab: 73%	Yes

continued

TABLE 2 *Quality of included RCTs: adalimumab (cont'd)*

Study	Sample size	Truly random allocation/ remain on randomised treatment	Adequate allocation concealment	Blinding			Important differences in baseline characteristics between groups (item)	Important differences in completion rates between groups (% randomised patients completed)	Use of ITT analysis
				Participants	Investigators	Assessors			
DE013 PREMIER: Breedveld, 2006[102,109]	MTX: 257 Adalimumab: 274 Combination: 268	Yes	Yes	Yes	Yes	Yes	No	Yes MTX: 66% Adalimumab: 61% Combination: 76%	Yes
DE019 Keystone, 2004[114]	Placebo: 200 Adalimumab: 419	Unclear	Yes	Yes	Yes	Yes	No	Yes Placebo: 70% Adalimumab: 78%	Yes (except radiographic outcomes)
DE031 STAR: Furst, 2003[115]	Placebo: 318 Adalimumab: 318	Yes	Yes	Yes	Yes	Yes	No	No Placebo: 91% Adalimumab: 91%	Yes

NA, not applicable.

change in modified total Sharp score from baseline to week 52 between the combination therapy and the methotrexate monotherapy only.

Keystone and colleagues, 2004 (DE019)[114]
This 52-week, double-blind, multicentre trial compared adalimumab 40 mg s.c. every other week, 20 mg s.c. every week and placebo in patients receiving concomitant methotrexate. Patients who either were rheumatoid factor positive or had at least one joint erosion on radiographs of the hands and feet were recruited. The primary end-points were ACR20 response at 24 weeks, change in modified Sharp score at week 52 and change in HAQ at week 52.

STAR: Furst and colleagues, 2003 (DE031)[115]
This 24-week, double-blind, multicentre safety trial compared adalimumab 40 mg s.c. every other week with placebo in RA patients who continued to receive their standard antirheumatic therapy (including DMARDs). Concomitant DMARDs were permitted if doses had been stable for at least 28 days before screening, and a single increase in DMARD dosage was allowed at week 12 or subsequent visits if a patient failed to meet or maintain ACR20 response. Eighty-three per cent of patients received at least one DMARD. The primary end-point, safety, was assessed by types and frequencies of adverse events, physical examination findings and standard laboratory test results.

Meta-analyses of adalimumab trials

The approaches to meta-analyses and data presentation are described in detail in the section 'Data analysis' (p. 14). The only adalimumab trial that recruited exclusively methotrexate-naïve patients with disease duration of less than 3 years was the PREMIER[102,109] trial and included three treatment arms which allow more than one comparison: adalimumab versus methotrexate and combination (adalimumab plus methotrexate) versus methotrexate.

Adalimumab versus methotrexate
The PREMIER[102,109] trial is the only trial that included head-to-head comparison between adalimumab and a DMARD (methotrexate). The results are summarised in *Table 3*.

Efficacy The only effectiveness result reaching conventional levels of statistical significance between adalimumab and methotrexate is radiographic joint damage. Patients treated with adalimumab had a smaller increase in modified Sharp score compared with those treated with methotrexate (mean difference over 2 years –4.90, 95% CI **[Commercial-in-confidence information removed]**). Adalimumab appears to be marginally less effective than methotrexate in reducing disease activity as measured by other means, for example the ACR20 response (RR 0.88, 95% CI 0.75 to 1.03) and ACR50 response (RR 0.86, 95% CI 0.70 to 1.06).

Tolerability No significant difference was found between adalimumab and methotrexate.

Safety One death occurred in the methotrexate arm and four occurred in the adalimumab arm. The number of patients with malignancy was similar (**[Commercial-in-confidence information removed]** in the methotrexate arm and four in the adalimumab arm). More patients experienced SAEs in the adalimumab arm, although this did not reach statistical significance (**[Commercial-in-confidence information removed]**). **[Commercial-in-confidence information removed]** patients had serious infections in the methotrexate arm compared with **[Commercial-in-confidence information removed]** in the adalimumab arm, but no difference was found in the risk of overall infection between the treatment groups.

Adalimumab versus placebo
Five trials[112–115,119] included a comparison of adalimumab with placebo at the licensed dose (or equivalent). Three additional trials[116–118] included this comparison at above or under licensed doses. The results of primary analyses (licensed dose only) for the comparison between adalimumab and placebo are summarised in *Table 4*. Forest plots for the ACR20, ACR50, ACR70, HAQ, SAEs and malignancy are shown in the upper parts of *Figures 2–12*.

Efficacy Adalimumab at the licensed dose is significantly more effective than placebo for all the efficacy outcomes included in the meta-analyses.

Tolerability Significantly **[Commercial-in-confidence information removed]** patients withdrew for any reasons and for lack of efficacy in the adalimumab group compared with the placebo group. Slightly more patients withdrew owing to adverse events in the adalimumab group, but these did not reach statistical significance.

Safety Adalimumab is associated with a slight, but significantly increased, risk of any infection compared with placebo. It also appears to be associated with an increased risk of death,

TABLE 3 *Summary of 2-year results from the PREMIER study: adalimumab s.c. licensed dose only (40 mg every other week) versus MTX alone in MTX-naïve patients, 2-year results*

Comparison or outcome	*N* included in analysis	Statistical method	Effect size (95% CI)
ACR20 responder	531	RR (fixed)	0.88 (0.75 to 1.03)
ACR50 responder	531	RR (fixed)	0.86 (0.70 to 1.06)
ACR70 responder	531	RR (fixed)	0.99 (0.75 to 1.30)
RD ACR20 responder	531	RD (fixed)	–0.07 (–0.15 to 0.02)
RD ACR50 responder	531	RD (fixed)	–0.06 (–0.14 to 0.02)
RD ACR70 responder	531	RD (fixed)	0.00 (–0.08 to 0.07)
SJC, mean change from baseline	335	WMD (fixed)	**[Commercial-in-confidence information removed]**
Patient's global assessment, mean change from baseline	329	WMD (fixed)	**[Commercial-in-confidence information removed]**
HAQ, mean change from baseline	328	WMD (fixed)	0.00 (–0.13 to 0.13)
DAS28-4, mean change from baseline	319	WMD (fixed)	**[Commercial-in-confidence information removed]**
Modified van de Heijde–Sharp score, mean change from baseline	531	WMD (fixed)	–4.90 **[Commercial-in-confidence information removed]***
Withdrawal for any reasons	531	RR (fixed)	1.14 (0.91 to 1.43)
Withdrawal due to lack of efficacy	531	RR (fixed)	1.06 (0.74 to 1.52)
Withdrawal due to adverse events	531	RR (fixed)	1.28 (0.73 to 2.26)
Death	531	RR (fixed)	3.75 (0.42 to 33.35)
SAEs	531	RR (fixed)	**[Commercial-in-confidence information removed]**
Malignancy: all	531	RR (fixed)	**[Commercial-in-confidence information removed]**
Malignancy: skin cancer excluding melanoma	531	RR (fixed)	**[Commercial-in-confidence information removed]**
Malignancy: all cancer excluding non-melanoma skin cancer	531	RR (fixed)	0.94 (0.24 to 3.71)
Serious infection	531	RR (fixed)	0.40 (0.11 to 1.54)
Any infection	531	RR (fixed)	**[Commercial-in-confidence information removed]**

* Statistically significant result ($p < 0.05$).

malignancy and serious infections, although these did not reach statistical significance. No difference in the risk of serious adverse events was observed.

Sensitivity analyses Results of sensitivity analyses that included the licensed dose and above, and all doses, are listed in *Tables 70* and *71* (Appendix 4). The results are in the same direction and very similar to the primary analysis. The increase in serious infection became statistically significant.

Adalimumab plus methotrexate versus methotrexate alone

Only the PREMIER[102,109] trial included this comparison in methotrexate-naïve, early RA patients, and the results are summarised in *Table 5*. The outcomes for ACR20, ACR50, ACR70, HAQ, SAEs, and malignancy are also displayed in the lower parts of *Figures 2–12*.

Efficacy The combination of adalimumab plus methotrexate is more effective than methotrexate

TABLE 4 *Meta-analyses: adalimumab s.c. licensed dose only (40 mg every other week or equivalent) versus placebo (with or without ongoing conventional DMARDs), end of trial*

Comparison or outcome	Studies	*N* included in analysis	Statistical method	Effect size (95% CI)
ACR20 responder	5[112–115,119]	1854	RR (fixed)	2.11 (1.84 to 2.42)*
ACR50 responder	5[112–115,119]	1854	RR (fixed)	3.58 (2.81 to 4.58)*
ACR70 responder	5[112–115,119]	1854	RR (fixed)	5.22 (3.45 to 7.89)*
RD ACR20 responder	5[112–115,119]	1854	RD (fixed)	0.28 (0.24 to 0.32)*
RD ACR50 responder	5[112–115,119]	1854	RD (fixed)	0.24 (0.20 to 0.27)*
RD ACR70 responder	5[112–115,119]	1854	RD (random)	0.13 (0.09 to 0.17)*
Swollen joint count, mean change from baseline	5[112–115,119]	1851	WMD (fixed)	–5.14 (–6.07 to –4.21)*
Patient's global assessment, mean change from baseline	5[112–115,119]	1850	WMD (fixed)	–1.62 (–1.89 to –1.35)*
HAQ, mean change from baseline	5[112–115,119]	1850	WMD (fixed)	–0.31 (–0.36 to –0.26)*
DAS28, mean change from baseline	2[113,119]	476	WMD (fixed)	–1.12 (–1.37 to –0.86)*
Modified van de Heijde–Sharp score, mean change from baseline	1[114]	551	WMD (fixed)	–2.20 (–3.33 to –1.07)*
Withdrawal for any reasons	5[112–115,119]	1861	RR (fixed)	**[Commercial-in-confidence information removed]***
Withdrawal due to lack of efficacy	5[112–115,119]	1861	RR (fixed)	**[Commercial-in-confidence information removed]***
Withdrawal due to adverse events	5[112–115,119]	1861	RR (fixed)	1.37 (0.87 to 2.16)
Death	5[112–115,119]	1861	RR (fixed)	2.02 (0.42 to 9.59)
SAEs	5[112–115,119]	1861	RR (fixed)	1.05 (0.78 to 1.41)
Malignancy: all	5[112–115,119]	1861	RR (fixed)	3.44 (0.94 to 12.60)
Malignancy: skin cancer excluding melanoma	5[112–115,119]	1861	RR (fixed)	2.11 (0.55 to 8.06)
Malignancy: all cancer excluding non-melanoma skin cancer	5[112–115,119]	1861	RR (fixed)	2.92 (0.50 to 17.13)
Serious infection	5[112–115,119]	1861	RR (fixed)	2.35 (1.00 to 5.53)
Any infection	4[112–115]	1719	RR (fixed)	1.18 (1.07 to 1.29)*

* Statistically significant result ($p < 0.05$).

alone for all the efficacy outcomes included in the meta-analysis, although the difference did not reach statistical significance for **[Commercial-in-confidence information removed]** and HAQ change.

Tolerability Compared with methotrexate alone, the combination was associated with significantly fewer withdrawals due to lack of efficacy and withdrawals for any reason. The combination was associated with a statistically non-significant increase in withdrawal due to adverse events.

Safety The only statistically significant difference between the combination and methotrexate monotherapy among the safety outcomes meta-analysed was **[Commercial-in-confidence information removed]**. There was also a non-significant increase in serious infection in the combination group compared with the methotrexate group (RR **[Commercial-in-confidence information removed]**).

Etanercept

Description of included etanercept trials

Eleven trials comprising a total of 3717 patients (3659 actually treated) were included. Clinical study reports were provided by Wyeth for ten of the studies: Moreland (three studies),[120–122] ERA,[123,124] Weinblatt,[125]; Wajdula,[126] Codreanu,[103]

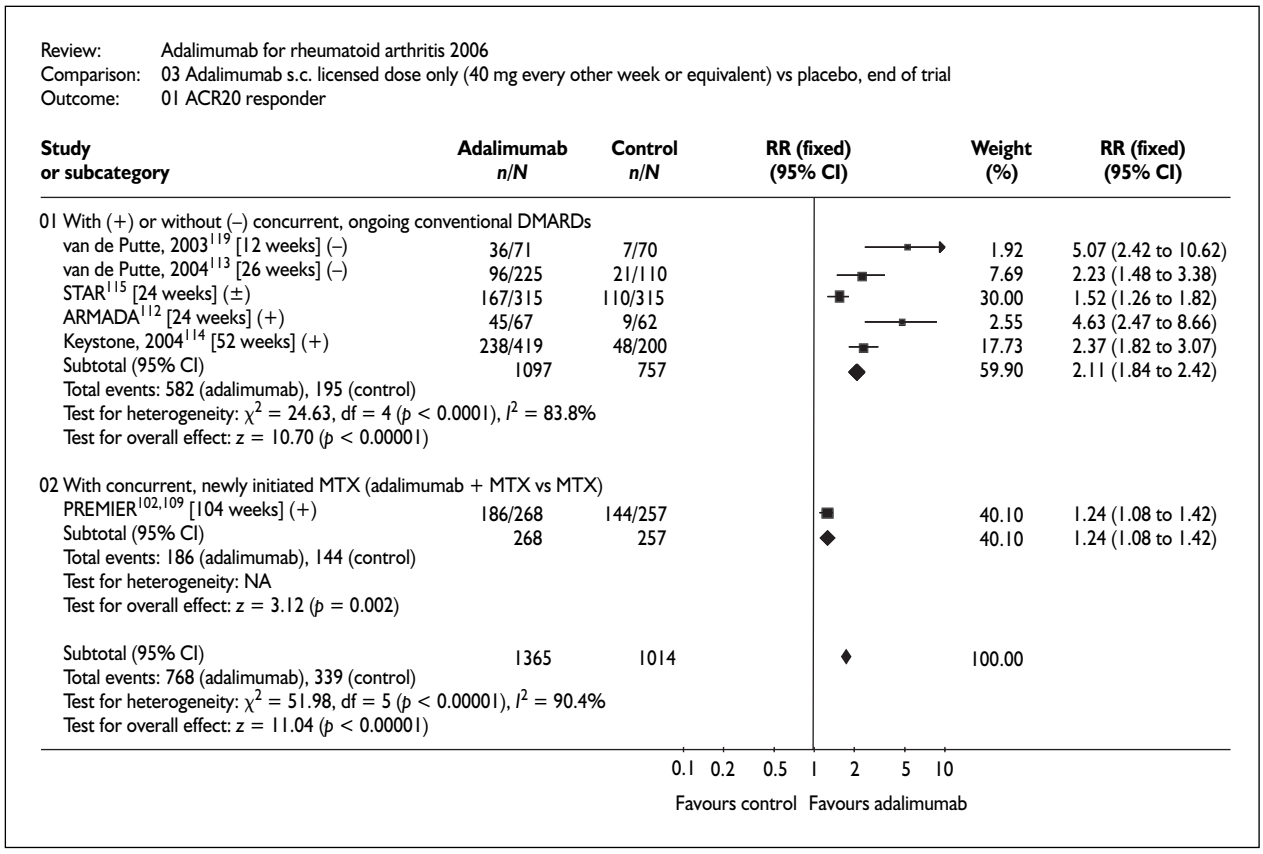

FIGURE 2 *ACR20 RR: adalimumab licensed dose versus placebo (including adalimumab plus MTX versus MTX)*

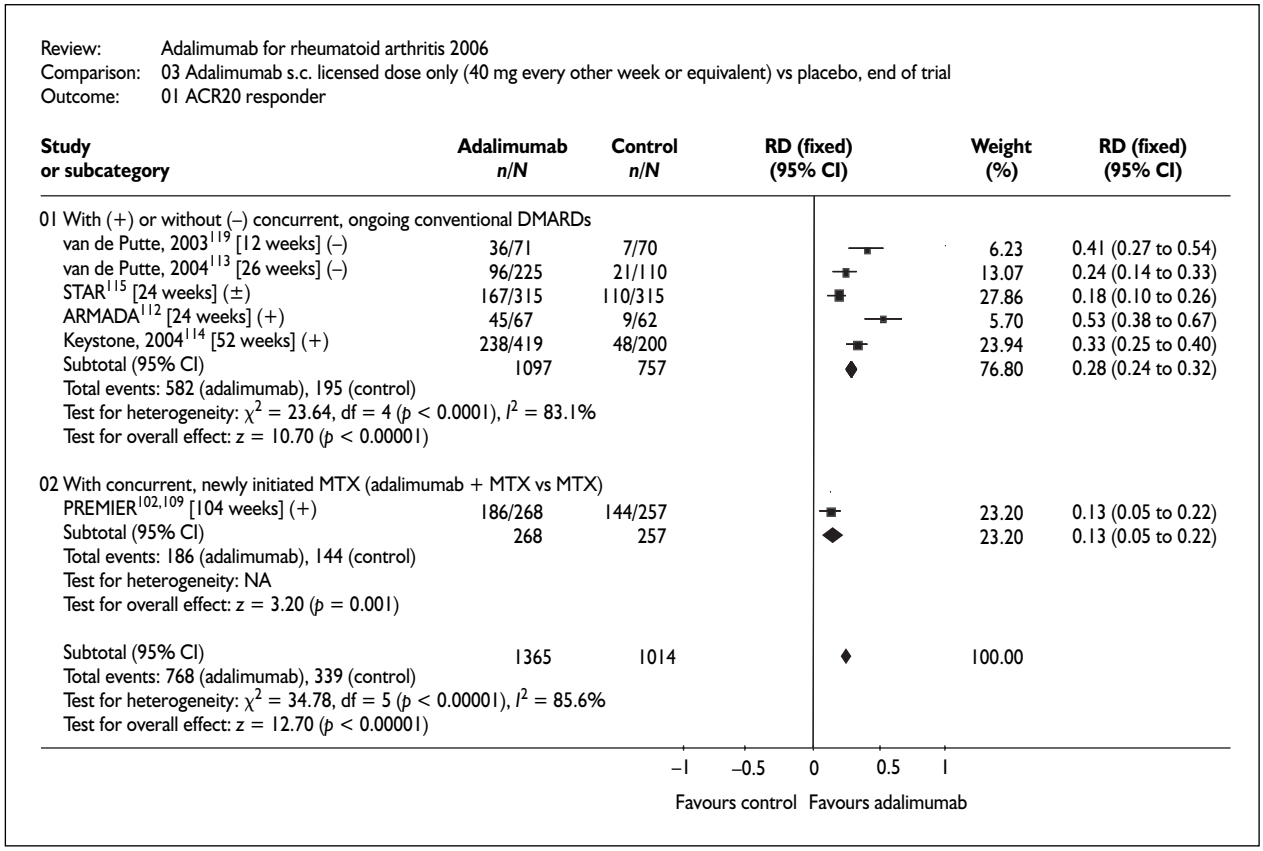

FIGURE 3 *ACR20 RD: adalimumab licensed dose versus placebo (including adalimumab plus MTX versus MTX)*

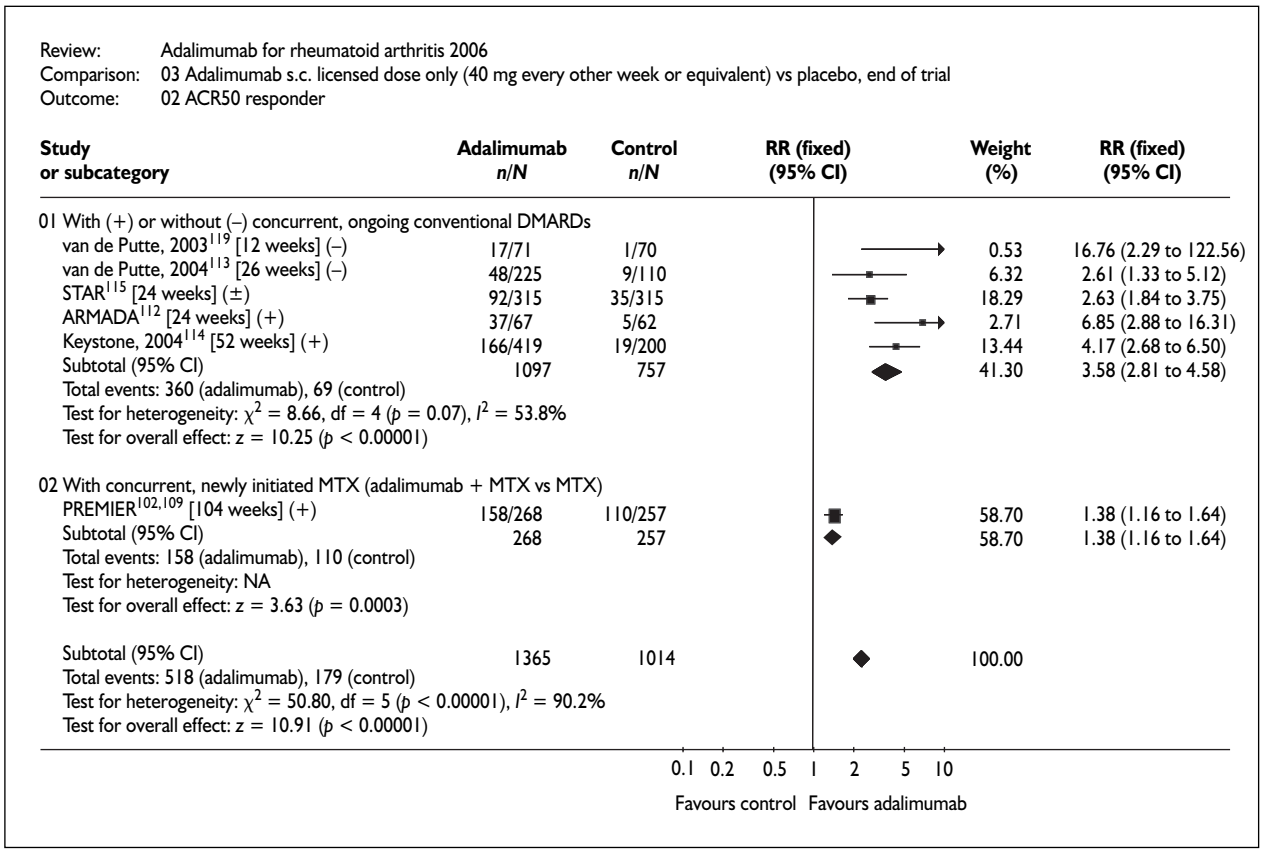

FIGURE 4 *ACR50 RR: adalimumab licensed dose versus placebo (including adalimumab plus MTX versus MTX)*

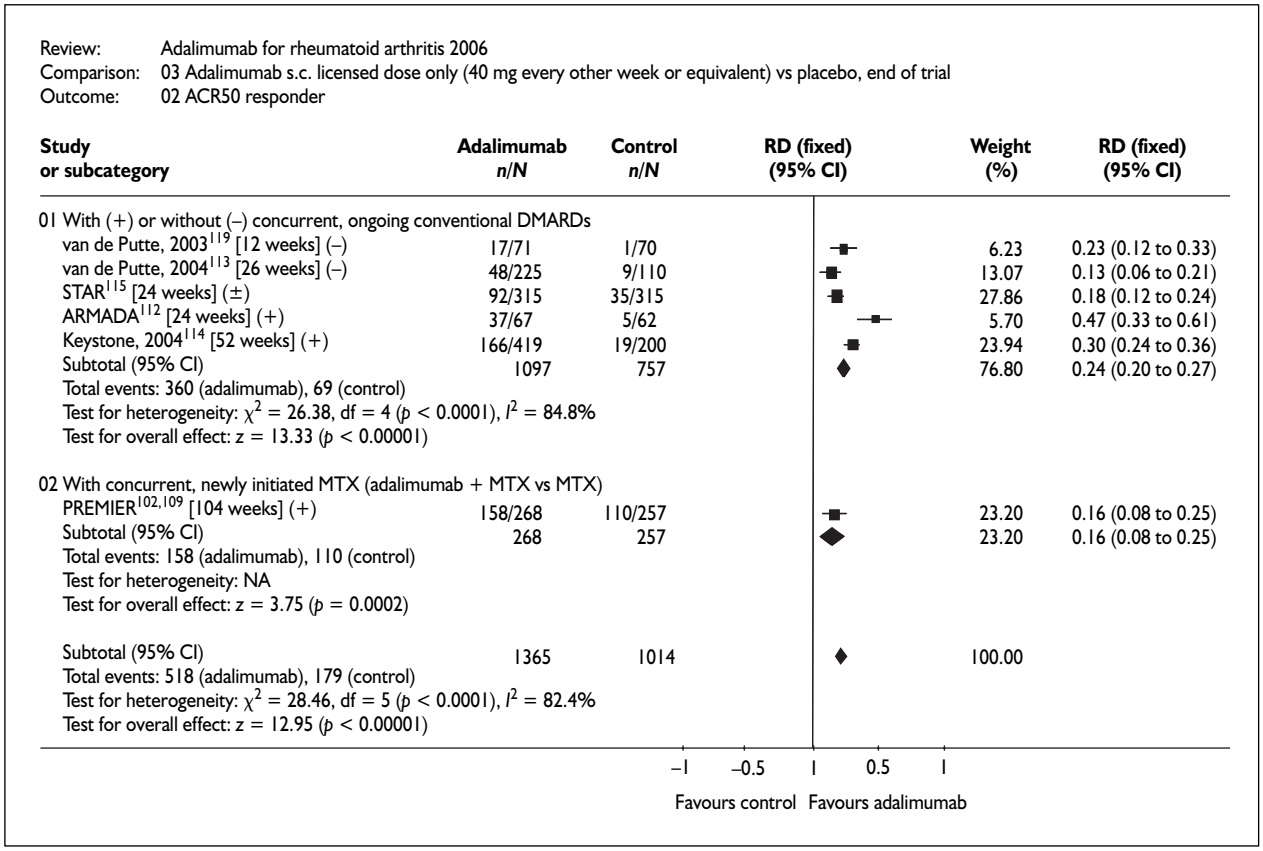

FIGURE 5 *ACR50 RD: adalimumab licensed dose versus placebo (including adalimumab plus MTX versus MTX)*

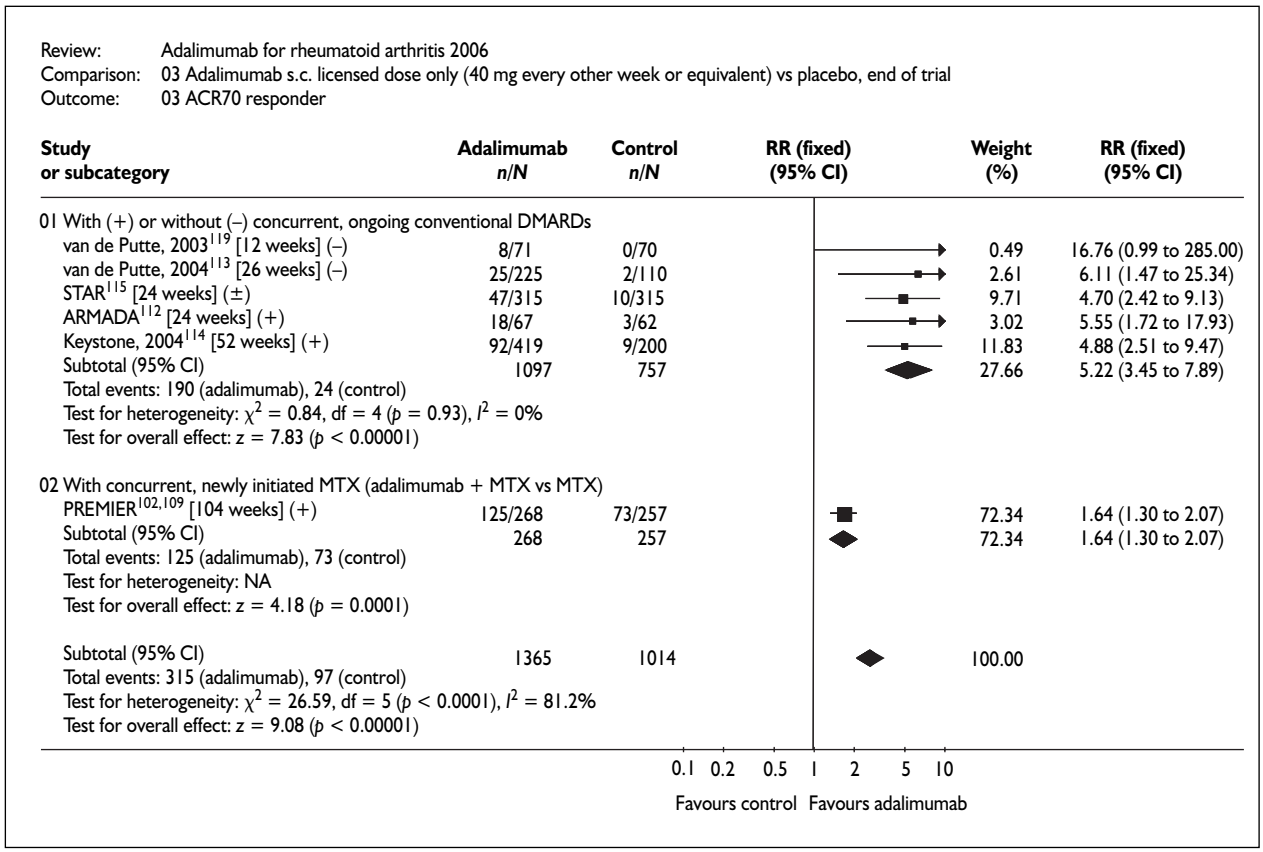

FIGURE 6 *ACR70 RR: adalimumab licensed dose versus placebo (including adalimumab plus MTX versus MTX)*

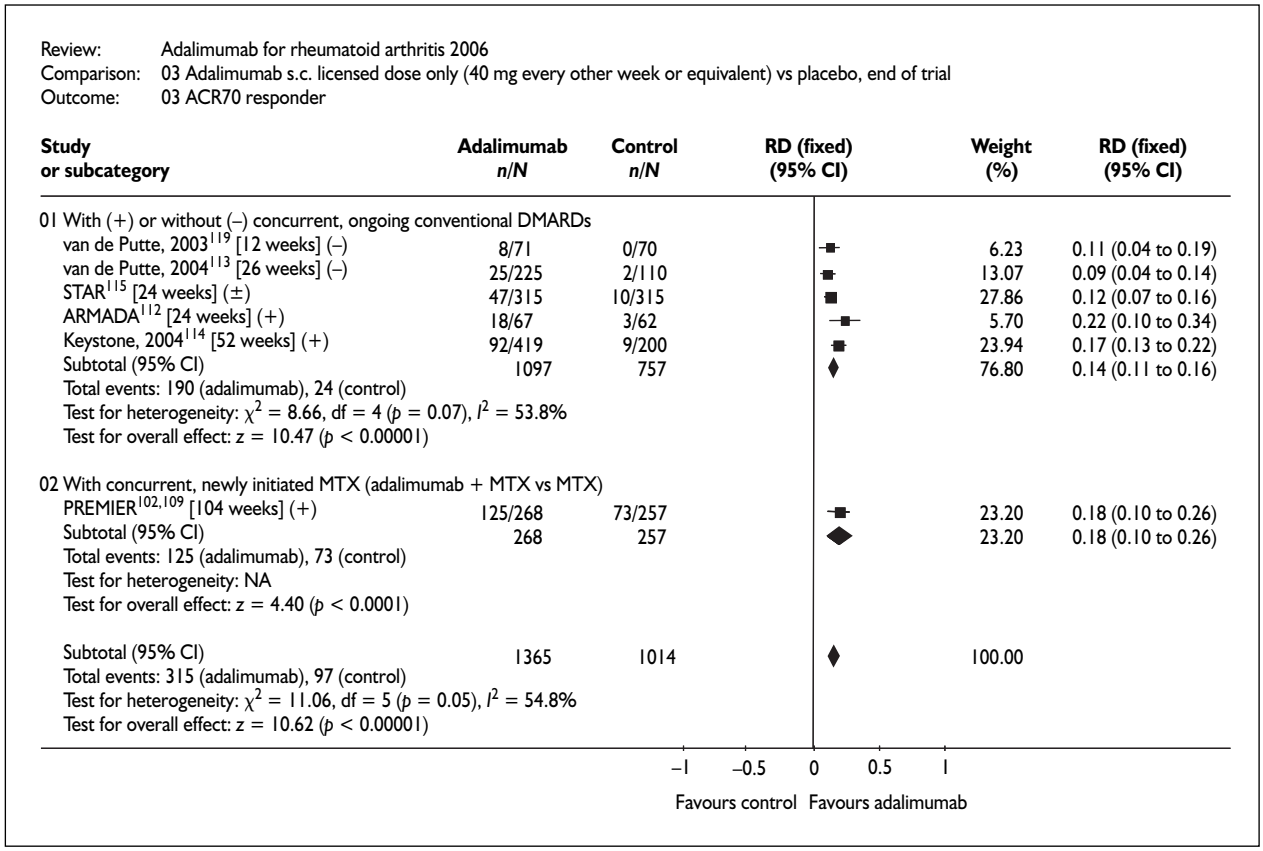

FIGURE 7 *ACR70 RD: adalimumab licensed dose versus placebo (including adalimumab plus MTX versus MTX)*

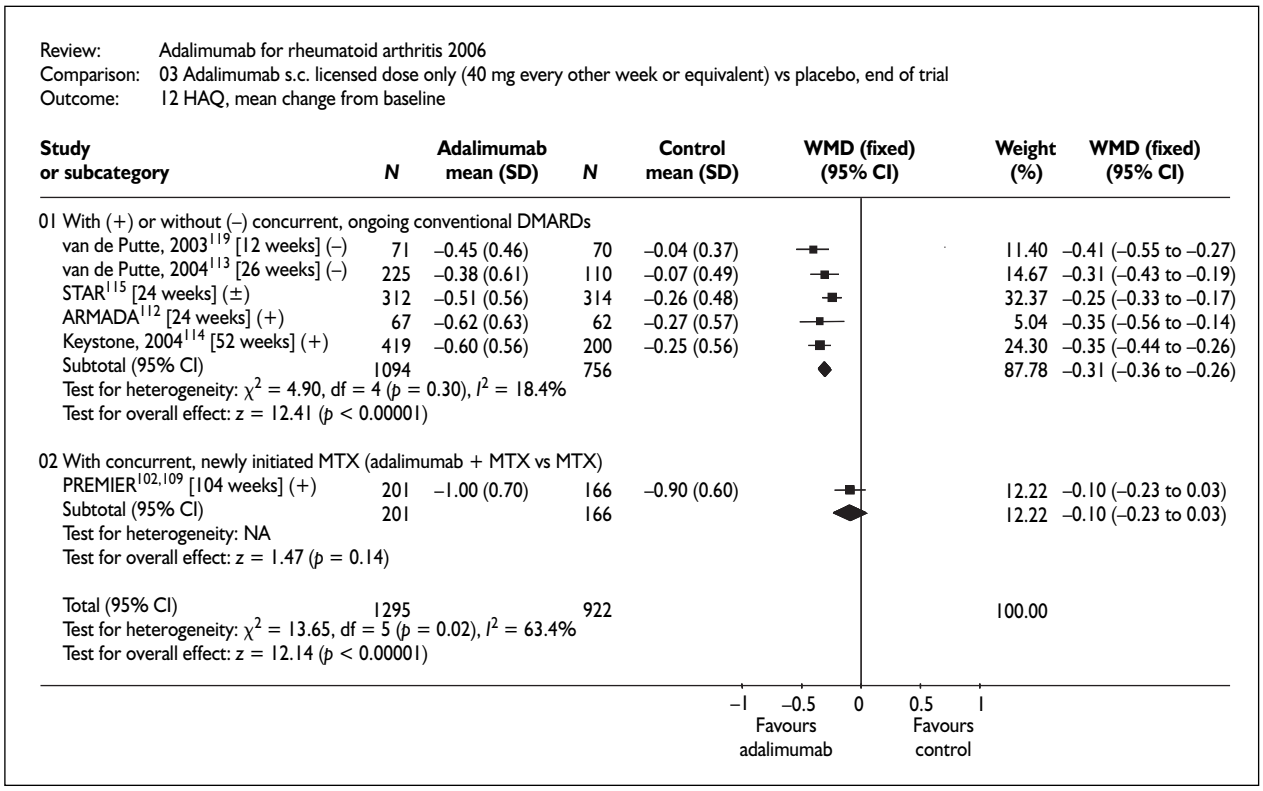

FIGURE 8 *HAQ change: adalimumab licensed dose versus placebo (including adalimumab plus MTX versus MTX)*

FIGURE 9 *SAE RR: adalimumab licensed dose versus placebo (including adalimumab plus MTX versus MTX)*
[Commercial-in-confidence information removed].

FIGURE 10 *SAE RD: adalimumab licensed dose versus placebo (including adalimumab plus MTX versus MTX)*
[Commercial-in-confidence information removed].

FIGURE 11 *Malignancy RR: adalimumab licensed dose versus placebo (including adalimumab plus MTX versus MTX)*
[Commercial-in-confidence information removed].

FIGURE 12 *Malignancy RD: adalimumab licensed dose versus placebo (including adalimumab plus MTX versus MTX)*
[Commercial-in-confidence information removed].

TEMPO,[127,128] Keystone,[129] and Baumgartner.[104] Additional data from these reports were included in this systematic review. The report by Lan and colleagues[130] was only available as a published paper.

A list of these trials, including comparators and baseline patient characteristics, is shown in *Table 6*. Quality assessments of these trials, which are generally of high quality, are summarised in *Table 7*. In all trials, except for Baumgartner,[104] patients had active disease defined according to a number of tender and swollen joints and other parameters such as ESR and CRP. All patients met agreed disease classification criteria. Stable doses of oral prednisolone (≤ 10 mg per day) and NSAIDs were allowed. With the exception of the trial by Baumgartner and colleagues,[104] patients with a recent history of infection and significant co-morbidity were excluded. Only one trial, ERA,[123,124] recruited exclusively early RA patients. Key features for each of the studies are described below.

Moreland and colleagues, 1996[120]
Results from this study are not included in the meta-analyses because of very small patient numbers (three or four patients in each treatment group), short duration and imbalances in baseline patient characteristics (*Table 6*).

Moreland and colleagues, 1997[121]
This double-blind, multicentre RCT compared three doses of etanercept (0.25, 2 or 16 mg m^{-2} body surface area s.c. twice weekly) with placebo for three months. Patients who had failed up to four DMARDs and had at least ten swollen joints and 12 tender joints were included. Primary efficacy measures were percentage change from baseline to 3 months in swollen joint count, tender joint count and total count of swollen or tender joints.

TABLE 5 *Summary of 2-year results from PREMIER study: combination of adalimumab s.c. licensed dose (40 mg every other week or equivalent) plus MTX versus MTX alone in MTX-naïve patients, 2-year results*

Comparison or outcome	*N* included in analysis	Statistical method	Effect size (95% CI)
ACR20 responder	525	RR (fixed)	1.24 (1.08 to 1.42)*
ACR50 responder	525	RR (fixed)	1.38 (1.16 to 1.64)*
ACR70 responder	525	RR (fixed)	1.64 (1.30 to 2.07)*
RD ACR20 responder	525	RD (fixed)	0.13 (0.05 to 0.22)*
RD ACR50 responder	525	RD (fixed)	0.16 (0.08 to 0.25)*
RD ACR70 responder	525	RD (fixed)	0.18 (0.10 to 0.26)*
SJC, mean change from baseline	369	WMD (fixed)	**[Commercial-in-confidence information removed]**
Patient's global assessment, mean change from baseline	366	WMD (fixed)	**[Commercial-in-confidence information removed]***
HAQ, mean change from baseline	367	WMD (fixed)	–0.10 (–0.23 to 0.03)
DAS28, mean change from baseline	352	WMD (fixed)	**[Commercial-in-confidence information removed]***
Modified van de Heijde–Sharp score, mean change from baseline	525	WMD (fixed)	–8.50 **[Commercial-in-confidence information removed]***
Withdrawal for any reasons	525	RR (fixed)	0.71 (0.54 to 0.93)*
Withdrawal due to lack of efficacy	525	RR (fixed)	0.27 (0.15 to 0.49)*
Withdrawal due to adverse events	525	RR (fixed)	1.62 (0.94 to 2.77)
Death	525	RR (fixed)	0.96 (0.06 to 15.25)
SAEs	525	RR (fixed)	**[Commercial-in-confidence information removed]**
Malignancy: all	525	RR (fixed)	**[Commercial-in-confidence information removed]**
Malignancy: skin cancer excluding melanoma	525	RR (fixed)	**[Commercial-in-confidence information removed]**
Malignancy: all cancer excluding non-melanoma skin cancer	525	RR (fixed)	0.48 (0.09 to 2.60)
Serious infection	525	RR (fixed)	**[Commercial-in-confidence information removed]**
Any infection	525	RR (fixed)	**[Commercial-in-confidence information removed]***

* Statistically significant result ($p < 0.05$).

Moreland and colleagues, 1999[122]
This 6-month double-blind, multicentre RCT compared etanercept 10 or 25 mg s.c. twice weekly with placebo. Patients who had failed up to four DMARDs were recruited. At least ten swollen joints and 12 tender joints were required at entry. The primary efficacy end-points were ACR20 and ACR50 response at 3 and 6 months.

Weinblatt and colleagues, 1999[125]
This 24-week, double-blind, multicentre RCT compared etanercept 25 mg s.c. twice weekly with placebo. Patients who had at least six swollen joints and six tender joints despite at least 6 months of methotrexate treatment were included. All patients remained on stable doses of methotrexate (15–25 mg per week). The primary end-point was ACR20 response at 24 weeks.

TABLE 6 *Description of included studies and baseline patient characteristics: etanercept*

Study and description	Interventions[a]	No. of patients	Mean age (years)	Mean disease duration (years)	No. of previous DMARDs	On steroids (%)	On NSAIDs (%)	Mean baseline HAQ score
Protocol 16.0002								
Moreland *et al.*, 1996[120]								
USA, single centre, double-blind	Placebo single i.v. injection followed by s.c. injection twice weekly	4	54	19.8	NR	NR	NR	NR
Duration of treatment and follow-up: 4 weeks	Etanercept 4 mg m^{-2} single i.v. injection followed by 2 mg m^{-2} s.c. injection twice weekly	3	56	5.3				
	Etanercept 8 mg m^{-2} single i.v. injection followed by 4 mg m^{-2} s.c. injection twice weekly	3	38	4.3				
	Etanercept 16 mg m^{-2} single i.v. injection followed by 8 mg m^{-2} s.c. injection twice weekly	3	53	4.7				
	Etanercept 32 mg m^{-2} single i.v. injection followed by 16 mg m^{-2} s.c. injection twice weekly	3	62	6.3				
Protocol 16.0004								
Moreland *et al.*, 1997[121]	Placebo s.c. twice weekly	44	55	71% > 5 years	34% MTX[b]	66	73	146[c]
USA, multicentre, double-blind	Etanercept 0.25 mg m^{-2} s.c. twice weekly	46	54	76% > 5 years	41% MTX	59	70	153
Duration of treatment and follow-up: 3 months	Etanercept 2 mg m^{-2} s.c. twice weekly	46	52	80% > 5 years	30% MTX	65	80	138
	Etanercept 16 mg m^{-2} s.c. twice weekly	44	52	80% > 5 years	27% MTX	77	75	135
Protocol 16.0009								
Moreland *et al.*, 1999[122]	Placebo s.c. twice weekly	80	51	12	3.0	58	84	1.7
North America, 13 centres, double-blind	Etanercept 10 mg s.c. twice weekly	76	53	13	3.4	66	67	1.7
Duration of treatment and follow-up: 6 months	Etanercept 25 mg s.c. twice weekly	78	53	11	3.3	81	67	1.6
Protocol 16.0012								
ERA: Bathon *et al.*, 2000;[123] Genovese *et al.*, 2002[124]	MTX (starting 7.5 and escalating to 20 mg per week by week 8; mean 19 mg per week) + placebo	217	49	1.0	0.6	41	80	1.4
USA and Canada, 69 centres, double-blind	Etanercept 10 mg s.c. twice weekly + placebo	208	50	0.9	0.5	42	76	1.4
Duration of treatment and follow-up: 24 months (double-blind for the first 12 months, and open-label for a further 12 months)	Etanercept 25 mg s.c. twice weekly + placebo	207	51	1.0	0.5	39	86	1.5

continued

TABLE 6 *Description of included studies and baseline patient characteristics: etanercept (cont'd)*

Study and description	Interventions[a]	No. of patients	Mean age (years)	Mean disease duration (years)	No. of previous DMARDs	On steroids (%)	On NSAIDs (%)	Mean baseline HAQ score
Protocol 16.0014								
Weinblatt *et al.*, 1999[125]	Placebo + ongoing MTX (12.5–25 mg per week; mean 18 mg per week)	30	53	13	2.8	70	80	1.3
USA, multicentre, double-blind								
Duration of treatment and follow-up: 24 weeks	Etanercept 25 mg s.c. twice weekly + ongoing MTX (12.5–25 mg per week; mean 19 mg per week)	59	48	13	2.7	53	75	1.5
Protocol 0881A1-300-EU								
Wajdula, 2000[126] (European Etanercept Investigators Group)	Placebo s.c. twice weekly	105	53	7.2	3.5	71	85	1.8
	Etanercept 10 mg s.c. once weekly	122	53	6.9	3.2	77	82	1.8
Europe, multicentre, double-blind[131]	Etanercept 10 mg s.c. twice weekly	110	54	6.8	3.0	71	86	1.8
Duration of treatment and follow-up: 12 weeks	Etanercept 25 mg s.c. once weekly	111	54	7.3	3.3	68	83	1.8
	Etanercept 25 mg s.c. twice weekly	111	53	7.5	3.6	70	86	1.9
Protocol 0881A1-309								
Codreanu *et al.*, 2003[103]	Sulfasalazine 2–3 g per day + placebo	50	53	5.6	2.1	32	86	1.6
Europe and Australia, multicentre, double-blind	Etanercept 25 mg s.c. twice weekly + placebo	103	51	7.1	2.7	50	82	1.7
Duration of treatment and follow-up: 24 weeks[d]	Etanercept 25 mg s.c. twice weekly + SSZ 2–3 g per day	101	51	6.5	2.3	40	83	1.6
Protocol 0881A1-308-EU/AU								
TEMPO: Klareskog *et al.*, 2004[110,127,128]	MTX (starting 7.5, escalating to 20 mg per week if any painful/swollen joint; mean 18 mg) + placebo	228	53	6.8	2.3	64	86	1.7
Europe and Australia, multicentre, double-blind	Etanercept 25 mg s.c. twice weekly + placebo	223	53	6.3	2.3	57	86	1.8
	Etanercept 25 mg s.c. twice weekly + MTX (starting 7.5, escalating to 20 mg per week if any painful/swollen joint; mean 18 mg)	231	53	6.8	2.3	62	86	1.8
Duration of treatment and follow-up: period one 52 weeks; period two ongoing double-blind extension, with year 2 results reported								

continued

TABLE 6 *Description of included studies and baseline patient characteristics: etanercept (cont'd)*

Study and description	Interventions[a]	No. of patients	Mean age (years)	Mean disease duration (years)	No. of previous DMARDs	On steroids (%)	On NSAIDs (%)	Mean baseline HAQ score
Protocol 16.0036					(Prior use)			
Keystone *et al.*, 2004[129]	Placebo (55% with ongoing MTX, mean 14 mg per week)	53	54	10.8	89%	NR	NR	1.4
USA and Canada, 48 centres, double-blind	Etanercept 25 mg s.c. twice weekly (52% with ongoing MTX, mean 15 mg per week)	153	52	8.2	90%			1.4
Duration of treatment and follow-up: 8 weeks[e]	Etanercept 50 mg s.c. once weekly (53% with ongoing MTX, mean 14 mg per week)	214	53	9.0	88%			1.4
Protocol 0881A-100093								
Lan *et al.*, 2004[130]	Placebo + MTX (12.5–20 mg per week)	29	51	NR	NR	NR	NR	1.2
Taiwan, single centre, double-blind	Etanercept 25 mg s.c. twice weekly + MTX	29	48					1.0
Duration of treatment and follow-up: 12 weeks	(same as above)							
Protocol 16.0029								
Baumgartner *et al.*, 2004[104]	Placebo twice s.c. weekly	269	60	10	NR	NR	NR	NR
USA, multicentre, double-blind	Etanercept 25 mg s.c. twice weekly	266						
Duration of treatment: 16 weeks								
Duration of follow-up: 20 weeks								

[a] Some of the groups receiving active treatment also received matching placebo (where necessary) to maintain blinding. These placebo injections are not listed.
[b] All patients had received at least one previous DMARD, but details are not reported. The values shown are percentages using methotrexate in the year before the study.
[c] On this scale, 45 is best and 245 worst.
[d] Double-blind extension up to 60–100 weeks is not included in current review: data not provided.
[e] The placebo group switched to etanercept 25 mg twice weekly from week 8 and all treatment groups were followed up to week 16. The results from week 8 onwards are not included in the current review.
SSZ, sulfasalazine.

TABLE 7 *Quality of included studies: etanercept*

Study	Sample size	Truly random allocation/ remain on randomised treatment	Adequate allocation concealment	Blinding			Important differences in baseline characteristics between groups (item)	Important differences in completion rates between groups (% randomised patients completed)	Use of ITT analysis
				Participants	Investigators	Assessors			
Moreland, 1996[120]	Placebo:4 Etanercept: 12	Unclear	Unclear	Yes	Yes	Unclear	Sample size too small	Sample size too small	Yes
Moreland, 1997[121]	Placebo: 44 Etanercept: 136	Yes	Yes	Yes	Yes	Yes	No	Yes Placebo: 52% Etanercept: 76%	Yes
Moreland, 1999[122]	Placebo: 80 Etanercept: 154	Yes	Yes	Yes	Yes	Yes	Yes (concurrent steroids and NSAIDs)	Yes Placebo: 33% Etanercept: 72%	Yes
ERA									
First 12 months: Bathon, 2000[123]	MTX: 217 Etanercept: 415	Yes	Yes	Yes	Yes	Yes	No	No MTX: 79% Etanercept: 82%	Yes
12–24 months Genovese, 2002[124]	MTX: 169 Etanercept: 343	Yes	NA	No	No	No (except radiograph readers)	No	Yes MTX: 59% Etanercept: 69%	Yes (except radiographic outcomes)
Weinblatt, 1999[125]	Placebo: 30 Etanercept: 59	Yes	Yes	Yes	Yes	Yes	No	Yes Placebo: 80% Etanercept: 97%	Yes
Wajdula, 2000[126]	Placebo: 105 Etanercept: 454	Yes	Yes	Yes	Yes	Yes	No	Yes Placebo: 81% Etanercept: 93%	No (except safety)
Codreanu, 2003[103]	SSZ: 50 Etanercept: 103 Etanercept + SSZ: 101	Yes	Yes	Yes	Yes	Yes	No	Yes SSZ: 66% Etanercept: 91% Etanercept + SSZ: 93%	Yes
TEMPO:									
Up to 52 weeks, Klareskog, 2004[127]	MTX: 228 Etanercept: 223 Etanercept + MTX: 231	Yes	Yes	Yes	Yes	Yes	No	Yes MTX: 70% Etanercept: 76% Etanercept + MTX: 84%	Yes

continued

TABLE 7 *Quality of included studies: etanercept (cont'd)*

Study	Sample size	Truly random allocation/ remain on randomised treatment	Adequate allocation concealment	Blinding			Important differences in baseline characteristics between groups (item)	Important differences in completion rates between groups (% randomised patients completed)	Use of ITT analysis
				Participants	Investigators	Assessors			
Week 52–100[110]	MTX: 152 Etanercept: 163 Etanercept + MTX: 188	Yes	NA	Yes	Yes	Yes	Unclear	Yes MTX: 52% Etanercept: 61% Etanercept + MTX: 71%	Yes
Keystone, 2004[129]	Placebo: 53 Etanercept: 367	Yes	Yes	Yes	Yes	Yes	No	No Placebo: 94% Etanercept: 95%	Yes
Lan 2004,[130]	Placebo: 29 Etanercept: 29	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Yes
Baumgartner, 2004[104]	Placebo: 269 Etanercept: 266	Yes	Yes	Yes	Yes	Yes	No	Yes Placebo: 72% Etanercept: 86%	Yes

NA, not applicable.

European Etanercept Investigators Study: Wajdula and colleagues, 2000[126]
This double-blind, multicentre RCT compared four etanercept treatment regimens (10 mg s.c. once weekly, 10 mg twice weekly, 25 mg once weekly, 25 mg twice weekly) with placebo. This study was planned to run for 6 months, but the protocol was modified to a 3-month double-blind study after inception for reasons that were unclear. Patients with at least six swollen joints and 12 tender joints, and who had failed to respond to at least one DMARD, were recruited. The primary efficacy end-points were change from baseline in the number of swollen and painful joints at 3 months.

ERA: Bathon and colleagues, 2000;[123] Genovese and colleagues, 2002[124]
This multicentre RCT compared etanercept 10 mg s.c. twice weekly or 25 mg s.c. twice weekly with methotrexate. There was a 12-month double-blind phase and a further 12-month open-label phase. Results at 2 years were provided by the manufacturer and are referred to as the end of study results in this review unless otherwise specified. Recruited patients had RA for less than 3 years, at least ten swollen joints and 12 tender joints, and were positive for rheumatoid factor or had at least three bony erosions on radiographs of hands, feet and wrists. Patients who had previously been treated with methotrexate were not eligible. Patients on other DMARDs at recruitment had a 4-week washout before entry. Fifty-nine per cent of patients had never received a DMARD.

The primary clinical end-point was ACR-N area under the curve (AUC) during the first 6 months, and the primary radiological end-point was the change in modified Sharp scores over 12 months.

This trial was originally designed to show the superiority of etanercept over methotrexate in preventing joint damage. However, this goal was changed to that of showing equivalence of etanercept and methotrexate.

TEMPO: Klareskog and colleagues, 2004;[127] van der Heijde and colleagues, 2005[128] 2006[110]
This multicentre trial consisted of two periods. Period one was a 52-week double-blind RCT, followed by a double-blind extension of variable duration during which patients remained on randomised treatment. Two-year results were provided by the manufacturer and are referred to as the end of study results unless otherwise specified. TEMPO compared methotrexate alone (7.5 mg per week escalated to 20 mg per week if any tender or swollen joints remained), etanercept alone (25 mg s.c. twice weekly), and a combination of the two. RA patients who had previously received methotrexate were allowed to enter (at the discretion of the investigator) provided that methotrexate had not been used within 6 months of study entry, had not been discontinued for lack of efficacy and had not caused toxicity.

Patients with disease durations between 6 months and 20 years who had failed at least one DMARD other than methotrexate were recruited. At least ten swollen joints and 12 tender joints were required. The primary clinical end-point was the 24-week AUC of the ACR-N. The 52-week change from baseline in van der Heijde modified total Sharp score was a conditional primary end-point. TEMPO appears to be the only trial in established RA (not early RA) that genuinely compares a conventional DMARD with a TNF inhibitor. However, around 42% of patients in each arm of this trial had previously tried methotrexate. It is not at all clear why these individuals discontinued methotrexate in the face of active disease if, as stated in the entry criteria, the drug was not ineffective or toxic.

Codreanu and colleagues, 2003[103]
The study was only published as an abstract at the time of review, but a clinical study report was made available to the authors. This multicentre trial consisted of two periods. Period one was a 24-week double-blind RCT, which was followed by a double-blind extension with patients participating between 60 to 100 weeks. The 24-week results were provided by the manufacturer and are referred to as the end of study results. The trial compared sulfasalazine alone (2–3 g per day), etanercept alone (25 mg s.c. twice weekly) and the combination of both in RA patients who were not adequately controlled while having received sulfasalazine for at least 4 months. The addition of other DMARDs was not permitted during the study. Patients with disease duration less than 20 years, with at least six swollen joints and ten tender joints were recruited. The primary end-point was ACR20 response at 24 weeks.

Lan and colleagues, 2004[130]
This single-centre, 12-week RCT compared etanercept (25 mg s.c. twice weekly) and placebo in patients who had been receiving stable doses (12.5–20 mg per week) of methotrexate for at least 4 weeks. Patients with duration of RA longer than 1 year, with at least six swollen joints and six tender joints despite methotrexate treatment were recruited. The baseline HAQ score of the patients in this trial (average 1.1) was better than in other

etanercept trials. The primary end-points were reduction in the number of swollen and tender joints from baseline to 12 weeks. Details of randomisation, allocation concealment and blinding were not described in the published paper and no trial report was made available.

Keystone and colleagues, 2004[129]
This 16-week multicentre RCT compared etanercept 50 mg s.c. once weekly, etanercept 25 mg twice s.c. weekly and placebo. Placebo-treated patients received etanercept 25 mg twice weekly at 8 weeks and thus results from week 8 onwards were excluded from this review. Patients with at least six swollen joints and six tender joints were recruited. Patients were allowed to continue with stable doses of methotrexate (≤ 25 mg per week), but other DMARDs were not allowed. Approximately half of the patients in each treatment group were receiving concomitant methotrexate. The primary efficacy end-point was the ACR20 response. Etanercept 50 mg once weekly was compared with placebo at week 8 and the comparative efficacy of the two etanercept treatment regimens was also studied.

Baumgartner and colleagues, 2004[104]
This 16-week multicentre safety trial compared etanercept 25 mg s.c. twice weekly and placebo in adult RA patients, with at least one qualifying co-morbid condition including diabetes, chronic obstructive pulmonary disease and recent infections. Randomisation was stratified by the presence of diabetes. Patients in this trial were older than those in other etanercept trials. Concomitant DMARDs (except for azathioprine, ciclosporin and cyclophosphamide) and NSAIDs were allowed and their use could be altered during the study. The overall prior and concurrent DMARD use was not reported, but 52% of all patients received concomitant methotrexate during the study. The primary end-point was the incidence of medically important infections, defined as infections that result in hospitalisation or treatment with intravenous antibiotics. No efficacy outcomes were measured. The initial study plan aimed to recruit 1000 patients, which allows an 84% power to detect a two-fold difference between the treatment groups (10% versus 20%). The study was, however, terminated early owing to the low incidence of medically important infections observed in the study (3% overall) and the slow recruitment of patients.

Meta-analyses of etanercept trials
The principles of analysis and data presentation of the etanercept trials are the same as those for adalimumab and are described in the section 'Data analysis' (p. 14). Two trials (TEMPO[110,127] and Codreanu[103]) included three treatment arms, which allow more than one comparison.

Etanercept versus conventional DMARD
Three trials (ERA,[123] TEMPO[110,127] and Codreanu[103]) included comparisons between etanercept and a conventional DMARD. Only the ERA trial, however, allows a genuine head-to-head comparison between etanercept and methotrexate in early RA patients who were naïve to both treatments. Around 40% of patients in TEMPO had previously taken methotrexate without experiencing treatment failure due to lack of efficacy or toxicity. This, in theory, could introduce bias in favour of methotrexate. These patients, however, had not continued the methotrexate treatment for at least 6 months before the study. The reasons for this and their potential impact on study results are not clear. The investigators performed subgroup analyses and found no significant interaction between previous use of methotrexate and treatment effects in terms of ACR responses, DAS and total Sharp score.[127] The trial by Codreanu and colleagues[103] recruited patients who had had an inadequate response to sulfasalazine, and thus this trial should not be regarded as a head-to-head comparison. This section therefore focuses on the results from ERA (*Table 8*) and TEMPO (*Table 9*). The outcomes for ACR20, ACR50, ACR70, HAQ, SAEs, and malignancy from all three trials are also shown in the lower parts of *Figures 13–23*.

Efficacy Although the mean disease duration for the patients was only 1 year in ERA compared with over 6 years in the TEMPO, the results from these two studies are remarkably similar – no statistical heterogeneity between the studies was found in any of the outcomes that were meta-analysed. Overall, the results demonstrate that etanercept monotherapy is marginally more effective than methotrexate in improving RA symptoms and physical function. The differences between etanercept and methotrexate for ACR20 response and modified Sharp score were statistically significant in both studies, while the difference for ACR50 response was significant only in the TEMPO trial.

Tolerability Etanercept monotherapy appears to be better tolerated than methotrexate monotherapy. Fewer patients withdrew either owing to lack of efficacy or because of adverse events in etanercept-treated groups.

TABLE 8 *Summary of 2-year results from ERA study: etanercept s.c. licensed dose alone (25 mg twice weekly) versus MTX alone in MTX-naïve patients, 2-year results*

Comparison or outcome	*N* included in analysis	Statistical method	Effect size (95% CI)
ACR20 responder	424	RR (fixed)	1.22 (1.06 to 1.40)*
ACR50 responder	424	RR (fixed)	1.16 (0.94 to 1.44)
ACR70 responder	424	RR (fixed)	1.23 (0.89 to 1.70)
RD ACR20 responder	424	RD (fixed)	0.13 (0.04 to 0.22)*
RD ACR50 responder	424	RD (fixed)	0.07 (–0.03 to 0.16)
RD ACR70 responder	424	RD (fixed)	0.05 (–0.03 to 0.14)
SJC, end of study result	424	WMD (fixed)	–1.50 (–3.44 to 0.44)
Patient's global assessment, end of study result	424	WMD (fixed)	0.00 (–0.46 to 0.46)
HAQ, end of study result	424	WMD (fixed)	–0.10 (–0.23 to 0.03)
DAS, end of study result	424	Not estimable	No data available
Modified van de Heijde–Sharp score, mean change from baseline (1-year result)	417	WMD (fixed)	–0.97 (–1.65 to –0.29)*
Withdrawal for any reasons	424	RR (fixed)	0.63 (0.48 to 0.84)*
Withdrawal due to lack of efficacy	424	RR (fixed)	0.73 (0.40 to 1.34)
Withdrawal due to adverse events	424	RR (fixed)	0.58 (0.32 to 1.06)
Death	424	RR (fixed)	3.14 (0.13 to 76.75)
SAEs	424	RR (fixed)	No data available
Malignancy: all	424	RR (fixed)	1.05 (0.31 to 3.57)
Malignancy: skin cancer excluding melanoma	424	RR (fixed)	1.05 (0.15 to 7.37)
Malignancy: all cancer excluding non-melanoma skin cancer	424	RR (fixed)	1.05 (0.21 to 5.14)
Serious infection	424	RR (fixed)	0.82 (0.31 to 2.15)
Any infection	424	RR (fixed)	0.99 (0.90 to 1.09)

* Statistically significant result ($p < 0.05$).

Safety No significant differences between etanercept and methotrexate were found. Malignancy occurred in five patients with etanercept and two patients with methotrexate in TEMPO, while equal numbers of patients (five each) developed cancer in the two treatment arms in ERA.

Subgroup analyses In addition to the subgroup analyses of prior use of methotrexate, extensive analyses were performed in TEMPO to explore potential interactions between disease duration and treatment effects. The outcomes in the early RA cohort (disease duration ≤ 3 years at baseline), which accounted for one-third of all patients in the trial, were generally similar to the overall study results. For example, the mean HAQ changes from baseline at 2 years were –0.7, –0.7 and –1.0 for methotrexate alone, etanercept alone and the combination group, respectively, for both the early RA cohort (baseline HAQ = 1.6) and the late RA cohort (baseline HAQ = 1.8).

Codreanu, 2003[103] The comparison between etanercept and sulfasalazine in sulfasalazine partial responders/non-responders is summarised in *Table 72* (Appendix 4). The results resemble those observed in trials comparing etanercept and placebo (described in the following section), which show that etanercept is significantly more effective and better tolerated. Significantly more patients in the etanercept arm had infections compared with patients in the sulfasalazine arm (RR 1.76, 95% CI 1.05 to 2.93).

TABLE 9 *Summary of 2-year results from TEMPO study: etanercept s.c. licensed dose alone (25 mg twice weekly) versus MTX alone in MTX-naïve patients/responders, 2-year results*

Comparison or outcome	*N* included in analysis	Statistical method	Effect size (95% CI)
ACR20 responder	451	RR (fixed)	1.28 (1.06 to 1.54)*
ACR50 responder	451	RR (fixed)	1.47 (1.15 to 1.89)*
ACR70 responder	451	RR (fixed)	1.46 (1.00 to 2.14)
RD ACR20 responder	451	RD (fixed)	0.12 (0.03 to 0.21)*
RD ACR50 responder	451	RD (fixed)	0.14 (0.05 to 0.23)*
RD ACR70 responder	451	RD (fixed)	0.08 (0.00 to 0.15)
SJC, end of study result	451	WMD (fixed)	–1.10 (–3.08 to 0.88)
Patient's global assessment, end of study result	451	WMD (fixed)	–0.20 (–0.51 to 0.11)
HAQ, end of study result	451	WMD (fixed)	–0.10 (–0.23 to 0.03)
DAS, end of study result	451	WMD (fixed)	–0.10 (–0.31 to 0.11)
Modified van de Heijde–Sharp score, mean change from baseline (1-year result)	424	WMD (fixed)	–2.28 (–4.11 to –0.45)*
Withdrawal for any reasons	451	RR (fixed)	0.81 (0.65 to 1.00)
Withdrawal due to lack of efficacy	451	RR (fixed)	0.93 (0.59 to 1.47)
Withdrawal due to adverse events	451	RR (fixed)	0.75 (0.50 to 1.11)
Death	451	RR (fixed)	1.02 (0.06 to 16.25)
SAEs	451	RR (fixed)	1.10 (0.75 to 1.61)
Malignancy: all	451	RR (fixed)	2.56 (0.50 to 13.04)
Malignancy: skin cancer excluding melanoma	451	RR (fixed)	2.04 (0.19 to 22.39)
Malignancy: all cancer excluding non-melanoma skin cancer	451	RR (fixed)	3.07 (0.32 to 29.27)
Serious infection	451	RR (fixed)	0.95 (0.47 to 1.93)
Any infection	451	RR (fixed)	0.95 (0.85 to 1.06)

* Statistically significant result ($p < 0.05$).

Etanercept versus placebo

Eight trials[103,104,121,122,125,126,129,130] compared etanercept at the licensed dose (or equivalent) to placebo. Three of the trials[121,122,126] also included sublicensed doses. No trial included doses above the licensed dose. Results of the primary analyses (licensed dose) are summarised in *Table 10*, and are also shown in the upper parts of *Figures 24–34*.

Efficacy Etanercept was significantly more effective than placebo for all the efficacy outcomes being meta-analysed. *Figure 24* shows a pattern of decreasing effect size for ACR20 in terms of relative risk in trials in that patients: (1) were not receiving any concurrent DMARDs; (2) were receiving concurrent DMARDs that had failed to provide adequate disease control; and (3) were receiving concurrent, newly initiated methotrexate. This pattern, however, is not clearly observed for other outcome measures, nor is it observed in trials of other TNF inhibitors.

Tolerability Etanercept is better tolerated than placebo.

Safety There were no significant differences between etanercept and placebo. In the trial by Baumgartner and colleagues,[104] which recruited patients with co-morbidity, five deaths occurred in the etanercept arm compared with one in the placebo arm.

Sensitivity analysis The results of the sensitivity analysis, which included sublicensed doses, are summarised in *Table 73* (Appendix 4). These are consistent with the primary analysis.

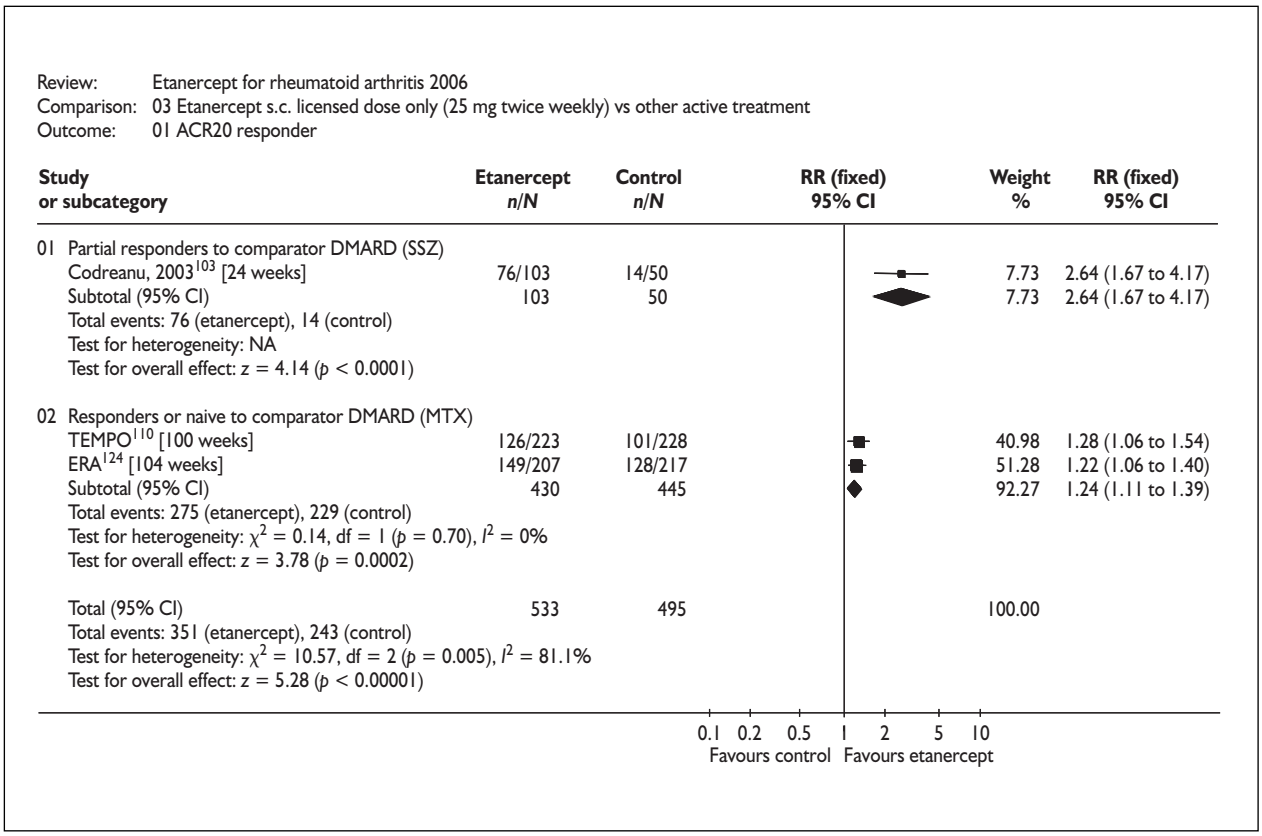

FIGURE 13 *ACR20 RR: etanercept licensed dose versus other active treatment*

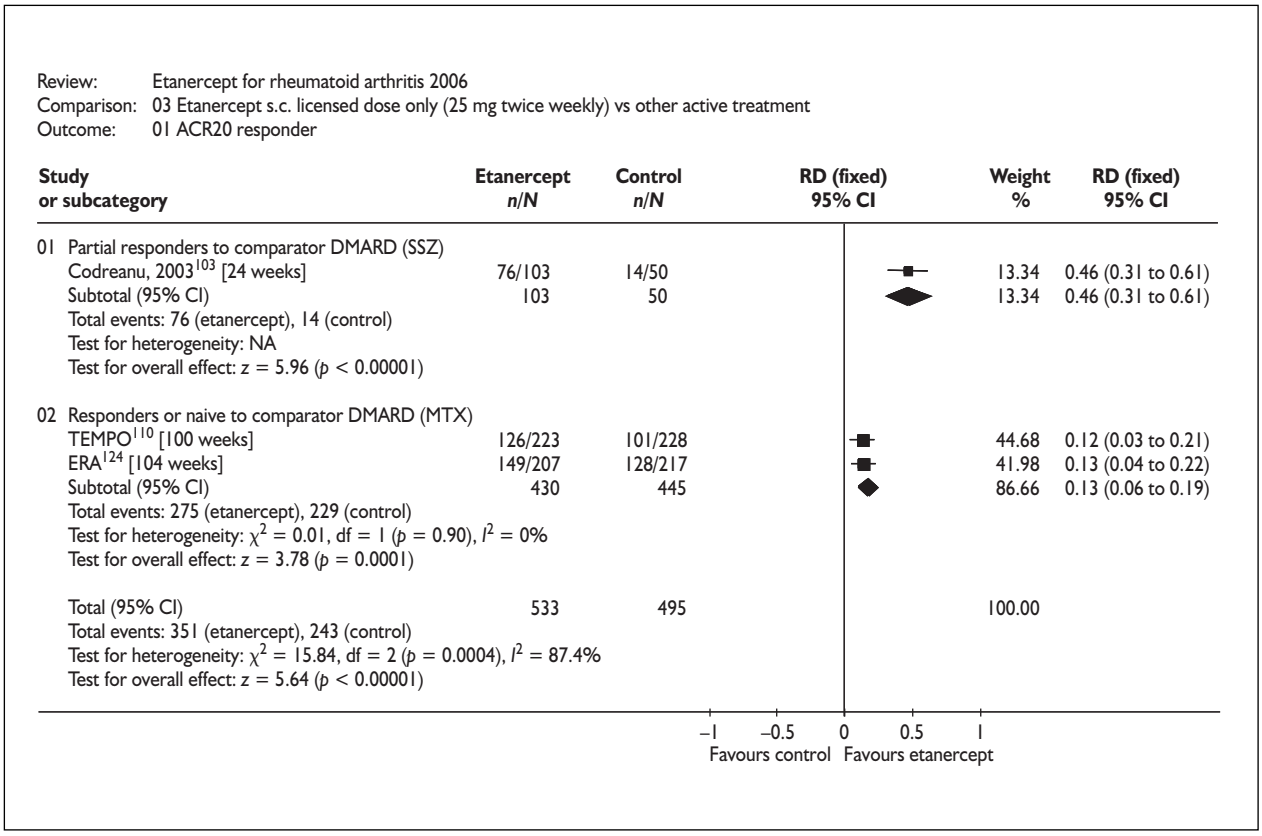

FIGURE 14 *ACR20 RD: etanercept licensed dose versus other active treatment*

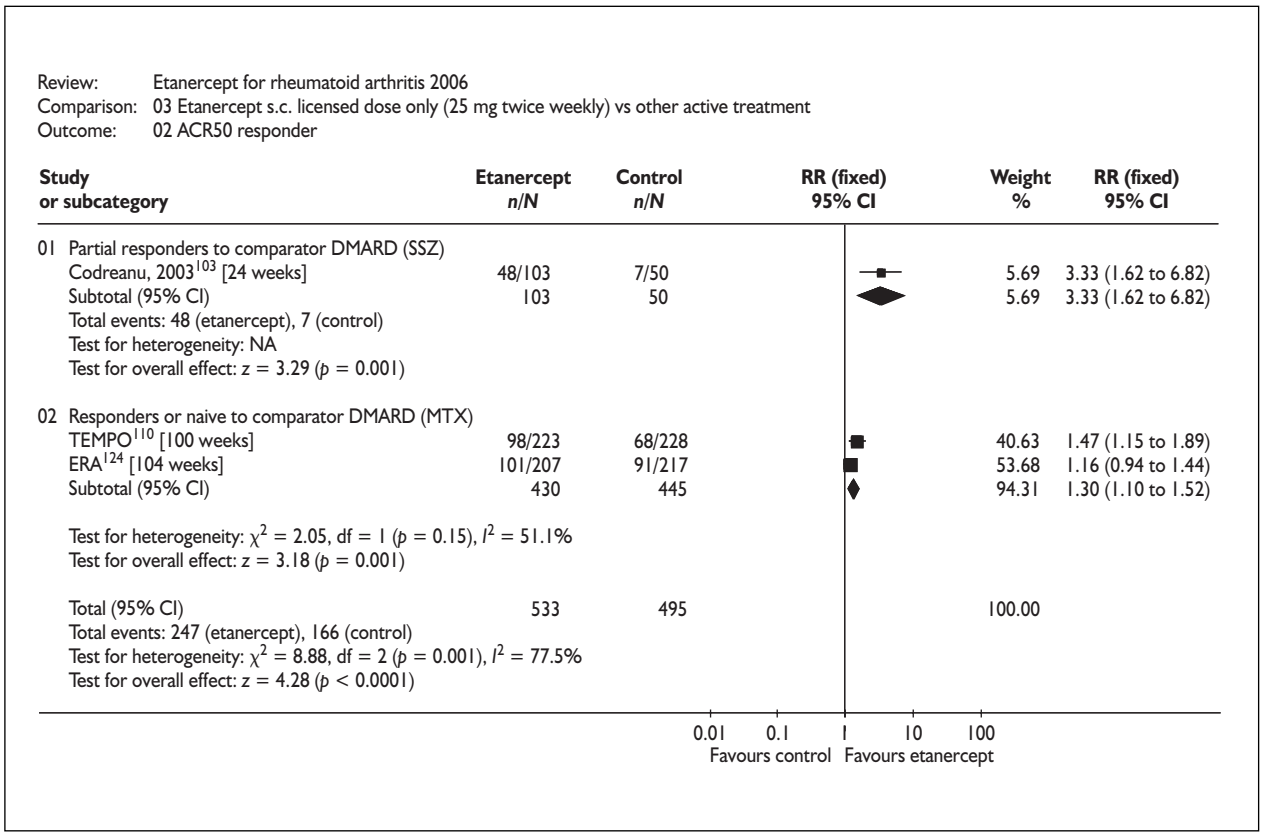

FIGURE 15 *ACR50 RR: etanercept licensed dose versus other active treatment*

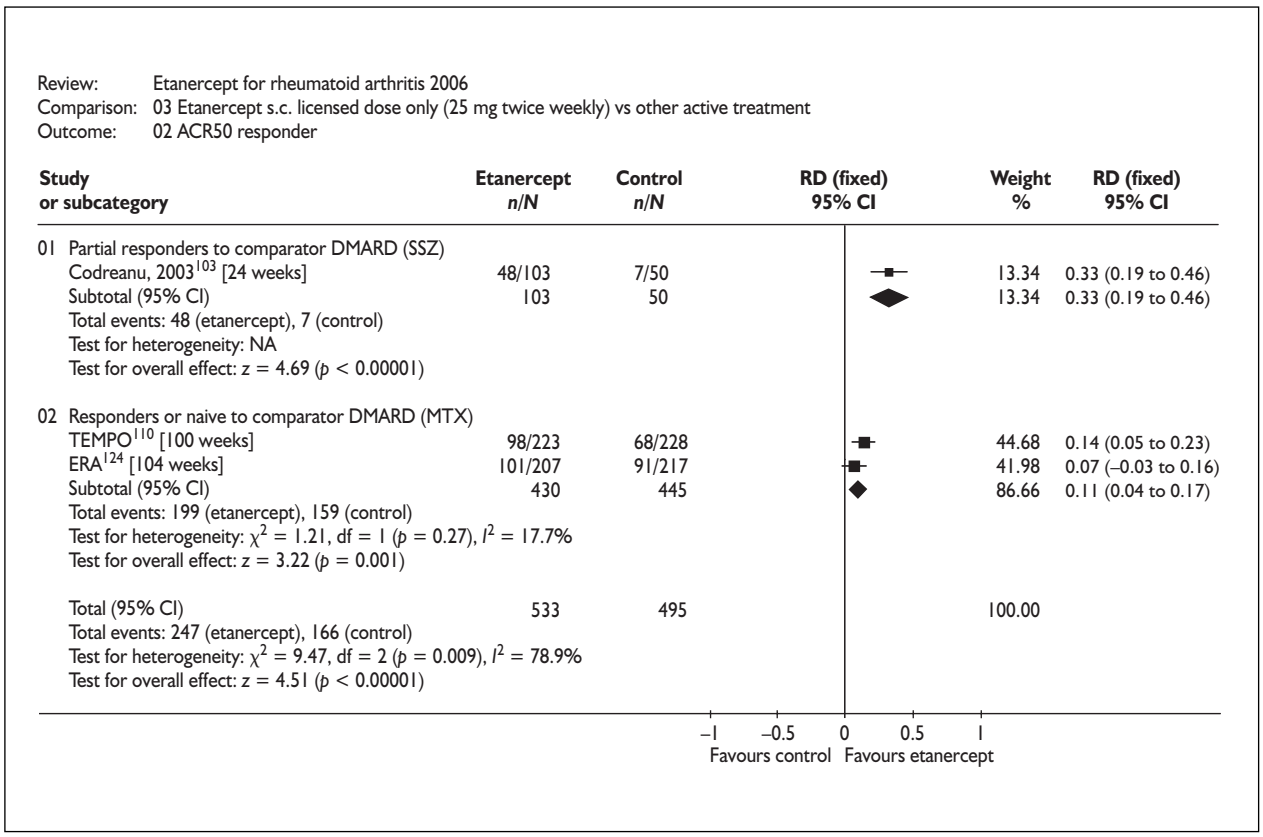

FIGURE 16 *ACR50 RD: etanercept licensed dose versus other active treatment*

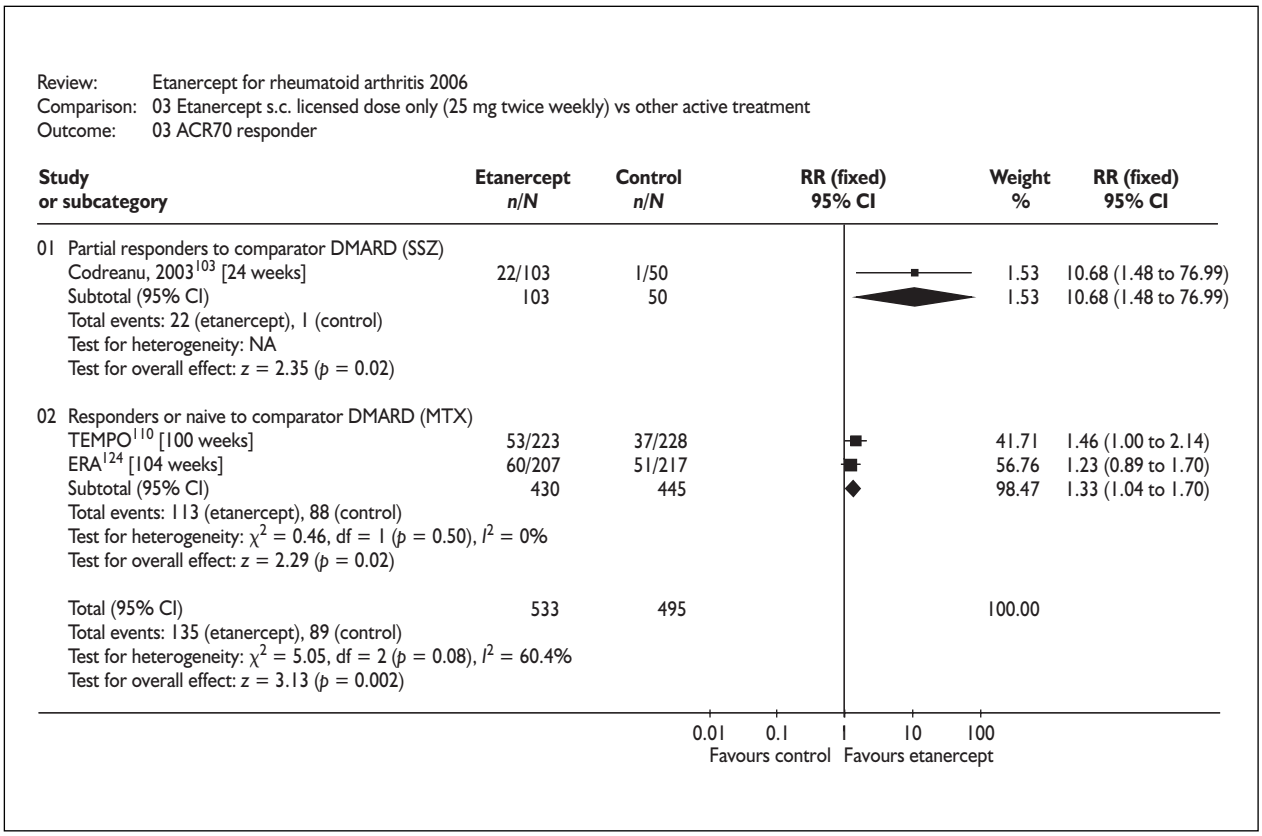

FIGURE 17 *ACR70 RR: etanercept licensed dose versus other active treatment*

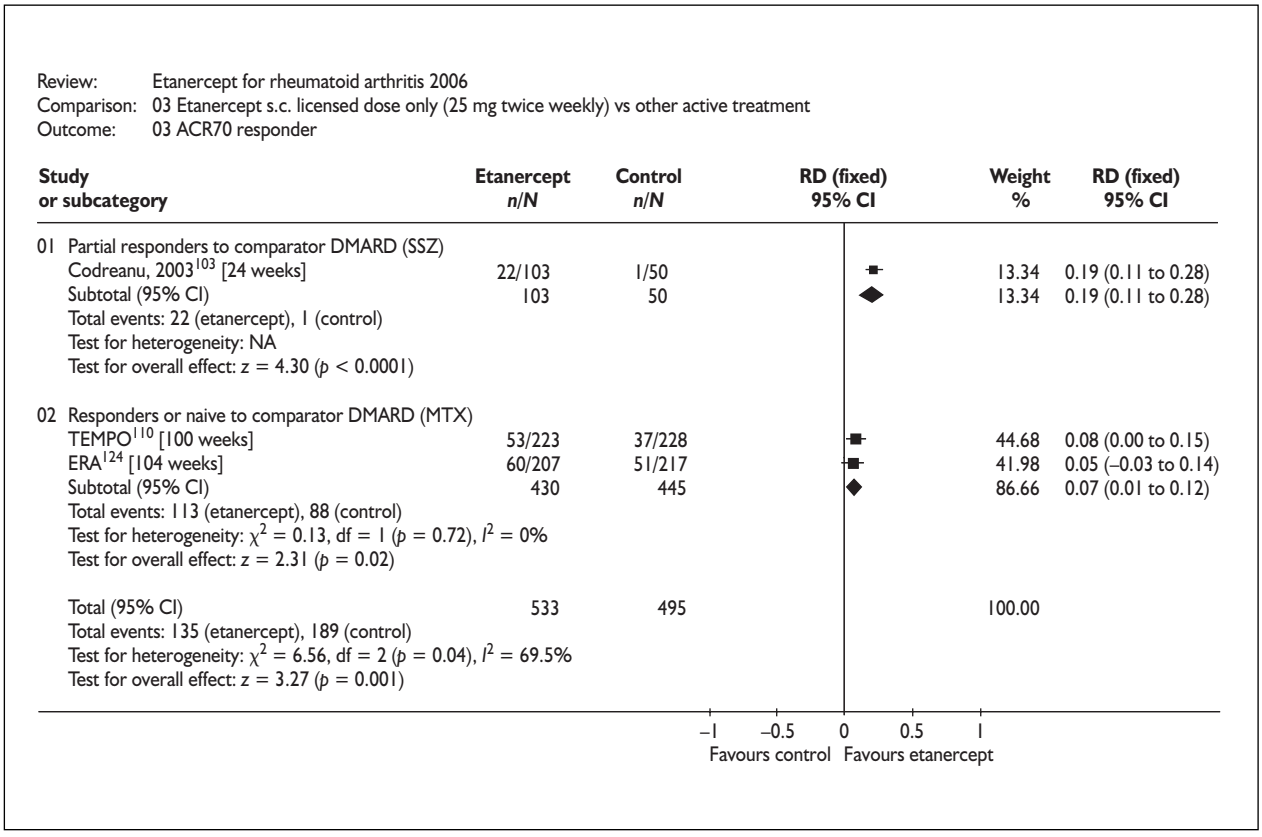

FIGURE 18 *ACR70 RD: etanercept licensed dose versus other active treatment*

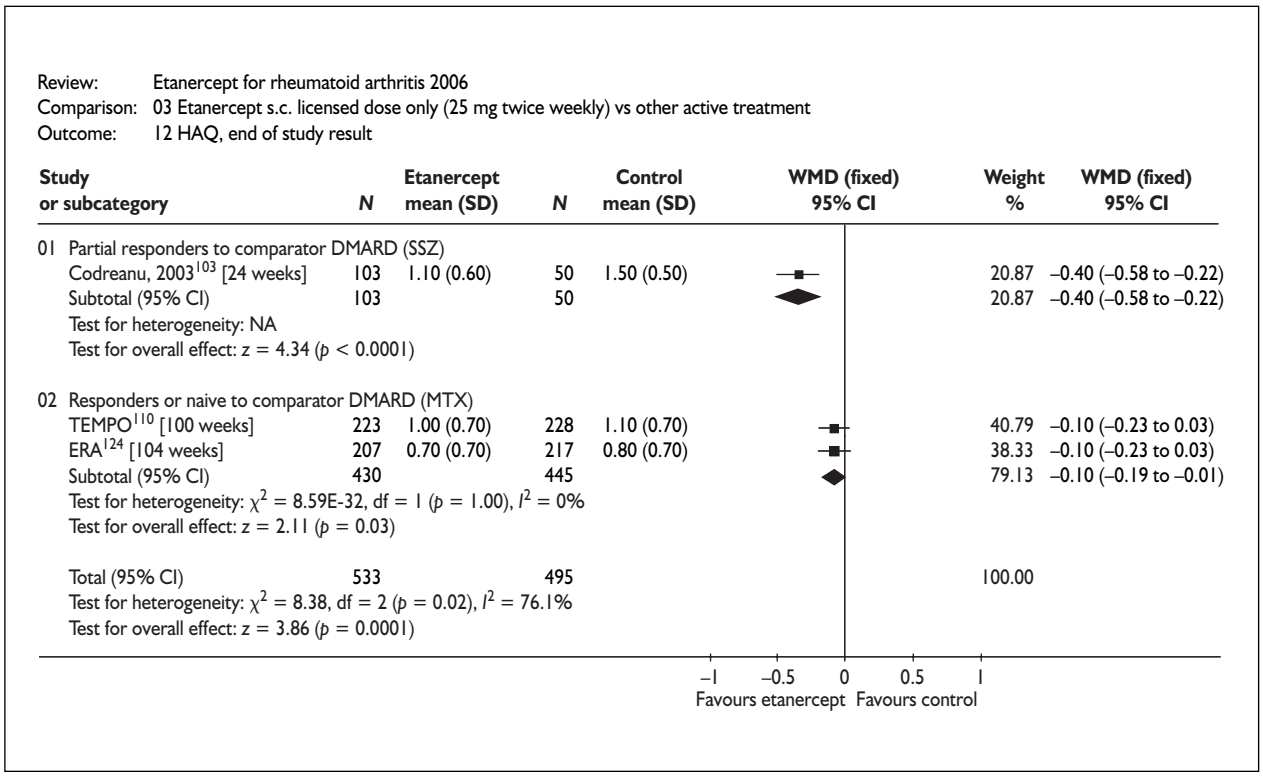

FIGURE 19 *HAQ change: etanercept licensed dose versus other active treatment*

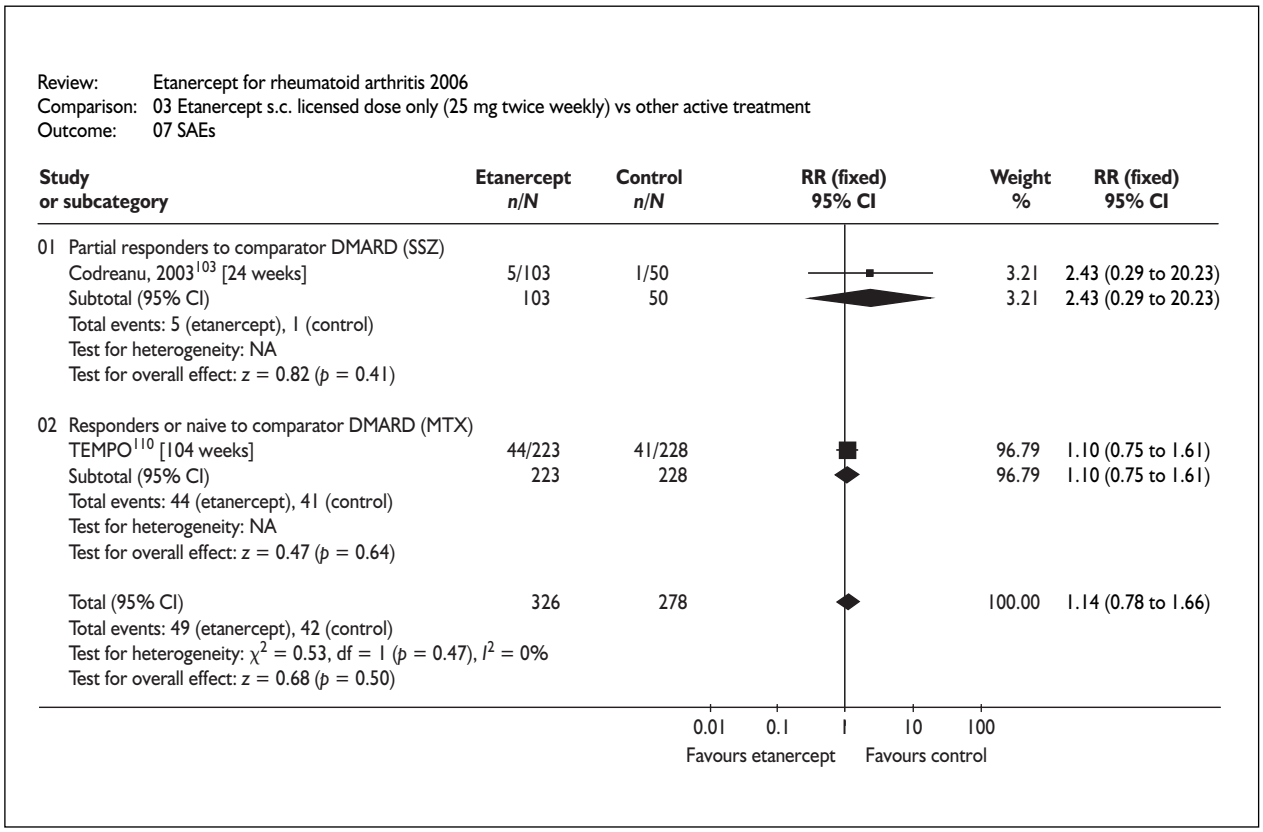

FIGURE 20 *SAE RR: etanercept licensed dose versus other active treatment*

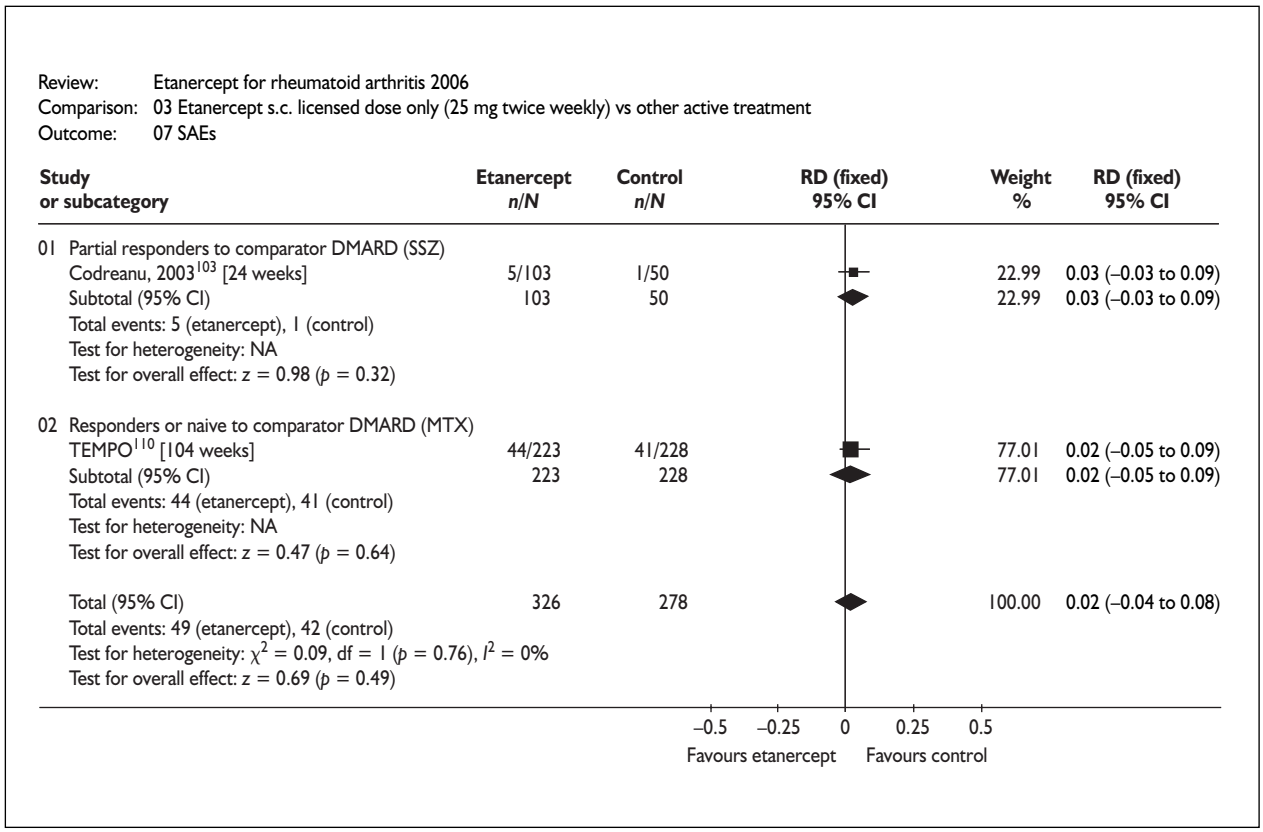

FIGURE 21 *SAE RD: etanercept licensed dose versus other active treatment*

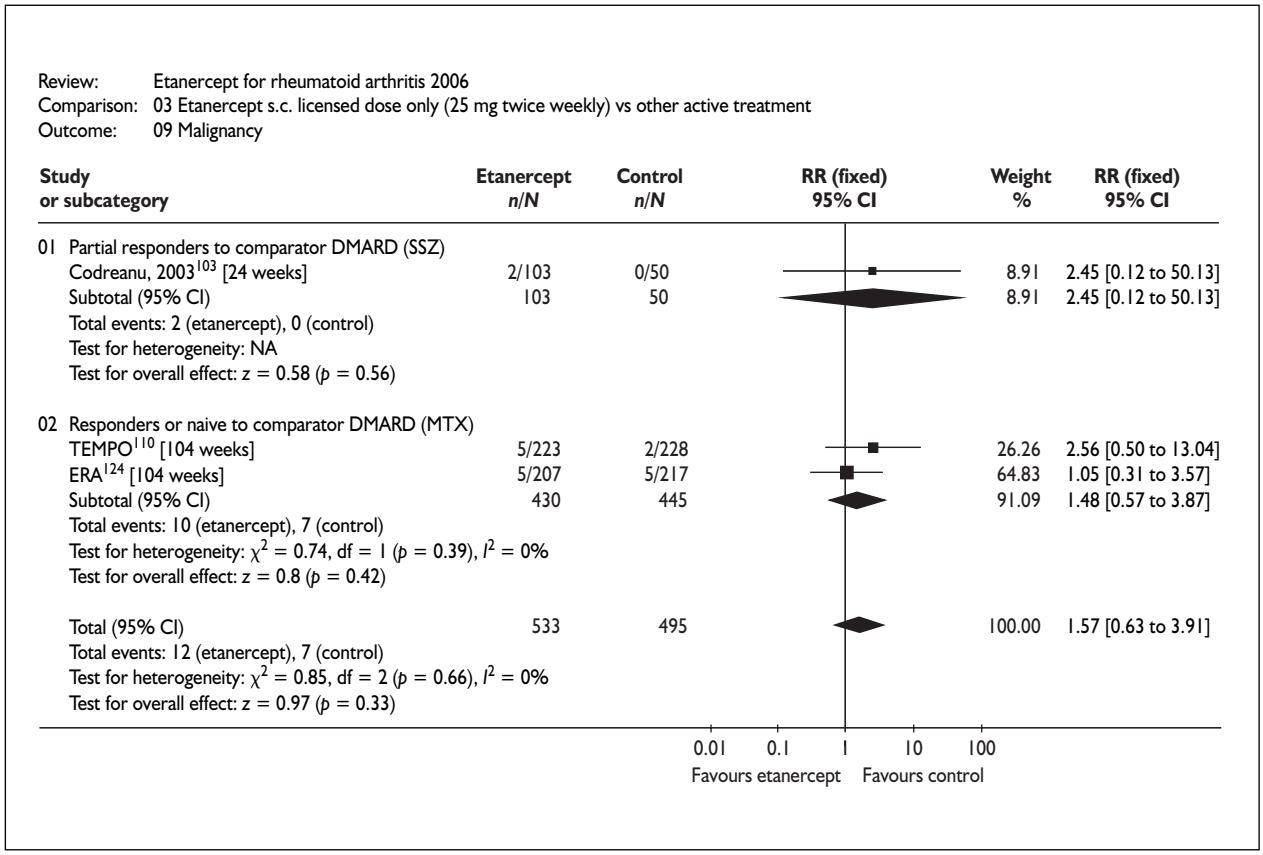

FIGURE 22 *Malignancy RR: etanercept licensed dose versus other active treatment*

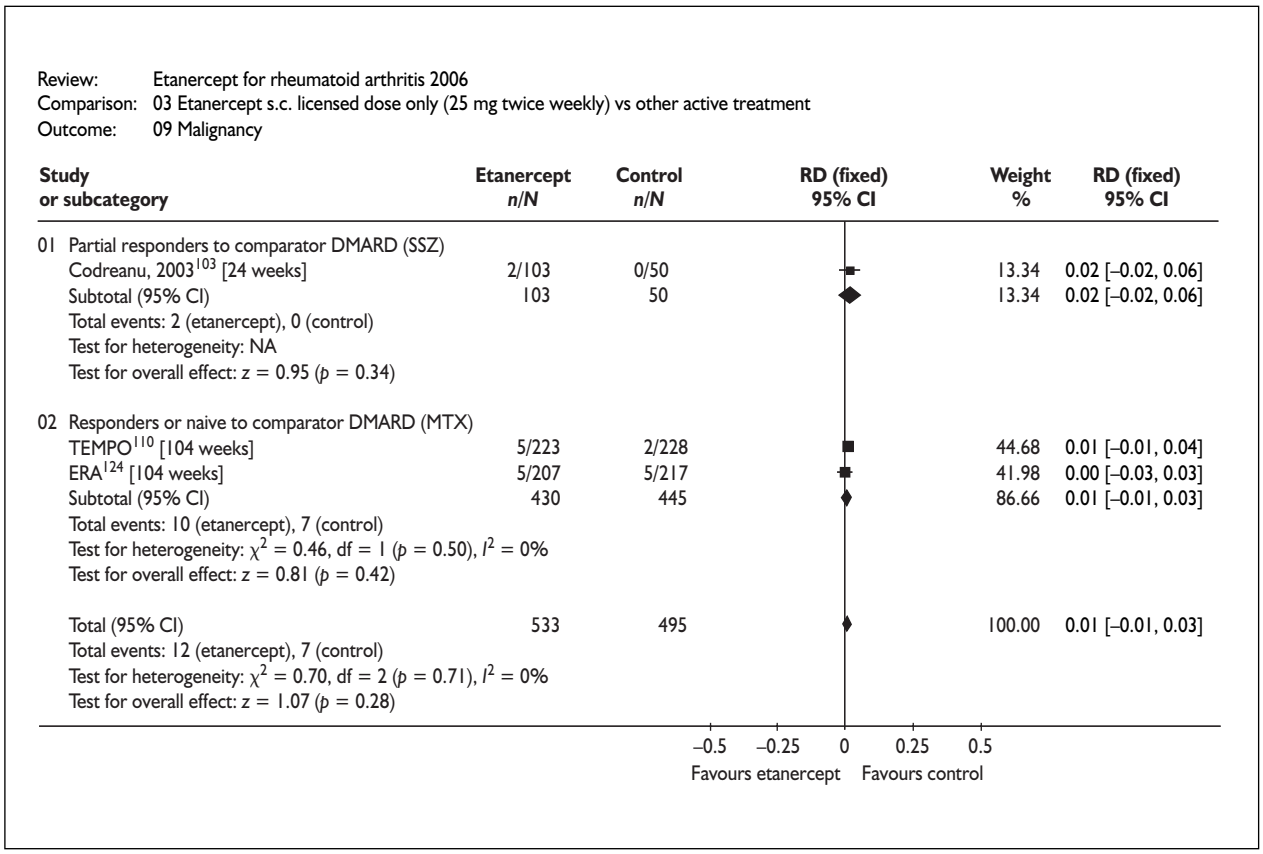

FIGURE 23 *Malignancy RD: etanercept licensed dose versus other active treatment*

Etanercept plus methotrexate versus methotrexate

Only TEMPO[110,127] included this comparison and the results are summarised in *Table 11* and are also shown in the lower parts of *Figures 24–34*.

Efficacy The combination of etanercept plus methotrexate was significantly more effective than methotrexate monotherapy for all the efficacy outcomes considered.

Tolerability The combination was better tolerated than methotrexate monotherapy. Significantly fewer patients withdrew owing to lack of efficacy and for any reason in the combination group.

Safety No significant differences were found in any of the outcomes being meta-analysed. Nevertheless, SAEs and malignancy occurred more frequently in the combination group.

Infliximab

Description of included infliximab trials

Nine trials comprising a total of 2835 patients (2823 actually treated) were included in the meta-analyses. A prepublication manuscript of BeSt was made available by the investigators, but did not meet the inclusion criteria. However, because of its importance it is described in detail, but the data are not used in the meta-analyses. Clinical study reports were provided by Schering-Plough for three of the studies: ATTRACT,[132–134] Active-controlled Study of Patient Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset, (ASPIRE)[135] and START.[105,111] Additional data from these reports were included in this systematic review. Data were available only from published papers for the remaining six studies: Elliott,[136] Maini,[137] Kavanaugh,[138] Durez,[139] Taylor,[140] and Quinn.[141]

Treatment comparators and baseline patient characteristics are shown in *Table 12*. Quality assessments of trials are summarised in *Table 13*. In most trials active RA was defined by six or more swollen joints (ten for ASPIRE), with additional criteria related to tender joints, ESR, CRP and morning stiffness. Taylor[140] and Quinn[141] focused on ultrasonographic and MRI outcomes, respectively. Low-dose oral steroids (<10 mg per day prednisolone) and NSAIDs were allowed at stable doses. DMARDs other than methotrexate

TABLE 10 *Meta-analyses: etanercept s.c. licensed dose only (25 mg twice weekly or equivalent) versus placebo (with or without ongoing conventional DMARDs), end of trial*

Comparison or outcome	Studies	*N* included in analysis	Statistical method	Effect size (95% CI)
ACR20 responder	7[103,121,122,125,126,129,130]	1172	RR (fixed)	3.59 (2.89 to 4.46)*
ACR50 responder	7[103,121,122,125,126,129,130]	1172	RR (fixed)	5.72 (3.92 to 8.34)*
ACR70 responder	6[103,122,125,126,129,130]	1084	RR (fixed)	9.44 (3.98 to 22.38)*
RD ACR20 responder	7[103,121,122,125,126,129,130]	1172	RD (fixed)	0.48 (0.42 to 0.53)*
RD ACR50 responder	7[103,121,122,125,126,129,130]	1172	RD (fixed)	0.32 (0.28 to 0.37)*
RD ACR70 responder	6[103,122,125,126,129,130]	1084	RD (fixed)	0.13 (0.10 to 0.16)*
SJC, end of study result	7[103,121,122,125,126,129,130]	1178	WMD (random)	–6.75 (–8.95 to –4.56)*
Patient's global assessment, end of study result	7[103,121,122,125,126,129,130]	1178	WMD (fixed)	–2.49 (–2.74 to –2.24)*
HAQ, end of study result	6[103,122,125,126,129,130]	1055	WMD (fixed)	–0.50 (–0.59 to, –0.42)*
DAS, end of study result	1[103]	150	WMD (fixed)	–1.50 (–1.89 to –1.11)*
Modified van de Heijde–Sharp score	0	0	Not estimable	No data available
Withdrawal for any reasons	7[103,104,121,122,125,126,129]	1657	RR (fixed)	0.37 (0.29 to 0.46)*
Withdrawal due to lack of efficacy	6[103,104,121,122,125,126]	1237	RR (fixed)	0.19 (0.13 to, 0.28)*
Withdrawal due to adverse events	7[103,104,121,122,125,126,129]	1657	RR (fixed)	0.80 (0.49 to 1.30)
Death	7[103,104,121,122,125,126,129]	1657	RR (fixed)	2.22 (0.50 to 9.80)
SAEs	5[103,104,122,125,129]	1353	RR (fixed	1.25 (0.75 to 2.08)
Malignancy: all	6[103,104,122,125,126,129]	1569	RR (fixed)	0.44 (0.11 to 1.68)
Malignancy: skin cancer excluding melanoma	6[103,104,122,125,126,129]	1569	RR (fixed)	0.98 (0.17 to 5.59)
Malignancy: all cancer excluding non-melanoma skin cancer	6[103,104,122,125,126,129]	1569	RR (fixed)	0.19 (0.02 to 1.71)
Serious infection	7[103,104,122,125,126,129,130]	1627	RR (fixed)	0.78 (0.37 to 1.62)
Any infection	6[103,104,122,125,126,129]	1569	RR (fixed)	1.00 (0.87 to 1.14)

* Statistically significant result ($p < 0.05$).

were not allowed, except in START.[105,111] Three trials (ASPIRE,[135] Taylor[140] and Quinn[141]) recruited exclusively early RA patients. Key features for studies that included the licensed dose of infliximab are described below.

Maini and colleagues, 1998[137]
This 26-week, multicentre, double-blind RCT compared three doses of infliximab (1, 3 or 10 mg kg^{-1}, with or without ongoing methotrexate 7.5 per mg week) with placebo plus ongoing methotrexate. Patients who had taken methotrexate at a dose of 7.5–15 mg per week for at least 6 months, with at least six swollen joints were recruited. Other DMARDs were not permitted. The primary efficacy measurement was the total time (in weeks) for which a patient exhibited a Paulus 20% response.

ATTRACT: Maini and colleagues, 1999;[132] Lipsky and colleagues, 2000[133]
This double-blind, multicentre RCT compared four dosing regimens of infliximab (3 or 10 mg kg^{-1}, i.v. at 0, 2 and 6 weeks and then every 4 or 8 weeks) with placebo, with concomitant methotrexate therapy. Patients who had been receiving methotrexate for at least 3 months and had been stable at 12.5 mg per week or more before screening were recruited. At least six swollen joints and six tender joints were required. The primary end-point was ACR20 response at week 30.

The study was planned to run for 54 weeks, but it was extended by a protocol amendment to 102 weeks based on FDA guidance.[134] A clinical study report for the 2-year results was provided by the

Review: Etanercept for rheumatoid arthritis 2006
Comparison: 01 Etanercept s.c. licensed dose only (25 mg twice weekly or 50 mg once weekly) vs placebo, end of trial
Outcome: 01 ACR20 responder

Study or subcategory	Etanercept n/N	Control n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
01 With (+) or without (–) concurrent, ongoing conventional DMARDs					
Moreland, 1997[121] [12 weeks] (–)	33/44	6/44		3.23	5.50 (2.56 to 11.79)
Wadjula, 2000[126] [12 weeks] (–)	76/109	12/100		6.74	5.81 (3.37 to 10.02)
Moreland, 1999[122] [26 weeks] (–)	46/78	9/80		4.78	5.24 (2.76 to 9.97)
Keystone, 2004[129] [8 weeks] (±)	182/367	10/53		9.41	2.63 (1.49 to 4.64)
Lan, 2004[130] [12 weeks] (+)	26/29	10/29		5.38	2.60 (1.55 to 4.36)
Weinblatt, 1999[125] [24 weeks] (+)	42/59	8/30		5.71	2.67 (1.44 to 4.94)
Codreanu, 2003[103] [24 weeks] (+)	74/100	14/50		10.05	2.64 (1.67 to 4.18)
Subtotal (95% CI)	786	386		45.29	3.59 (2.89 to 4.46)
Total events: 479 (etanercept), 69 (control)					
Test for heterogeneity: $\chi^2 = 10.78$, df = 6 ($p = 0.10$), $I^2 = 44.3\%$					
Test for overall effect: $z = 11.55$ ($p < 0.00001$)					
02 With concurrent, newly initiated MTX (etanercept + MTX)					
TEMPO[110] [100 weeks] (+)	152/231	101/228		54.71	1.49 (1.25 to 1.77)
Subtotal (95% CI)	231	228		54.71	1.49 (1.25 to 1.77)
Total events: 152 (etanercept), 101 (control)					
Test for heterogeneity: NA					
Test for overall effect: $z = 4.49$ ($p < 0.00001$)					
Total (95% CI)	1017	614		100.00	
Total events: 631 (etanercept), 170 (control)					
Test for heterogeneity: $\chi^2 = 57.50$, df = 7 ($p < 0.00001$), $I^2 = 86.4\%$					
Test for overall effect: $z = 12.47$ ($p < 0.00001$)					

0.01 0.1 1 10 100
Favours control Favours etanercept

FIGURE 24 *ACR20 RR: etanercept licensed dose versus placebo (including etanercept plus MTX versus MTX)*

Review: Etanercept for rheumatoid arthritis 2006
Comparison: 01 Etanercept s.c. licensed dose only (25 mg twice weekly or 50 mg once weekly) vs placebo, end of trial
Outcome: 01 ACR20 responder

Study or subcategory	Etanercept n/N	Control n/N	RD (fixed) 95% CI	Weight %	RD (fixed) 95% CI
01 With (+) or without (–) concurrent, ongoing conventional DMARDs					
Moreland, 1997[121] [12 weeks] (–)	33/44	6/44		6.42	0.61 (0.45 to 0.78)
Wadjula, 2000[126] [12 weeks] (–)	76/109	12/100		15.23	0.58 (0.47 to 0.68)
Moreland, 1999[122] [26 weeks] (–)	46/78	9/80		11.53	0.48 (0.35 to 0.61)
Keystone, 2004[129] [8 weeks] (±)	182/367	10/53		13.52	0.31 (0.19 to 0.42)
Lan, 2004[130] [12 weeks] (+)	26/29	10/29		4.23	0.55 (0.35 to 0.76)
Weinblatt, 1999[125] [24 weeks] (+)	42/59	8/30		5.81	0.45 (0.25 to 0.64)
Codreanu, 2003[103] [24 weeks] (+)	74/100	14/50		9.73	0.46 (0.31 to 0.61)
Subtotal (95% CI)	786	386		66.49	0.48 (0.42 to 0.53)
Total events: 479 (etanercept), 69 (control)					
Test for heterogeneity: $\chi^2 = 14.77$, df = 6 ($p = 0.02$), $I^2 = 59.4\%$					
Test for overall effect: $z = 17.47$ ($p < 0.00001$)					
02 With concurrent, newly initiated MTX (etanercept + MTX)					
TEMPO[110] [100 weeks] (+)	152/231	101/228		33.51	0.22 (0.13 to 0.30)
Subtotal (95% CI)	231	228		100.00	0.22 (0.13 to 0.30)
Total events: 152 (etanercept), 101 (control)					
Test for heterogeneity: NA					
Test for overall effect: $z = 4.74$ ($p < 0.00001$)					
Total (95% CI)	1017	614			
Total events: 631 (etanercept), 170 (control)					
Test for heterogeneity: $\chi^2 = 40.99$, df = 7 ($p < 0.00001$), $I^2 = 82.9\%$					
Test for overall effect: $z = 16.45$ ($p < 0.00001$)					

–1 –0.5 0 0.5 1
Favours control Favours etanercept

FIGURE 25 *ACR20 RD: etanercept licensed dose versus placebo (including etanercept plus MTX versus MTX)*

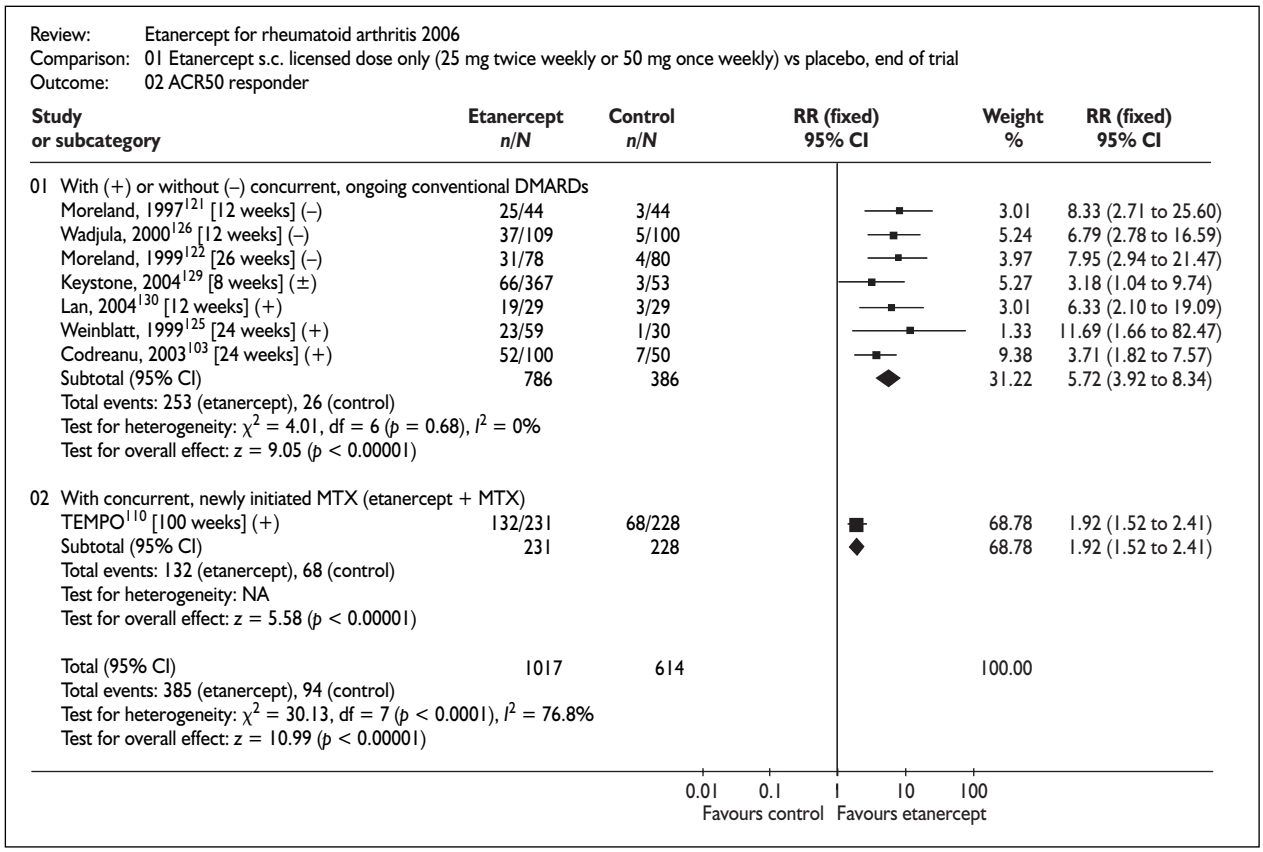

FIGURE 26 *ACR50 RR: etanercept licensed dose versus placebo (including etanercept plus MTX versus MTX)*

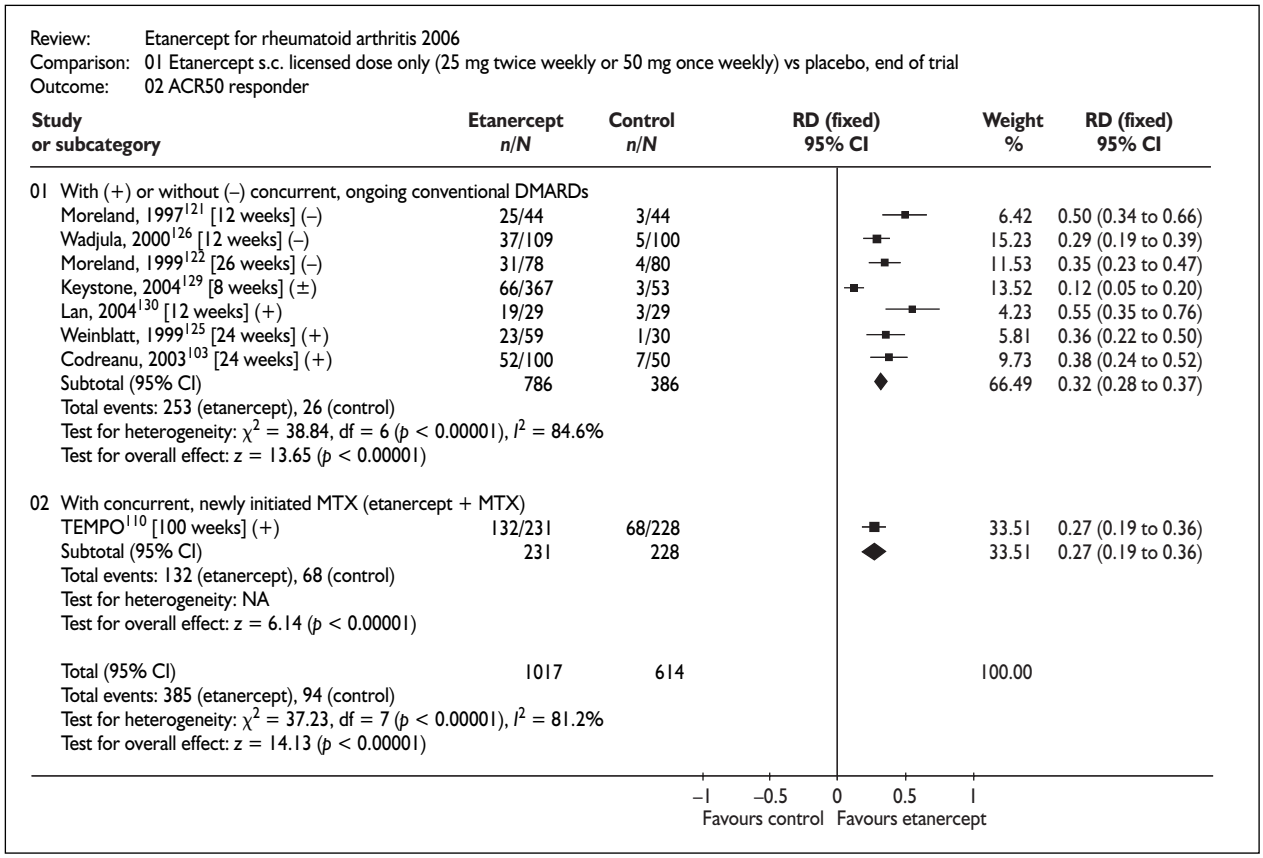

FIGURE 27 *ACR50 RD: etanercept licensed dose versus placebo (including etanercept plus MTX versus MTX)*

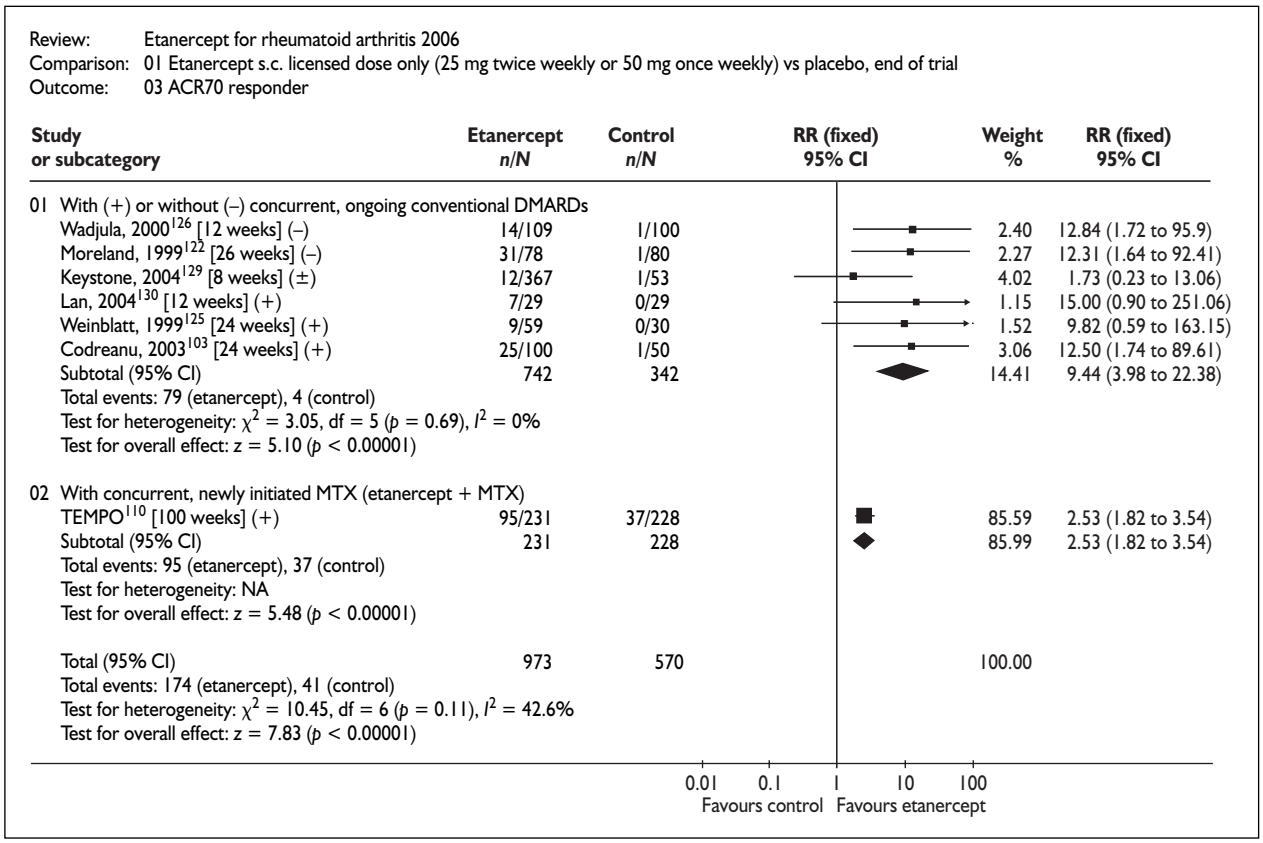

FIGURE 28 *ACR70 RR: etanercept licensed dose versus placebo (including etanercept plus MTX versus MTX)*

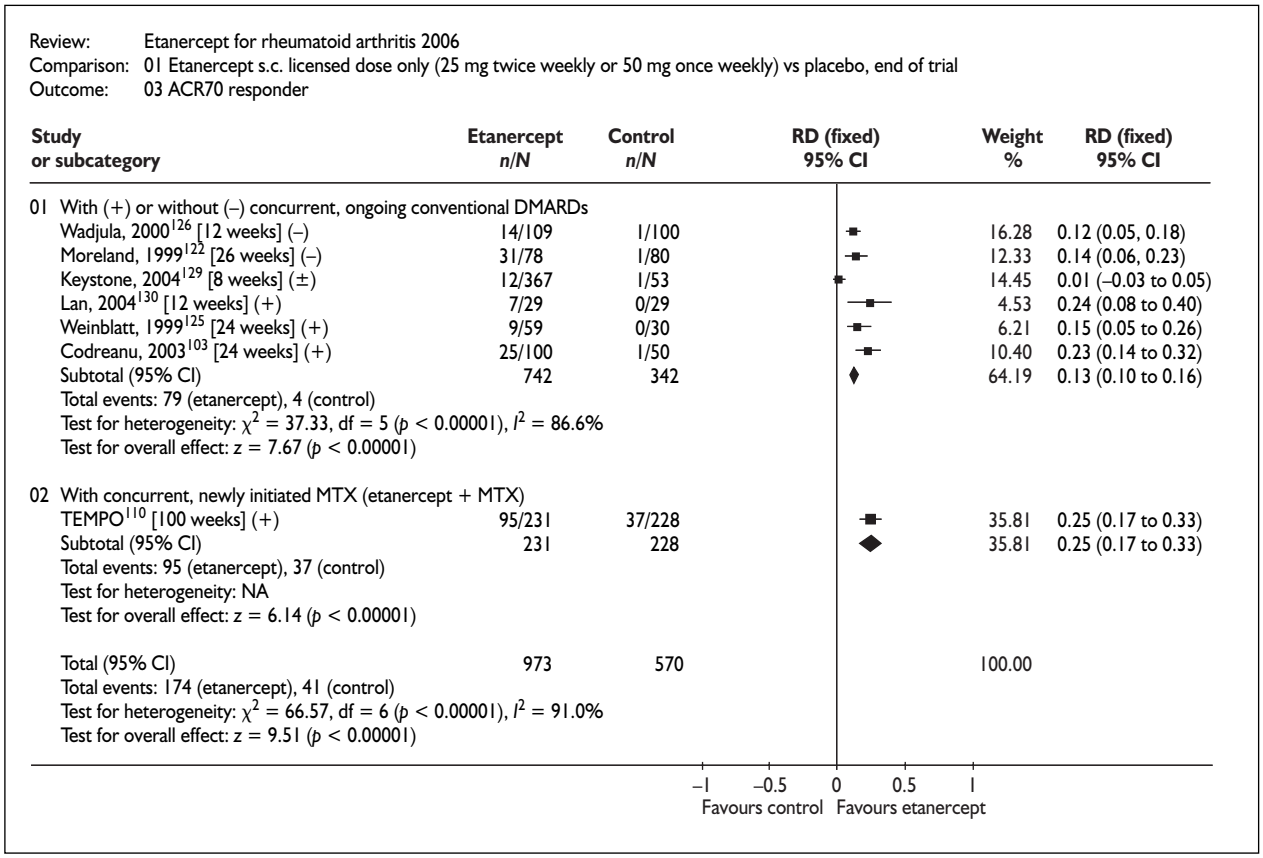

FIGURE 29 *ACR70 RD: etanercept licensed dose versus placebo (including etanercept plus MTX versus MTX)*

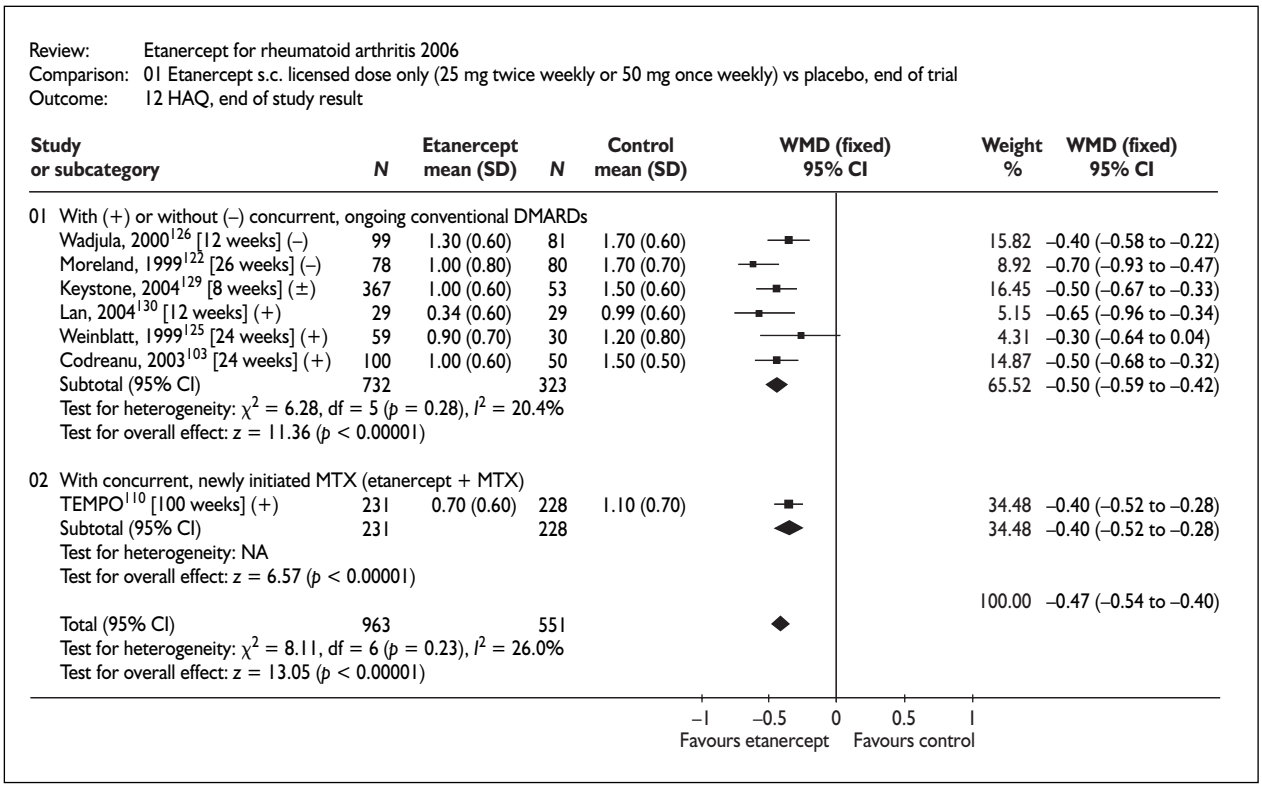

FIGURE 30 *HAQ change: etanercept licensed dose only versus placebo (including etanercept plus MTX versus MTX)*

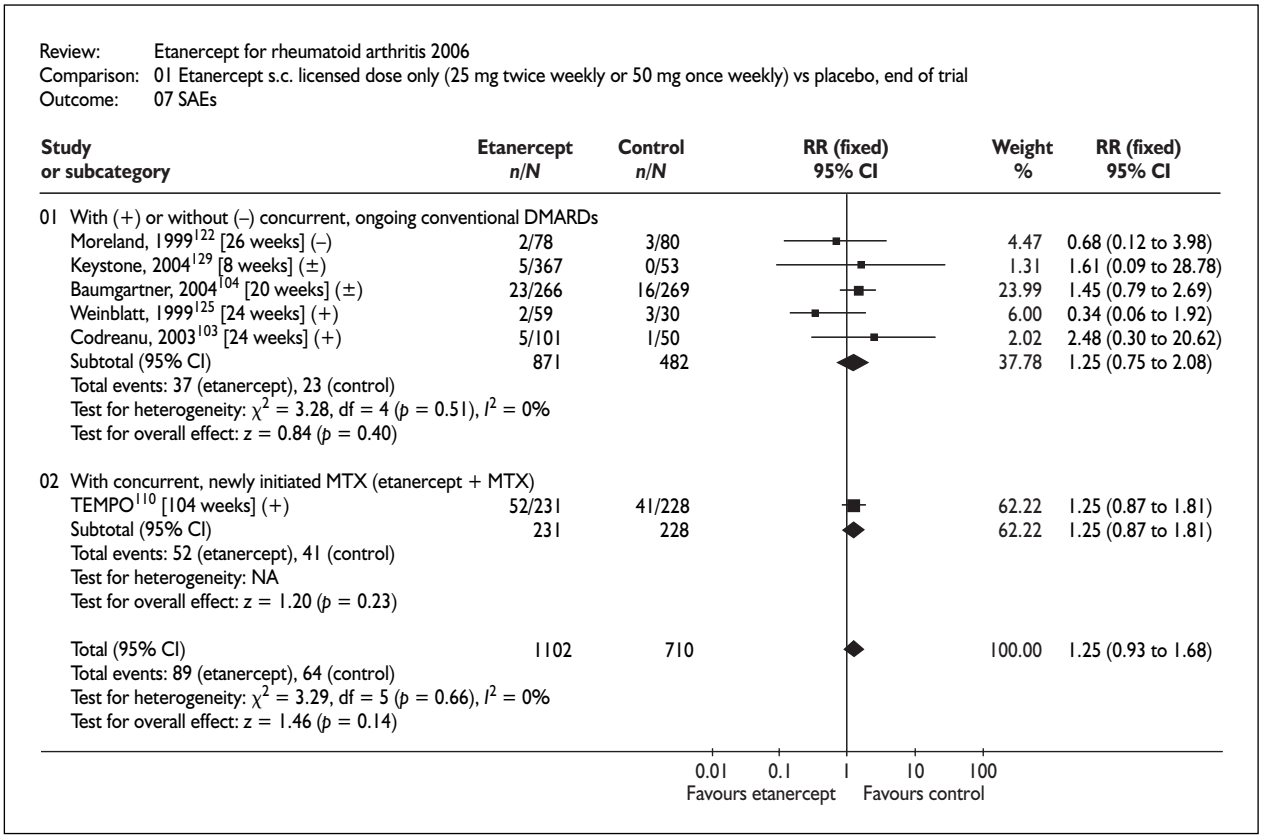

FIGURE 31 *SAE RR: etanercept licensed dose only versus placebo (including etanercept plus MTX versus MTX)*

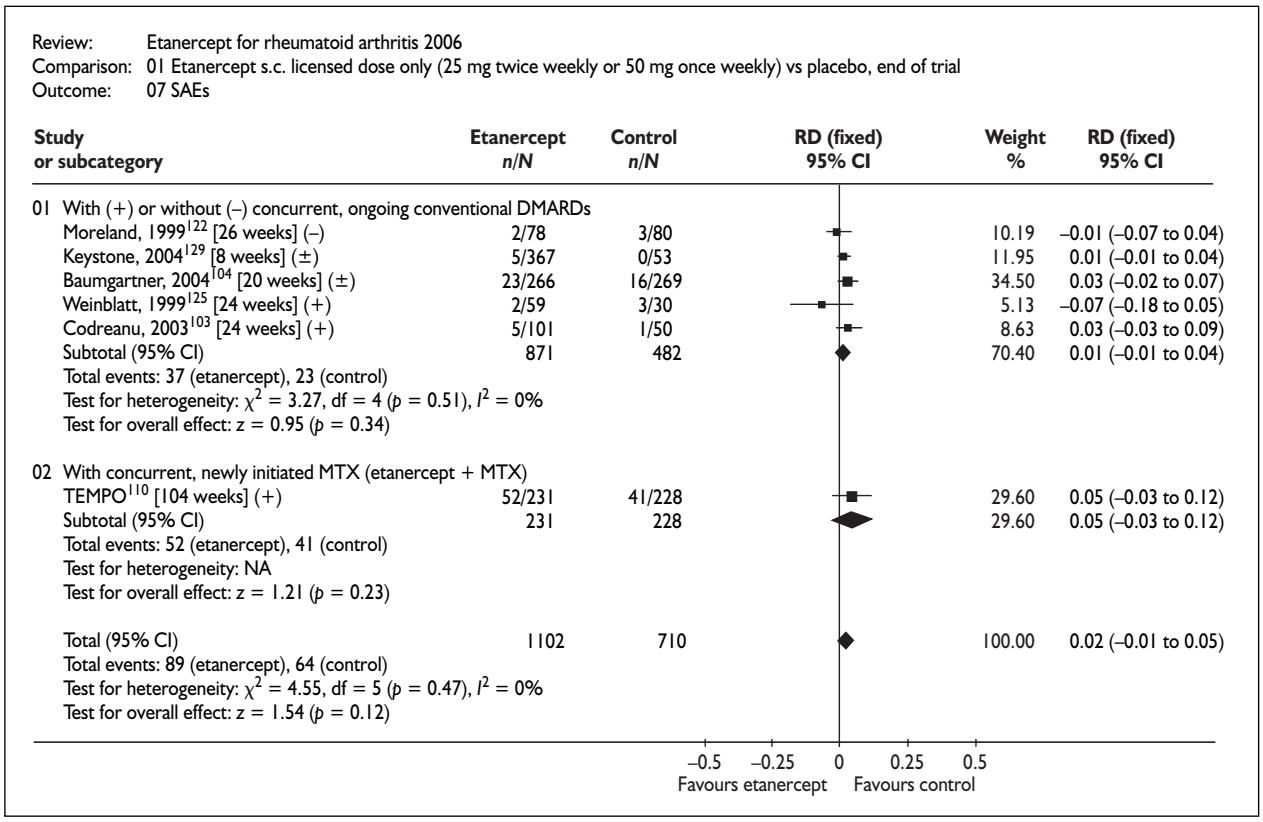

FIGURE 32 *SAE RD: etanercept licensed dose only versus placebo (including etanercept plus MTX versus MTX)*

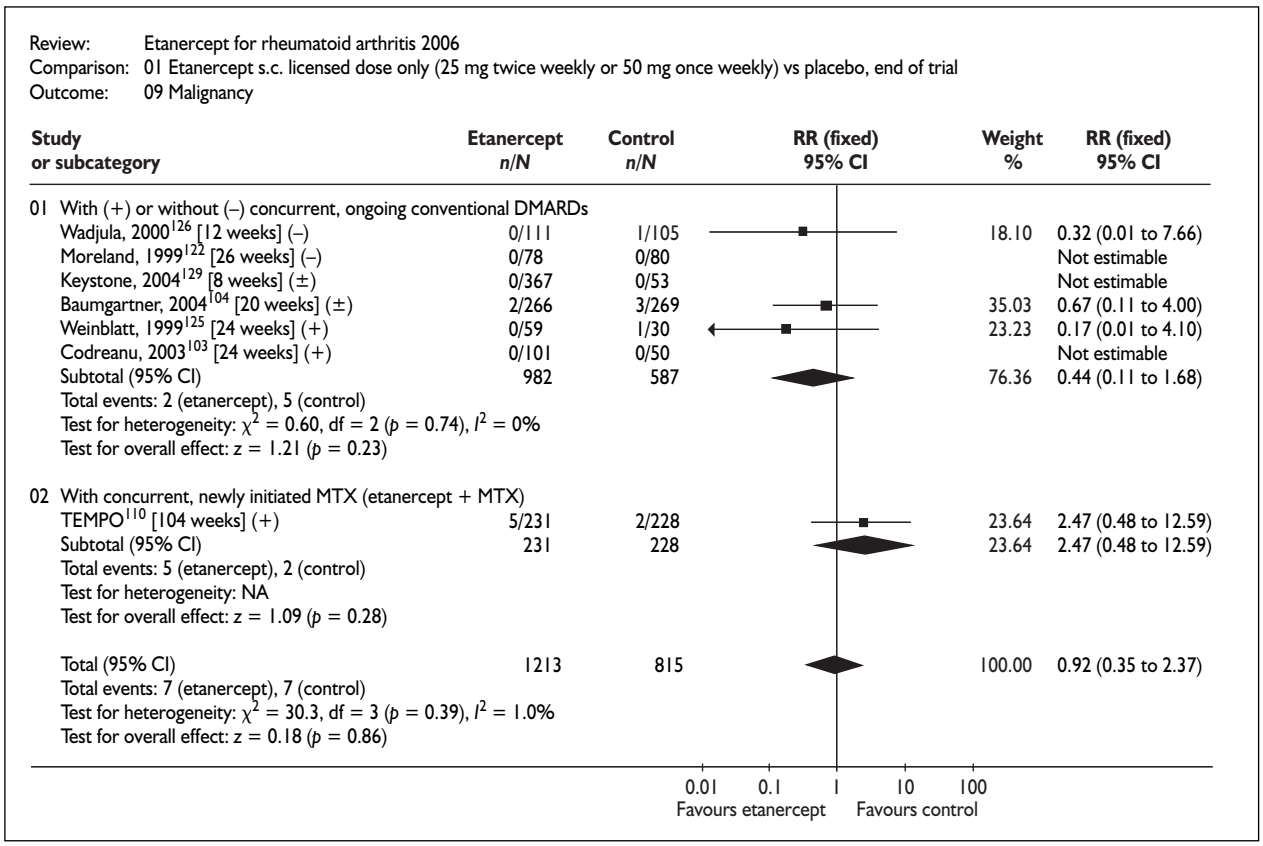

FIGURE 33 *Malignancy RR: etanercept licensed dose only versus placebo (including etanercept plus MTX versus MTX)*

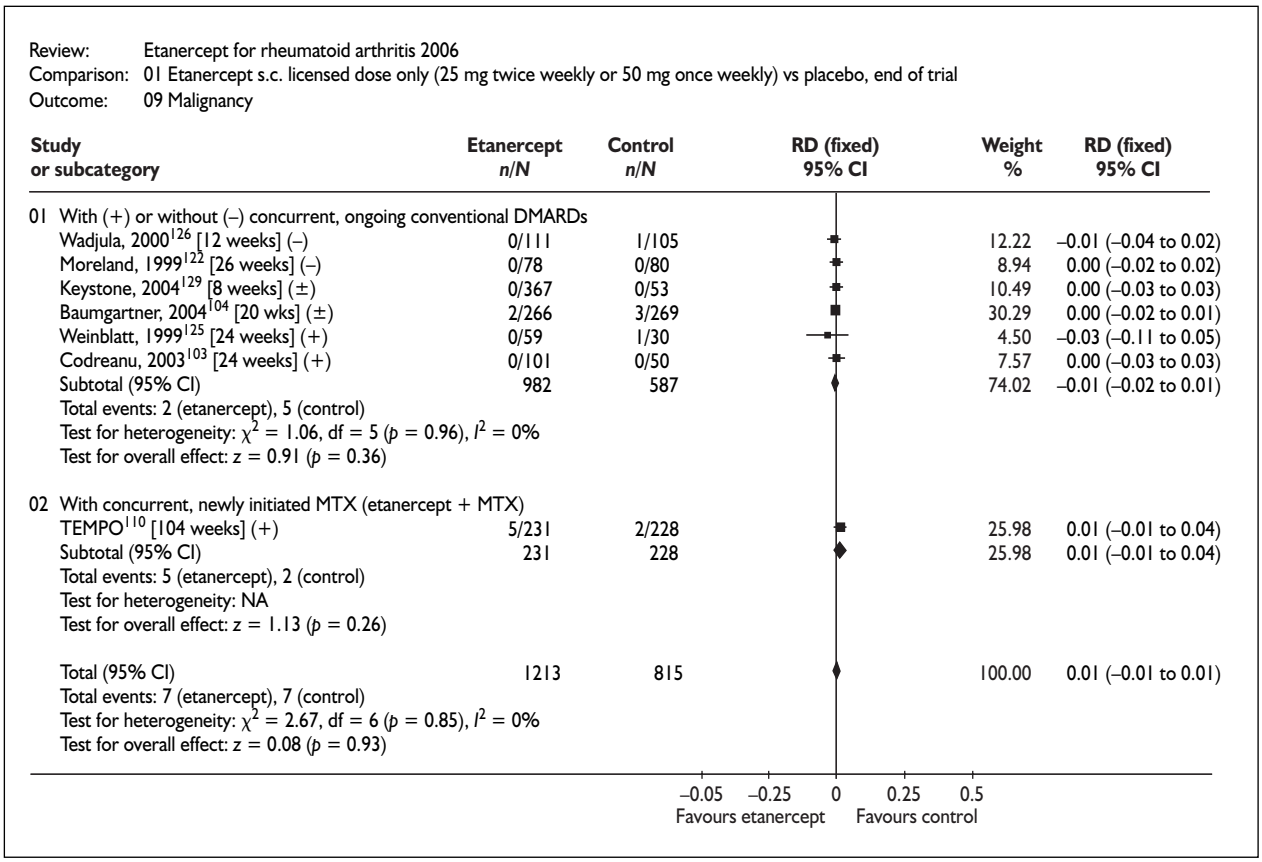

FIGURE 34 *Malignancy RD: etanercept licensed dose only versus placebo (including etanercept + MTX versus MTX)*

manufacturer. Results beyond week 54 were not included in meta-analyses for the following reasons: first, there was a substantial difference in the proportion of patients entering the second year between treatment arms (32% for the placebo plus methotrexate arm and 68% for the infliximab plus methotrexate arms combined); secondly, treatment was unblinded for 12% of the patients before completion of all HAQ evaluations; and thirdly, 94 of the 259 patients in the infliximab groups had a treatment gap between first year and second year of more than 8 weeks (mean 19.4 weeks) because of the timing of the protocol amendment. Consequently, the 54-week results are referred to as the end of study results in meta-analyses, unless otherwise specified.

ASPIRE: St Clair and colleagues, 2004[135]

This 54-week, double-blind, multicentre RCT compared treatment with methotrexate alone (starting at 7.5 mg per week and escalated to 20 mg per week) and infliximab (3 or 6 mg kg^{-1} i.v. every 8 weeks) with methotrexate. Only patients with early RA, disease duration of 3 months to 3 years, were included. A minimum of ten swollen joints and 12 tender joints were required. Patients who had received more than three doses of methotrexate or received other DMARDs within 4 weeks of study entry were not eligible.

Forty-five patients from two study sites out of 1049 randomised patients were excluded from efficacy analysis because the data could not be verified with source documents. The study had three primary end-points: ACR-N from baseline to week 54 (for reduction of signs and symptoms), van der Heijde modification of the total Sharp score (for radiographic progression of joint damage) and change from baseline in HAQ scores averaged over weeks 30–54 (for improvement in physical function). The safety outcomes for this trial were reported and analysed according to the actual treatment that the patient had received.

Durez and colleagues, 2004[139,142]

This small open-label, single-centre RCT compared a single pulse of methylprednisolone (1 gm i.v.) with three infusions (at weeks 0, 2 and 6) of infliximab 3 mg kg^{-1} i.v. in patients receiving concurrent methotrexate (10–15 mg per week). Patients with disease for more than 1 year and at

TABLE 11 *Summary of 2-year results from TEMPO study: combination of etanercept (25 mg s.c. twice weekly) plus MTX versus MTX alone in MTX-naïve patients/responders*

Comparison or outcome	*N* included in analysis	Statistical method	Effect size (95% CI)
ACR20 responder	459	RR (fixed)	1.49 (1.25 to 1.77)*
ACR50 responder	459	RR (fixed)	1.92 (1.52 to 2.41)*
ACR70 responder	459	RR (fixed)	2.53 (1.82 to 3.54)*
RD ACR20 responder	459	RD (fixed)	0.22 (0.13 to 0.30)*
RD ACR50 responder	459	RD (fixed)	0.27 (0.19 to 0.36)*
RD ACR70 responder	459	RD (fixed)	0.25 (0.17 to 0.33)*
SJC, end of study result	459	WMD (fixed)	–3.70 (–5.71 to –1.69)*
Patients' global assessment, end of study result	459	WMD (fixed)	–1.20 (–1.51 to –0.89)*
HAQ, end of study result	459	WMD (fixed)	–0.40 (–0.52 to –0.28)*
DAS, end of study result	459	WMD (fixed)	–0.80 (–1.02 to –0.58)*
Modified van de Heijde–Sharp score, mean change from baseline (1-year result)	430	WMD (fixed)	–3.34 (–5.12 to –1.56)*
Withdrawal for any reasons	459	RR (fixed)	0.61 (0.48 to 0.77)*
Withdrawal due to lack of efficacy	459	RR (fixed)	0.27 (0.13 to 0.55)*
Withdrawal due to adverse events	459	RR (fixed)	0.80 (0.55 to 1.17)
Death	459	RR (fixed)	0.99 (0.06 to 15.68)
SAEs	459	RR (fixed)	1.25 (0.87 to 1.81)
Malignancy: all	459	RR (fixed)	2.47 (0.48 to 12.59)
Malignancy: skin cancer excluding melanoma	459	RR (fixed)	1.97 (0.18 to 21.62)
Malignancy: all cancer excluding non-melanoma skin cancer	459	RR (fixed)	2.96 (0.31 to 28.26)
Serious infection	459	RR (fixed)	0.86 (0.42 to 1.76)
Any infection	459	RR (fixed)	1.00 (0.91 to 1.11)

* Statistically significant result at ($p < 0.05$)

least six swollen joints and six tender joints were recruited and followed for 14 weeks. The primary end-point was not stated, although various disease activity measures and serum matrix metalloproteinase-3 (MMP-3) were evaluated. Methods of randomisation, allocation concealment, patient withdrawals and use of ITT analysis were not clearly described.

START: Westhovens and colleagues, 2006[105,111]
This double-blind, multicentre safety trial compared infliximab, at two doses (3 or 10 mg kg^{-1}, i.v., at week 0, 2 and 6, then every 8 weeks thereafter), and placebo in patients receiving concurrent methotrexate. Patients were treated for 46 weeks, but patients in the placebo group were switched to receive infliximab 3 mg kg^{-1} every 8 weeks at week 22. Thus results beyond week 22 are excluded from this review and the 22-week results are referred to as the end of trial results.

Patients who were receiving methotrexate for at least 3 months and at a stable dose (≤ 25 mg per week) for at least 4 weeks, with a minimum of six swollen joints and six tender joints were recruited. Concomitant stable doses of other DMARDs were allowed. Twenty-five per cent of the patients were receiving one or more DMARDs in addition to methotrexate. The primary end-point was any occurrence of a serious infection within the first 22 weeks after initiating therapy.

Quinn and colleagues, 2005[141]
This small, double-blind, single-centre RCT compared methotrexate alone (started at 7.5 mg

TABLE 12 *Description of included RCTs and baseline patient characteristics: infliximab*

Study and description	Interventions	No. of patients	Mean age (years)	Mean disease duration (years)	No. of previous DMARDs	On steroids (%)	On NSAIDs (%)	Mean baseline HAQ score
Elliott *et al.*, 1994[136]					(Median)			
Europe, four centres, double-blind	Placebo (single i.v. infusion 0.1% albumin)	24	48	9.0	3.7	NR	NR	NR
Infliximab treatment: single infusion	Infliximab single infusion 1 mg kg^{-1} i.v.	25	56	7.5	2.8			
Duration of follow-up: four weeks	Infliximab single infusion 10 mg kg^{-1} i.v.	24	51	7.3	3.1			
Maini *et al.*, 1998[137]					(Median)			(Median)
Europe, six centres, double-blind:	Placebo (0.1% albumin i.v.) + MTX 7.5 mg per week	14	49	7.6	2	50	NR	2.0
Infliximab treatment: five	Infliximab 1 mg kg^{-1} i.v. + MTX 7.5 mg per week	14	54	14.3	2	43		1.4
infusions at 0, 2, 6, 10 and 14 weeks	Infliximab1 mg kg^{-1} i.v. without MTX	15	49	7.6	3	67		1.4
Duration of follow-up: 26 weeks	Infliximab 3 mg kg^{-1} i.v. + MTX 7.5 mg per week	15	59	12.1	2	60		2.0
	Infliximab 3 mg kg^{-1} i.v. without MTX	14	47	7.8	2.5	50		1.8
	Infliximab 10 mg kg^{-1} i.v. + MTX 7.5 mg per week	14	50	11.1	2	29		1.9
	Infliximab 10 mg kg^{-1} i.v. without MTX	15	56	9.7	2	60		1.9
C0168T22					(Mean)[b]			(Mean)
ATTRACT: Maini *et al.*, 1999;[132] Lipsky *et al.*, 2000[133]	Placebo (0.1% albumin or saline) + MTX (median 15 mg per week)	88	51	11	2.5	64	72	1.7
North America and Europe, 34 centres, double-blind	Infliximab 3 mg kg^{-1} i.v. every 8 weeks + MTX (median 15 mg per week)	86	54	10	2.8	63	79	1.8
Infliximab treatment: repeated infusion at 0, 2 and 6 weeks then every 8 weeks until week 54[a]	Infliximab 3 mg kg^{-1} i.v. every 4 weeks + MTX (median 15 mg per week)	86	52	9	2.6	54	76	1.7
	Infliximab 10 mg kg^{-1} i.v. every 8 weeks + MTX (median 15 mg per week)	87	54	11	2.5	58	77	1.7
	Infliximab 10 mg per kg^{-1} i.v. every 4 weeks + MTX (median 15 mg per week)	81	52	12	2.5	65	68	1.7
Kavanaugh *et al.*, 2000[138]								(Mean)
USA, three centres, double-blind	Placebo (single i.v. infusion 0.1% albumin) + MTX 10 mg per week	7	45	4.9	NR	2/7	4/7	1.6
Infliximab treatment: single infusion								
Duration of follow-up: 12 weeks[c]	Infliximab single infusion 5 mg per kg^{-1} i.v. + MTX 10 mg per week	7	47	7.4		5/7	7/7	1.6
	Infliximab single infusion 10 mg kg^{-1} i.v. + MTX 10 mg per week	7	53	7.5		5/7	6/7	1.4
	Infliximab single infusion 20 mg kg^{-1} i.v. + MTX 10 mg per week	7	37	4.9		6/7	5/7	1.5

continued

TABLE 12 *Description of included RCTs and baseline patient characteristics: infliximab (cont'd)*

Study and description	Interventions	No. of patients	Mean age (years)	Mean disease duration (years)	No. of previous DMARDs	On steroids (%)	On NSAIDs (%)	Mean baseline HAQ score
C0168T29					DMARD naïve			(Mean)
ASPIRE: St Clair *et al.*, 2004[135]	Placebo + MTX (starting 7.5 and increasing to 20 mg per week by week 8)	282	50	0.9	65%	38	82	1.5
North America, Europe and Israel, multicentre, double-blind	Infliximab 3 mg kg^{-1} i.v. every 8 weeks + MTX (as above)	359	51	0.8	71%	37	85	1.5
Infliximab treatment: repeated infusion at 0, 2 and 6 weeks then every 8 weeks until week 46	Infliximab 6 mg kg^{-1} i.v. every 8 weeks + MTX (as above)	363	50	0.9	68%	39	82	1.5
Duration of follow-up: 54 weeks								
Durez *et al.*, 2004[139]			(Median)	(Median)	(Median)			(Median)
Belgium, two centres, open-label	Methylprednisolone single IV infusion 1 g + MTX 10–15 mg per week	15	56	12	3	NR	NR	1.5
Infliximab treatment: three infusions at weeks 0, 2 and 6	Infliximab 3 mg kg^{-1} i.v. + MTX (as above)	12	48	10	3			1.3
Duration of follow-up: 14 weeks								
Taylor *et al.*, 2004[140]								
UK, single centre, double-blind	Placebo (normal saline) + MTX (12.5–17.5 mg per week at baseline, increasing to 25 mg per week if needed)	12	51	1.6	NR	NR	NR	NR
Infliximab treatment: repeated infusion at 0, 2 and 6 weeks then every 8 weeks until week 46	Infliximab 5 mg kg^{-1} i.v. every 8 weeks + MTX (as above)	12	55	1.3				
Duration of follow-up: 54 weeks								
C0168T41								
START: Westhovens 2006[105,111]								(Mean)
Multicentre, double-blind	Placebo + MTX (mean 14 mg per week)	363	52	10.2	NR (25%	59	39	1.4
Infliximab treatment: four infusions at 0, 2 and 6 weeks and 14 weeks	Infliximab 3 mg kg^{-1} i.v. + MTX (mean 14 mg per week)	360	53	10.3	receiving 2 or more	59	43	1.5
Duration of follow-up: 22 weeks[d]	Infliximab 10 mg kg^{-1} i.v. + MTX (mean 14 mg per week)	361	51	9.1	DMARDs)	59	41	1.4

continued

TABLE 12 *Description of included RCTs and baseline patient characteristics: infliximab (cont'd)*

Study and description	Interventions	No. of patients	Mean age (years)	Mean disease duration (years)	No. of previous DMARDs	On steroids (%)	On NSAIDs (%)	Mean baseline HAQ score
Quinn *et al.*, 2005[141]								(Median)
UK, single centre, double-blind	Placebo + MTX (starting 7.5, increasing to 15–25 mg per week according to clinical response)	10	53	0.5	0	0	NR	1.3
Infliximab treatment: repeated infusion at 0, 2 and 6 weeks then every 8 weeks until week 46	Infliximab 3 mg kg^{-1} i.v. every 8 weeks + MTX (as above)	10	51	0.6	0 (Not permitted)	0 (Not permitted)		1.3
Duration of follow-up: 54 weeks[e]								

[a] Extension study with continuous treatment and follow-up to 102 weeks not included in the current review; see text for details (p. 53).
[b] Excluding MTX.
[c] Open label, non-comparative extension with three additional infusions of infliximab 10 mg kg^{-1} at weeks 12, 20 and 28 and follow-up to week 40 not included in the current review.
[d] Patients in placebo arm switched to infliximab 3 mg kg^{-1} at week 22 and all group continued treatments for 46 weeks. Results beyond 22 weeks are not included in the current review.
[e] Open-label extension and follow-up to 104 weeks not included in the current review as other DMARDs could be introduced during the extension.

TABLE 13 *Quality of included RCTs: infliximab*

Study	Sample size	Truly random allocation/ Remain on randomised treatment	Adequate allocation concealment	Blinding			Important differences in baseline characteristics between groups (item)	Important differences in completion rates between groups (% randomised patients completed)	Use of ITT analysis
				Participants	Investigators	Assessors			
Elliott, 1994[136]	Placebo: 24 Infliximab: 49	Yes	Unclear	Yes	Yes	Yes	No	No (only one patient withdrew and was replaced)	Yes
Maini, 1998[137]	Placebo: 14 Infliximab: 87	Unclear	Yes	Yes	Unclear	Yes	Yes (HAQ)	Yes Placebo: 43% Infliximab: 83%	Unclear (yes for Paulus response)
Kavanaugh, 2000[138]	Placebo: 7 Infliximab: 21	Yes	Yes	Yes	Unclear	Unclear	NA (sample size too small)	No Placebo: 100% Infliximab:100%	No (except ACR responses)
ATTRACT									
Up to week 54: Maini, 1999;[132] Lipsky, 2000[133]	Placebo: 88 Infliximab: 340	Yes	Yes	Yes	Yes	Yes	No	Yes Placebo: 50% Infliximab: 79%	Yes (except radiographic and safety outcomes)
Week 102: Maini, 2004;[134] clinical study report	Placebo: 28 Infliximab: 231	Partially[a]	NA	Partially[a]	Partially[a]	Partially[a]	(61% randomised patients entering extension)	Yes Placebo: 16% Infliximab: 59%	Yes (except SF-36, radiographic and safety outcomes)
START: Westhovens, 2006;[111] clinical study report	Placebo: 363 Infliximab: 721	Yes	Yes	Yes	Yes	Yes	No	No Placebo: 94% Infliximab: 92%	Yes
ASPIRE: St Clair, 2004;[135] clinical study report	Placebo: 291 Infliximab: 749	Yes	Yes	Yes	Yes	Yes	No	No Placebo: 82% Infliximab: 86%	No[b]

continued

TABLE 13 *Quality of included RCTs: infliximab (cont'd)*

Study	Sample size	Truly random allocation/ Remain on randomised treatment	Adequate allocation concealment	Blinding			Important differences in baseline characteristics between groups (item)	Important differences in completion rates between groups (% randomised patients completed)	Use of ITT analysis
				Participants	Investigators	Assessors			
Taylor, 2004[140]	Placebo: 12 Infliximab: 12	Unclear	Yes	Yes	Yes	Yes	No	No (one patient withdrew, but did not state which arm)	No
Durez, 2004[139]	Methylprednisolone: 15 Infliximab: 12	Unclear	Unclear	No	Unclear	Yes	No	Unclear	Unclear
Quinn, 2005[141]	Placebo: 10 Infliximab: 10	Yes	Unclear	Yes	Yes	Yes	No	No Placebo: 10/10 Infliximab: 9/10	Yes

[a] Only 28 (32%) of the those allocated MTX in year 1 continued compared with 231 (68%) of those on infliximab plus MTX. For ethical reasons the study was unblinded at week 54. Unblinding occurred in 12% of patients before completion of all HAQ evaluations. Ninety-four of the 259 patients had a gap of more than 8 weeks between treatments because of the timing of the protocol amendment. The mean length of time for which infliximab was suspended was 19.4 weeks.

[b] Before unblinding, 45 patients at two study sites were excluded from the efficacy analysis (16 in the MTX–placebo group, 14 in the MTX–3 mg kg^{-1} infliximab group and 15 in the MTX–6 mg kg^{-1} infliximab group) because their study data could not be verified with source documents.

per week and escalated to up to 25 mg per week depending on disease activity) and methotrexate combined with infliximab 3 mg kg^{-1} i.v. every 8 weeks. Patients with early RA, judged to have a poor prognosis, were treated for 12 months, with a further open-label phase up to 24 months. The latter data are not included in this review as other DMARDs could be introduced during the extension. RA patients with symptoms for less than 12 months and no previous treatment with DMARDs or oral corticosteroids were recruited. Metacarpophalangeal joint disease and poor prognosis according to a scoring system based on rheumatoid factor positivity, genetic markers, CRP, gender and HAQ score were required. The primary end-point was MRI-measured synovitis at week 14. Allocation concealment was not clearly stated.

BeSt: Goekoop-Ruiterman and colleagues[108,143,144]

This important trial compared four strategies for using DMARDs, rather than individual drugs. Patients with RA diagnosed within 2 years were recruited. Because patients received infliximab in all arms, this trial does not meet the inclusion criteria defined in the current protocol, which sought comparative studies of TNF inhibitors against alternative treatments. Nor can its results be incorporated meaningfully in the meta-analyses. Nevertheless, it is reported in detail here, as it is important evidence to inform guidance on appropriate use of infliximab. The primary end-points of BeSt were HAQ and radiographic joint damage according to the van der Heijde modified Sharp score after 1 year of follow-up. A sequence of drug treatments was strictly defined and patients moved along the sequence of therapies based on their response. Those who did not achieve a DAS of 2.4 or less, based on evaluation of 44 joints (Appendix 1), moved to the next step in the defined sequence. A sustained response to therapy, defined as DAS of <2.4 for 6 months, led to a tapering of drug treatment (prednisolone and infliximab were always tapered first) that was strictly specified and included contingencies for disease relapse. The protocol also specified the required steps when drug toxicity occurred. This trial was co-sponsored by Schering-Plough and the Dutch College of Health Insurance. Drugs used in the treatment strategies were as follows.

- Group 1: sequential monotherapy (126 patients): methotrexate 15 mg per week; methotrexate 25 mg per week; sulfasalazine 2 g per day; leflunomide 20 mg per day; methotrexate 25 mg per week and infliximab 3 mg kg^{-1} (according to licensed use in RA); methotrexate 25 mg week and infliximab 6 mg kg^{-1} (maintenance interval 8 weeks); methotrexate 25 mg week and infliximab 7.5 mg kg^{-1} (maintenance interval 8 weeks); methotrexate 25 mg per week and infliximab 10 mg kg^{-1} (maintenance interval 8 weeks); intramuscular gold 50 mg weekly with intramuscular methylprednisolone (120 mg at weeks 1, 4 and 8); methotrexate 25 mg per week and ciclosporin 2.5 mg kg^{-1} and prednisolone 7.5 mg per day.
- Group 2: step-up combination therapy (121 patients): methotrexate 15 mg per week; methotrexate 25 mg per week; methotrexate 25 mg per week and sulfasalazine 2 g per day; methotrexate 25 mg per week and sulfasalazine 2 g per day and hydroxychloroquine 400 mg per day; the previous sequence and prednisolone 7.5 mg per day; methotrexate 25 mg per week and infliximab 3 mg kg^{-1} (licensed schedule); this combination with increasing doses of infliximab, as above; methotrexate, ciclosporin and prednisolone, as above; leflunomide 20 mg per day.
- Group 3: initial combination with prednisolone (133 patients): methotrexate 7.5 mg per week, sulfasalazine 2 g per day and prednisolone (60 mg reducing to 7.5 mg over 7 weeks); methotrexate, ciclosporin A and prednisolone, as above; methotrexate and infliximab with increasing doses of infliximab, as above; leflunomide 20 mg per day; gold and methylprednisolone, as above; azathioprine 2–3 mg per kg^{-1} and prednisolone 7.5 mg per day.
- Group 4: initial combination with infliximab (128 patients): methotrexate 25 mg per week and infliximab starting at 3 mg kg^{-1} (licensed schedule) and increasing dose of infliximab, as above, up to 10 mg kg^{-1}; sulfasalazine alone 2 g per day; leflunomide 20 mg per day; methotrexate, ciclosporin and prednisolone, as above; gold and methylprednisolone, as above; azathioprine and prednisolone, as above.

Concomitant therapy with NSAIDs and intra-articular steroid injections, but no other parenteral or oral steroids, was allowed. Permitted doses of intra-articular steroids were not stated; it is known that intra-articular steroids produce high serum levels and can inhibit adrenal steroid production.[145]

A total of 508 patients was randomly allocated to a treatment strategy and assessed every 3 months by

TABLE 14 *Key outcomes for the BeSt study*

Outcome	Treatment sequence			
	Group 1 Sequential monotherapy	**Group 2 Step-up combination**	**Group 3 Initial combination with prednisolone**	**Group 4 Initial combination with infliximab**
HAQ (mean ± SD)				
Baseline	1.4 ± 0.7	1.4 ± 0.6	1.4 ± 0.7	1.4 ± 0.7
3 months	1.0 ± 0.7	1.0 ± 0.6	0.6 ± 0.6	0.6 ± 0.6
12 months	0.7 ± 0.7	0.7 ± 0.6	0.5 ± 0.5	0.5 ± 0.5
DAS44 (mean ± SD)				
Baseline	4.5 ± 0.9	4.5 ± 0.8	4.4 ± 0.9	4.3 ± 0.9
3 months	3.5 ± 1.1	3.5 ± 1.2	2.4 ± 1.0	2.6 ± 1.1
12 months	2.3 ± 1.1	2.2 ± 1.0	2.0 ± 0.9	2.0 ± 1.0
ACR20				
3 months	30%	37%	71%	60%
12 months	64%	63%	78%	79%
ACR50				
3 months	7%	9%	48%	39%
12 months	43%	46%	62%	62%
ACR70				
3 months	2%	3%	21%	19%
12 months	19%	22%	30%	40%
Increase in total van der Heijde–Sharp score: Median (IQR)	2.0 (0.0–7.4)	2.5 (0.0–6.0)	1.0 (0.0–2.5)	0.5 (0.0–2.3)

a research nurse who was blinded to treatment allocation. Patients had a mean age of between 54 and 55 years, 68% were women, all met ARA disease classification criteria despite a median time from diagnosis of 2 weeks, and 65% had a positive rheumatoid factor blood test.

Key outcomes of this study are shown in the *Table 14*. Patients in groups 3 and 4 improved more rapidly than those in groups 1 and 2 ($p < 0.001$), but at 1 year differences were less marked ($p < 0.009$). No statistically significant differences were found on comparing group 1 with group 2, or on comparing group 3 with group 4. Similarly, significantly less radiographic progression ($p < 0.007$ or less) was seen in groups 3 and 4 than in groups 1 and 2, at 1 year. Radiographic joint damage did not progress in 67%, 73%, 87% and 93% of patients in groups 1 to 4, respectively. Minor gastrointestinal and skin reactions were the most frequently reported adverse events. Ten patients (8%) in group 4 had an infusion reaction to infliximab necessitating drug cessation. SAEs occurred in 6%, 7%, 13% and 5% in groups 1–4, respectively; no clear pattern of adverse reactions was noted.

Of the 128 patients allocated to group 4, which included infliximab at inception, two patients (1.6%), who had latent tuberculosis, declined prophylactic antituberculosis therapy. The percentages of patients receiving infliximab in groups 1, 2 and 3 after 12 months or more were 20%, 3% and 6%, respectively; recall that patients in this trial had therapies withdrawn because of a sustained DAS of <2.4, starting first with prednisolone followed by infliximab in group 1, for example.

After 1 year, 81% of patients in group 4 had not progressed to the next treatment. For groups 1–3 this figure was 39%, 37% and 74%, respectively. Notably, 50% of these patients in group 4 had stopped infliximab and 78% in group 3 had stopped prednisolone because of a sustained DAS of <2.4. By contrast, less than 50% of patients in groups 1 and 2 could be managed with methotrexate alone and had moved along the sequence to another DMARD. The data for groups 1 and 2 are inconsistent with clinical experience and published data for methotrexate in early RA. The authors concluded that initial combination therapy with infliximab or prednisolone had

significant advantages over sequential monotherapy with DMARDs or step-up combination DMARD use.

Meta-analysis of infliximab results

The principles of analysis and data presentation of infliximab trials are the same as described in the section 'Data analysis' (p. 14), towards the beginning of this chapter.

Infliximab versus other active treatment

The licence for infliximab stipulates that infliximab has to be used in conjunction with methotrexate, thus head-to-head comparison between infliximab and methotrexate is not considered here. However, relevant data from a small, dose-ranging study[137] are summarised in *Table 74* (Appendix 4). Infliximab 3 mg kg^{-1} at 0, 2 and 6 weeks was more effective in all efficacy outcomes than a single infusion of methylprednisolone (1 g i.v.) in a small open-label RCT by Durez and colleagues.[139]

Infliximab versus placebo (with concurrent, ongoing methotrexate)

Two trials (START[105,111] and ATTRACT[133]) compared infliximab at licensed dose to placebo in patients who had had an inadequate response to methotrexate treatment. The results for these primary analyses (licensed dose) are summarised in *Table 15* and the upper parts of *Figures 35–45*. Additional data from a small, dose-ranging study[136] for the comparison between infliximab alone (not licensed use) and placebo without concomitant methotrexate are not considered here but are summarised in *Table 74* (Appendix 4).

Efficacy Infliximab was significantly more effective than placebo for all the efficacy outcomes being meta-analysed.

Tolerability Significant heterogeneity in withdrawal for any reasons was observed between ATTRACT and START (test for heterogeneity p = 0.03). Infliximab was better tolerated than placebo in ATTRACT but not in the START.

Safety No significant differences were found between infliximab and placebo in any of the safety outcomes being meta-analysed. The number of patients who had malignancy **[Commercial-in-confidence information removed]**.

Sensitivity analyses Three trials (Maini,[137] Kavanaugh[138] and Taylor[140]) included comparisons between infliximab and placebo at

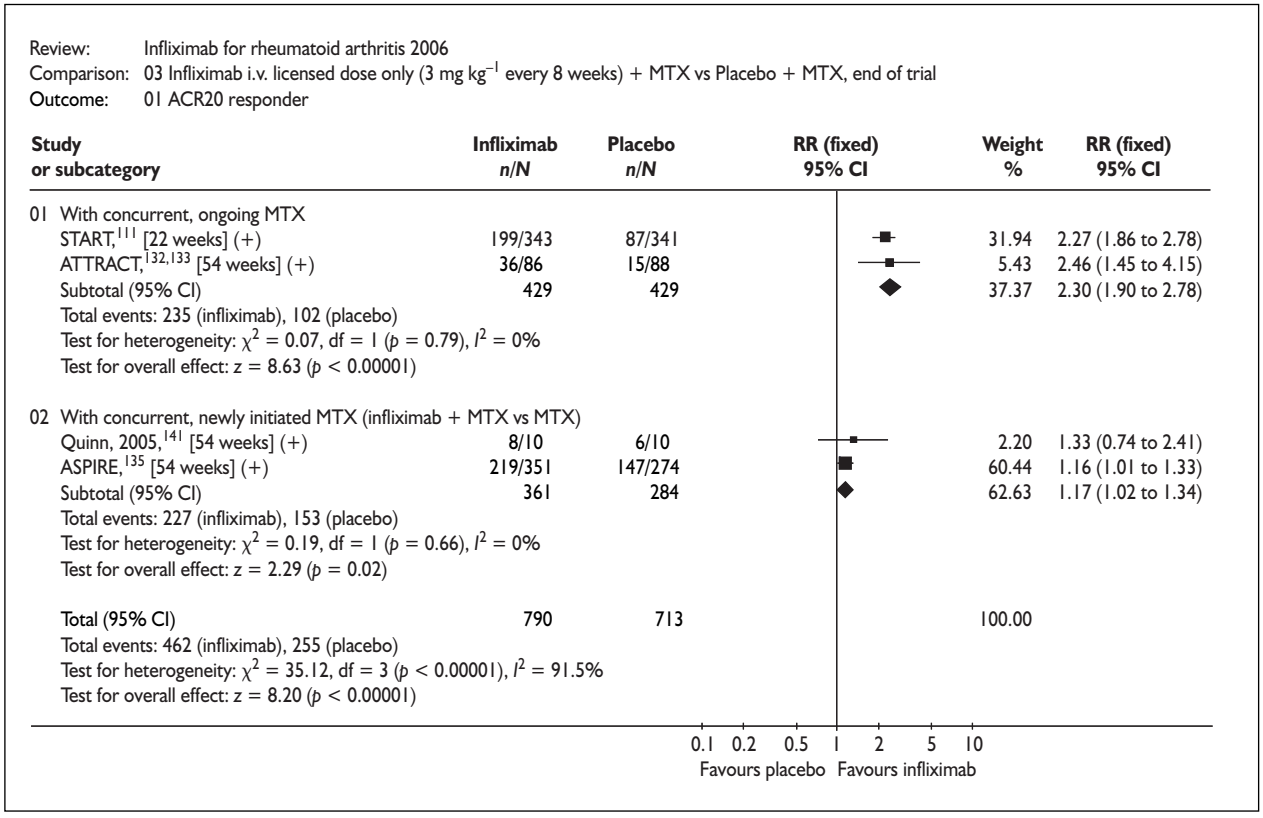

FIGURE 35 *ACR20 RR: infliximab licensed dose versus placebo (with concurrent MTX)*

TABLE 15 *Meta-analyses: infliximab i.v. licensed dose (3 mg kg^{-1} every 8 weeks) versus placebo with ongoing MTX in MTX partial responders/non-responders, end of trial*

Comparison or outcome	Studies	*N* included in analysis	Statistical method	Effect size (95% CI)
ACR20 responder	2[111,133]	858	RR (fixed)	2.30 (1.90 to 2.78)*
ACR50 responder	2[111,133]	858	RR (fixed)	3.20 (2.30 to 4.44)*
ACR70 responder	2[111,133]	858	RR (fixed)	3.16 (1.89 to 5.27)*
RD ACR20 responder	2[111,133]	858	RD (fixed)	0.31 (0.25 to 0.37)*
RD ACR50 responder	2[111,133]	858	RD (fixed)	0.20 (0.15 to 0.26)*
RD ACR70 responder	2[111,133]	858	RD (fixed)	0.09 (0.05 to 0.13)*
SJC, mean change from baseline	2[111,133]	830	WMD (fixed)	–5.08 (–6.23 to –3.94)*
Patient's global assessment, mean change from baseline	2[111,133]	829	WMD (fixed)	–1.52 (–1.89 to –1.15)*
HAQ, mean change from baseline	2[111,133]	818	WMD (fixed)	–0.27 (–0.35 to –0.19)*
DAS28, end of study result	0	0	Not estimable	No data available
Modified van de Heijde–Sharp score, mean change from baseline	1[133]	135	WMD (fixed)	–5.70 (–8.58 to –2.82)*
Withdrawal for any reasons	2[111,133]	895	RR (random)	0.76 (0.36 to 1.60)
Withdrawal due to lack of efficacy	1[133]	174	RR (fixed)	0.54 (0.33 to 0.90)*
Withdrawal due to adverse events	2[111,133]	895	RR (fixed)	1.55 (0.82 to 2.93)
Death	2[111,133]	895	RR (fixed)	0.33 (0.05 to 2.06)
SAEs	2[111,133]	895	RR (fixed)	0.84 (0.56 to 1.26)
Malignancy: all	2[111,133]	895	RR (fixed)	2.48 (0.49 to 12.70)
Malignancy: skin cancer excluding melanoma	2[111,133]	895	RR (fixed)	1.49 (0.25 to 8.80)
Malignancy: all cancer excluding non-melanoma skin cancer	2[111,133]	895	RR (fixed)	2.32 (0.34 to 15.62)
Serious infection	2[111,133]	895	RR (fixed)	0.61 (0.26 to 1.46)
Any infection	2[111,133]	896	RR (fixed)	**[Commercial-in-confidence information removed]**

* Statistically significant result ($p < 0.05$).

doses or dosing schedules other than that in the licence. Sensitivity analyses which include patients from these trials are summarised in *Table 75* (licensed dose and above) and *Table 76* (all doses including sublicensed dose) (Appendix 4). Results are generally consistent with the primary analyses. However, when doses above the licensed doses are included, infliximab was associated with a slight **[Commercial-in-confidence information removed]** in any infection (RR **[Commercial-in-confidence information removed]**).

Contrary to the observations from TEMPO, data from ATTRACT indicated that there was an inverse relationship between absolute HAQ improvement and disease duration in infliximab-treated patients.

Infliximab plus methotrexate versus methotrexate (newly initiated methotrexate)

ASPIRE[135] and the study by Quinn and colleagues[141] compared the combination of infliximab and methotrexate with methotrexate alone in methotrexate-naïve, early RA patients. The results of primary analyses (at licensed dose) are summarised in *Table 16* and are also shown in the lower parts of *Figures 35–45*.

Efficacy Infliximab combined with methotrexate is more effective than methotrexate alone. The differences between the combination and

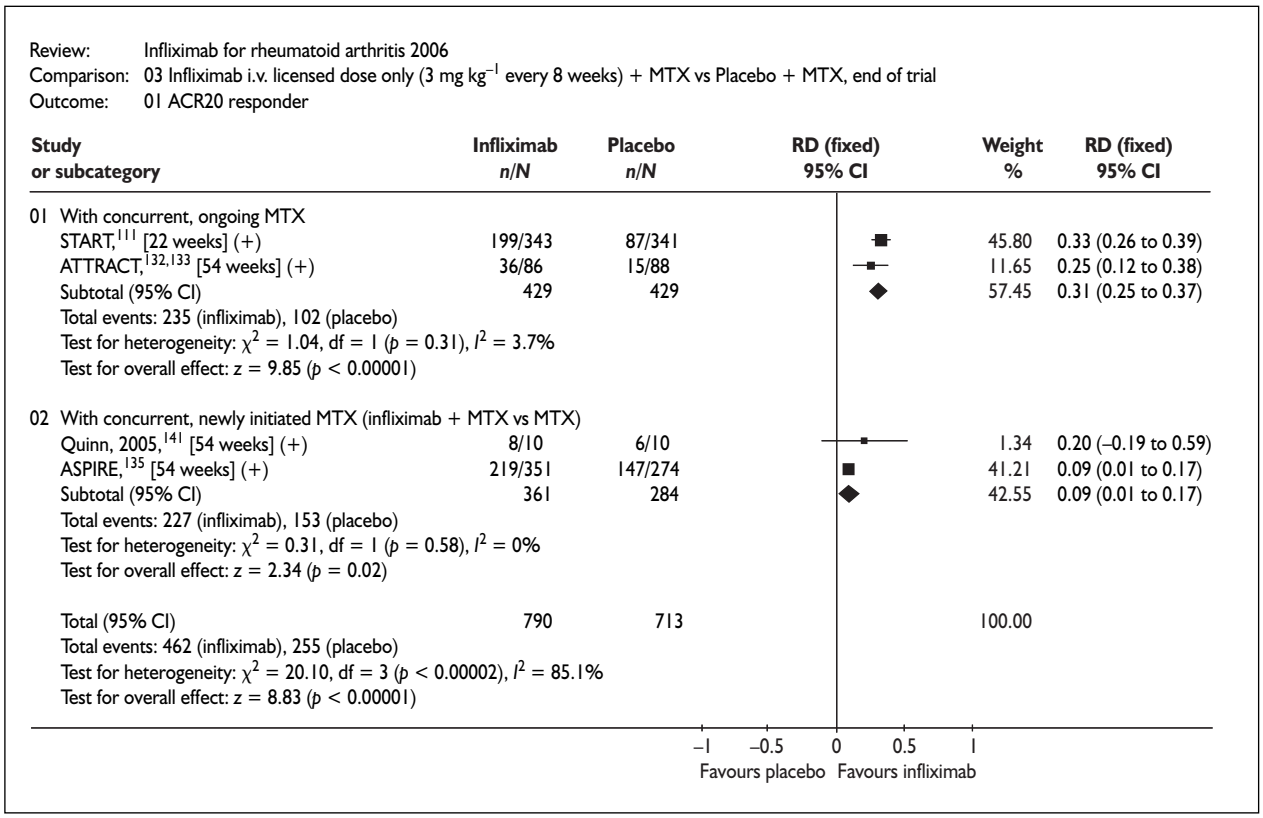

FIGURE 36 *ACR20 RD: infliximab licensed dose versus placebo (with concurrent MTX)*

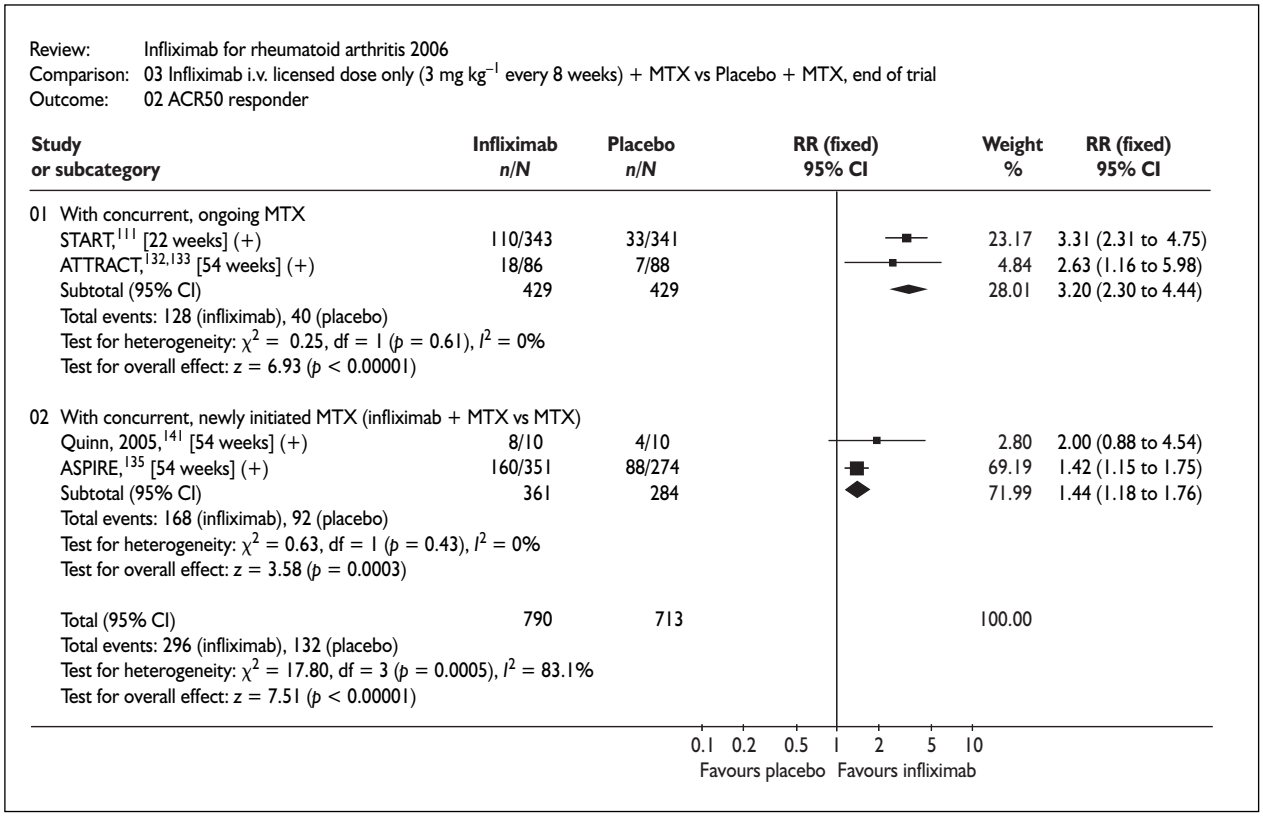

FIGURE 37 *ACR50 RR: infliximab licensed dose versus placebo (with concurrent MTX)*

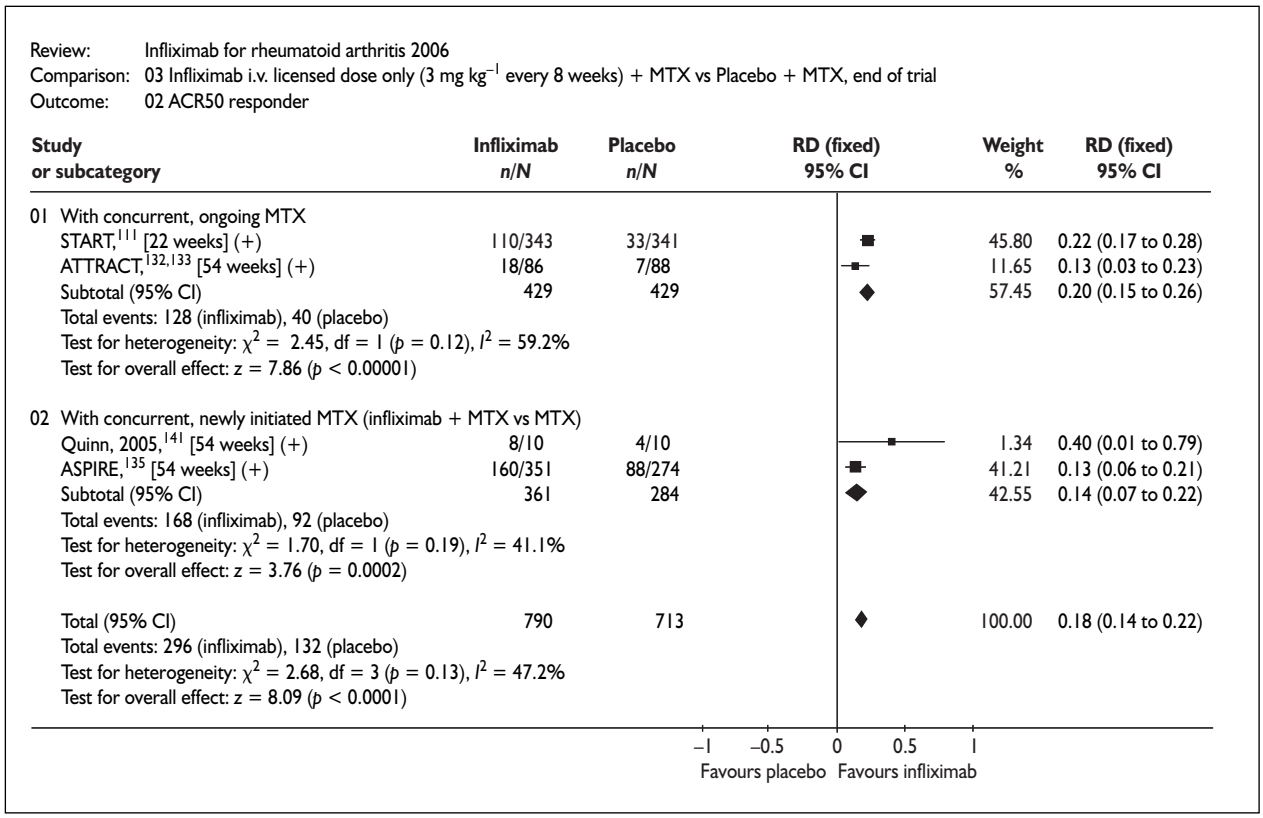

FIGURE 38 *ACR50 RD: infliximab licensed dose versus placebo (with concurrent MTX)*

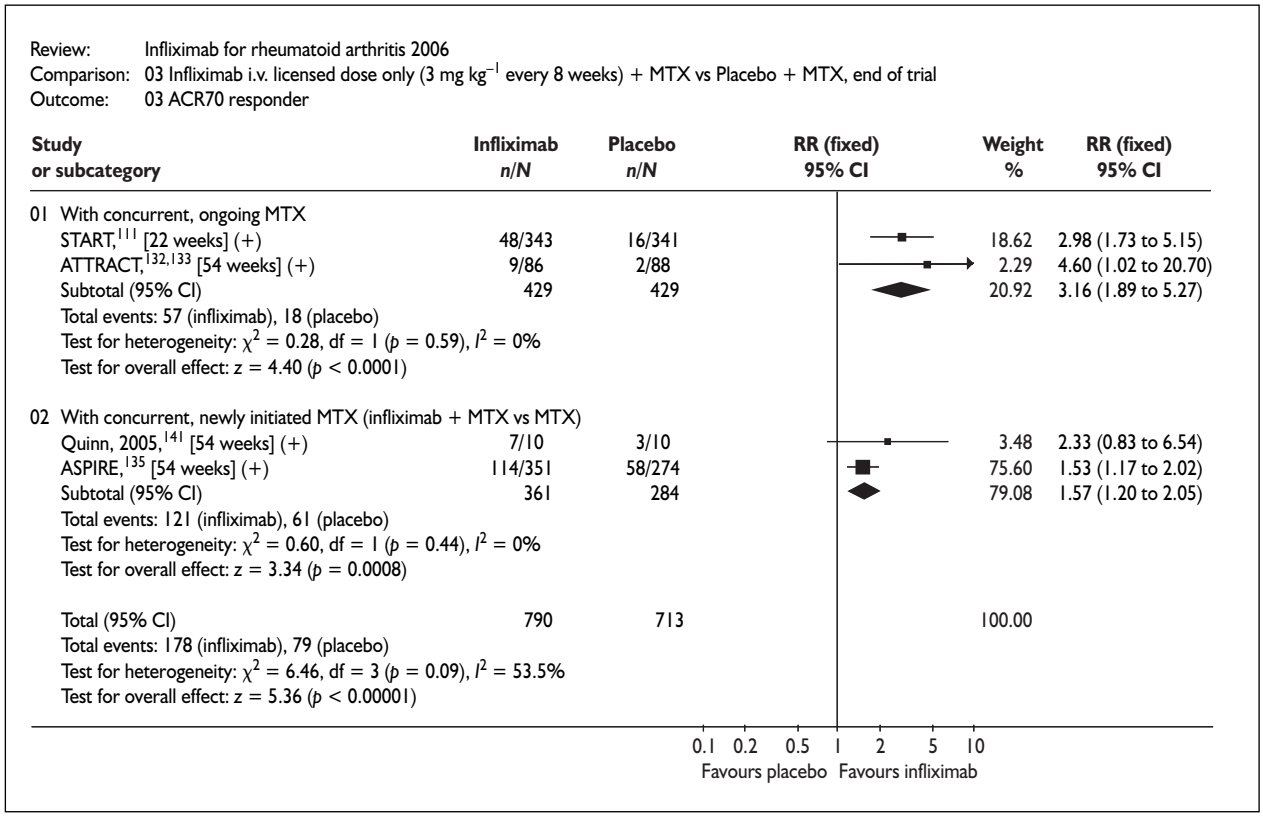

FIGURE 39 *ACR70 RR: infliximab licensed dose versus placebo (with concurrent MTX)*

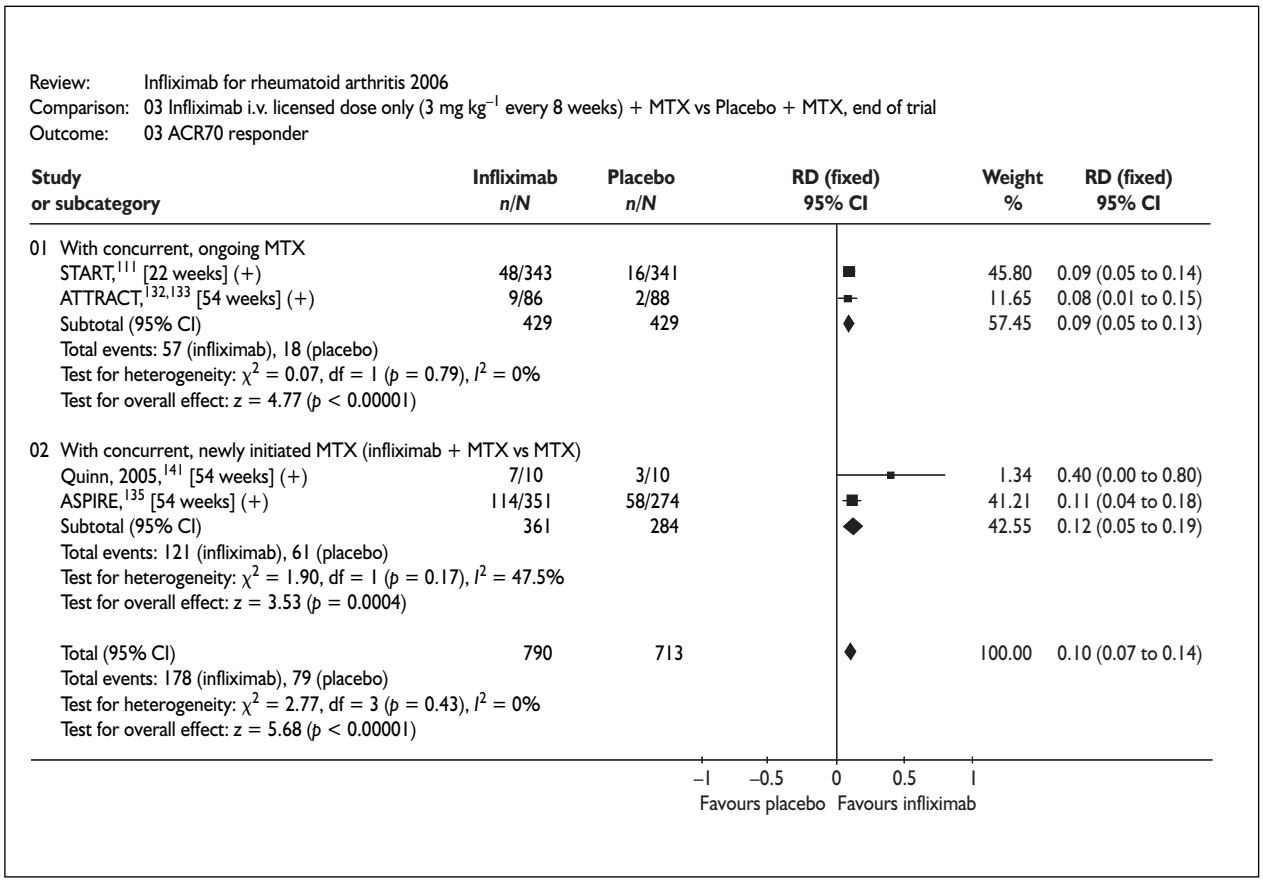

FIGURE 40 *ACR70 RD: infliximab licensed dose versus placebo (with concurrent MTX)*

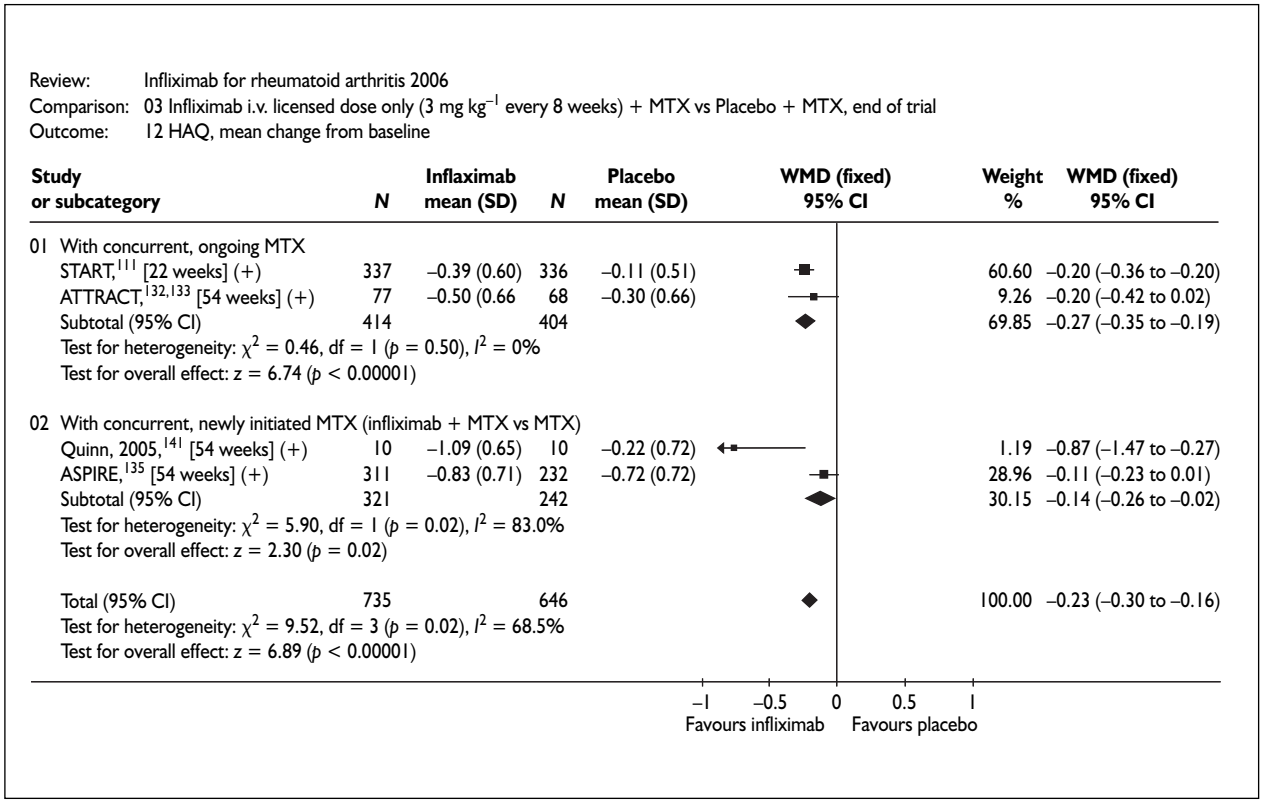

FIGURE 41 *HAQ change: infliximab licensed dose only versus placebo (with concurrent MTX)*

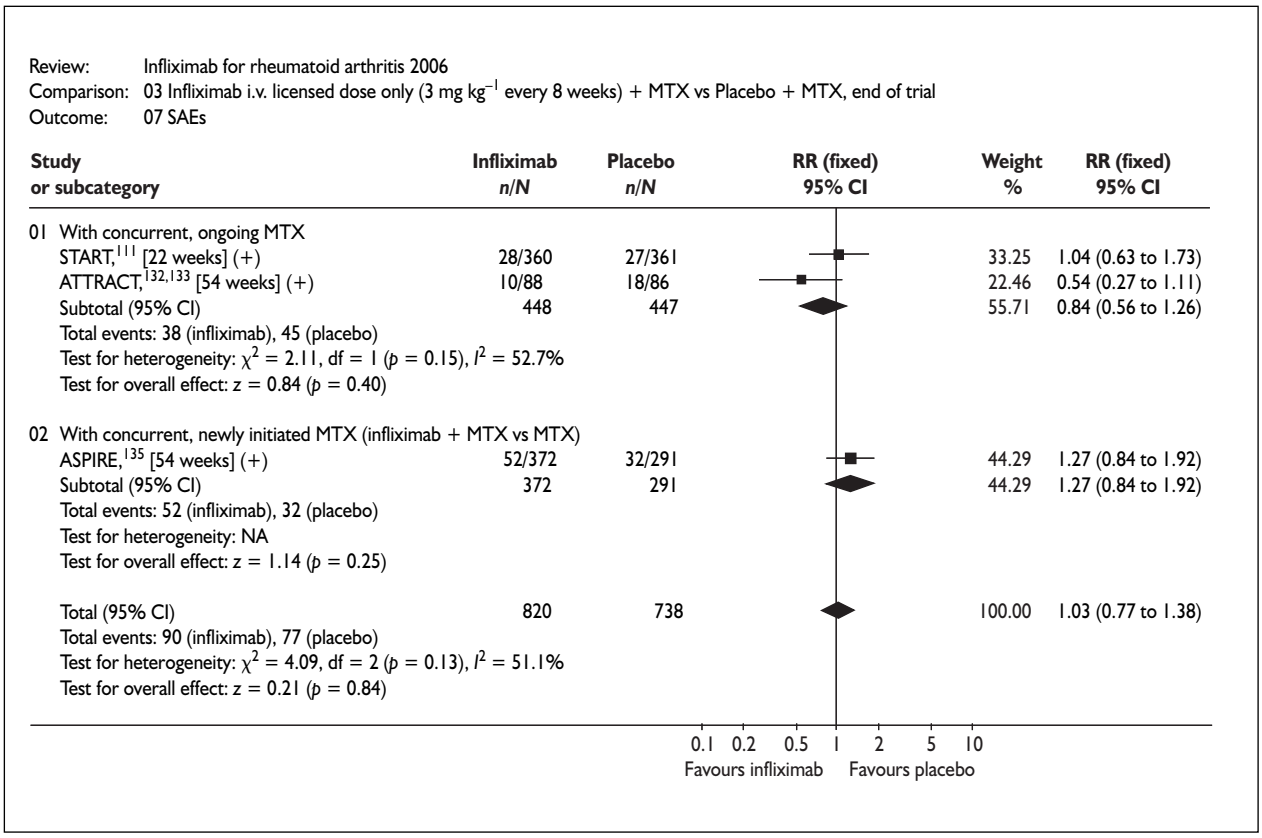

FIGURE 42 *SAE RR: infliximab licensed dose versus placebo (with concurrent MTX)*

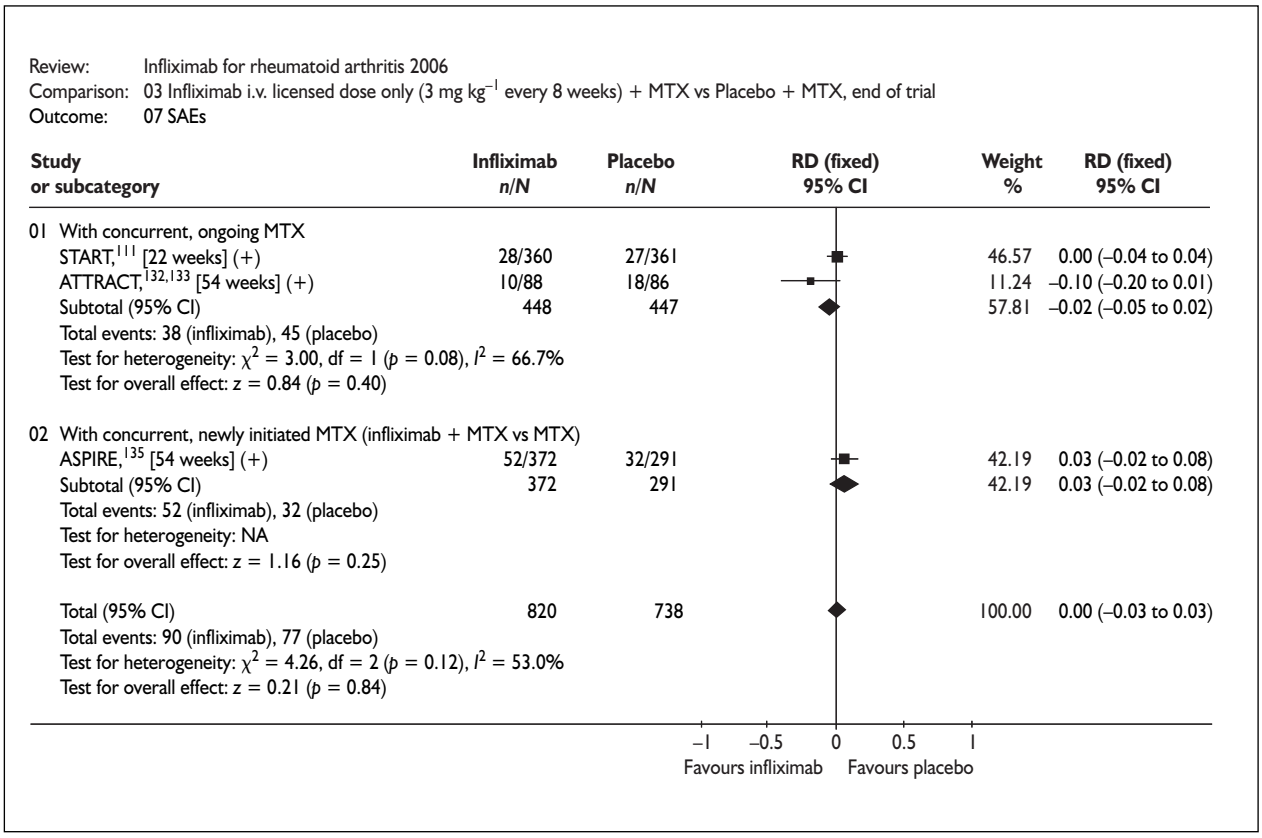

FIGURE 43 *SAE RD: infliximab licensed dose versus placebo (with concurrent MTX)*

FIGURE 44 *Malignancy RR: infliximab licensed dose versus placebo (with concurrent MTX)*
[Commercial-in-confidence information removed].

FIGURE 45 *Malignancy RD: infliximab licensed dose versus placebo (with concurrent MTX)*
[Commercial-in-confidence information removed].

methotrexate monotherapy were statistically significant for all the efficacy outcomes being meta-analysed, except for patient's global assessment of disease activity.

Tolerability The combination is associated with significantly fewer withdrawals owing to lack of efficacy (RR = 0.21, 95% CI 0.09 to 0.47), but significantly more withdrawals owing to adverse events (RR 2.99, 95% CI 1.49 to 6.03).

Safety The combination is associated with a significantly increased risk of serious infection (RR 2.74, 95% CI 1.12 to 6.70). No significant differences were found for other safety outcomes being meta-analysed.

TABLE 16 *Meta-analyses: combination of infliximab i.v. licensed dose only) plus MTX versus MTX alone in MTX-naïve patients, end of trial*

Infliximab i.v. licensed dose (3 mg kg^{-1} every 8 weeks) + MTX vs placebo + MTX in MTX-naïve patients, end of trial				
Comparison or outcome	**Studies**	***N* included in analysis**	**Statistical method**	**Effect size (95% CI)**
ACR20 responder	2[135,141]	645	RR (fixed)	1.17 (1.02 to 1.34)*
ACR50 responder	2[135,141]	645	RR (fixed)	1.44 (1.18 to 1.76)*
ACR70 responder	2[135,141]	645	RR (fixed)	1.57 (1.20 to 2.05)*
RD ACR20 responder	2[135,141]	645	RD (fixed)	0.09 (0.01 to 0.17)*
RD ACR50 responder	2[135,141]	645	RD (fixed)	0.14 (0.07 to 0.22)*
RD ACR70 responder	2[135,141]	645	RD (fixed)	0.12 (0.05 to 0.19)*
SJC, mean change from baseline	1[135]	540	WMD (fixed)	–3.00 (–4.91 to –1.09)*
Patient's global assessment, mean change from baseline	1[135]	536	WMD (fixed)	–0.40 (–0.95 to 0.15)
HAQ, mean change from baseline	2[135,141]	563	WMD (fixed)	–0.14 (–0.26 to –0.02)*
DAS28, end of study result	2[135,141]	549	WMD (fixed)	–0.69 (–0.99 to –0.39)*
Modified van de Heijde–Sharp score, mean change from baseline	1[135]	641	WMD (fixed)	–3.28 (–4.55 to –2.01)*
Withdrawal for any reasons	1[135]	665	RR (fixed)	0.87 (0.64 to 1.19)
Withdrawal due to lack of efficacy	1[135]	665	RR (fixed)	0.21 (0.09 to 0.47)*
Withdrawal due to adverse events	2[135,141]	685	RR (fixed)	2.99 (1.49 to 6.03)*
Death	1[135]	663	RR (fixed)	0.39 (0.04 to 4.29)
SAEs	1[135]	663	RR (fixed)	1.27 (0.84 to 1.92)
Malignancy: all	1[135]	663	RR (fixed)	**[Commercial-in-confidence information removed]**
Malignancy: skin cancer excluding melanoma	1[135]	663	RR (fixed)	**[Commercial-in-confidence information removed]**
Malignancy: all cancer excluding non-melanoma skin cancer	1[135]	663	Not estimable	No event
Serious infection	1[135]	663	RR (fixed)	2.74 (1.12 to 6.70)*
Any infection	1[135]	663	RR (fixed)	**[Commercial-in-confidence information removed]**

* Statistically significant result ($p < 0.05$).

Sensitivity analyses Results which include additional patients treated with above the licensed dose (6 mg kg^{-1} every eight weeks) in the ASPIRE trial are summarised in *Table 77* (Appendix 4). Data are generally consistent with the primary analyses and show a slightly increased effect size for efficacy outcomes, except for the modified Sharp score. When the above-licensed dose is included, the combination of infliximab plus methotrexate is associated with an increased risk of both serious infection (RR 2.59, 95% CI 1.11 to 6.04) and **[Commercial-in-confidence information removed]**. **[Commercial-in-confidence information removed]** patients developed malignancy in the 6 mg kg^{-1} group compared with **[Commercial-in-confidence information removed]** in the 3 mg kg^{-1} group in ASPIRE.

Summary of effectiveness review and additional evidence

Results of the primary meta-analyses (licensed dose only) for the three TNF inhibitors for the key outcomes are summarised in *Table 17*. A brief description for each type of comparison is provided below.

TNF inhibitors versus DMARDs

Volume of evidence

Only one adalimumab trial (PREMIER[102], $n = 531$ in the relevant arms) and two etanercept trials (ERA[123], $n = 424$ and TEMPO[127], $n = 451$) allow head-to-head comparison between a TNF inhibitor (at licensed dose) and methotrexate. No trial compared a TNF inhibitor with other conventional DMARDs.

Direction of effect

Adalimumab monotherapy was marginally less effective than methotrexate monotherapy in reducing RA symptoms and improving physical function in early RA patients naïve to methotrexate treatment, and did not offer better tolerability over methotrexate. By contrast, etanercept alone was slightly more effective than methotrexate alone in early RA patients who were naïve to methotrexate treatment and in patients with longer disease duration who had no history of treatment failure with methotrexate. Etanercept was better tolerated than methotrexate in these patients. Both adalimumab and etanercept were significantly more effective than methotrexate in slowing radiographic joint damage, but the clinical relevance of these differences is unclear. No significant differences between methotrexate and adalimumab and etanercept were found for the safety outcomes, including deaths, SAEs, malignancy, serious infections and any infections. However, this may be due to the relatively small number of patients included in the analyses. Large pragmatic trials and careful postmarketing surveillance, including record linkage studies, are needed to compare the relative safety of TNF inhibitors compared with methotrexate and other DMARDs.

TNF inhibitors versus placebo

Volume of evidence

The majority of RCTs included in this review compared TNF inhibitors with placebo. Five adalimumab trials[112–115,119] involving 1861 patients, eight etanercept trials[103,104,121,122,125,126,129,130] involving 1715 patients, and two infliximab trials[105,133] involving 895 patients were included in the primary meta-analyses.

Direction of effect

All three TNF inhibitors were significantly more effective in controlling the symptoms of RA, improving physical function and retarding radiographic joint damage and were associated with few treatment withdrawals compared with placebo. Use of above-licensed doses slightly increased the treatment effect for adalimumab and infliximab, but was associated with an increased risk of any infection and serious infections. More patients treated with adalimumab and infliximab had cancer, but this did not reach statistical significance. No increased risk of infection or malignancy was found for etanercept compared with placebo.

Combination of TNF inhibitor plus methotrexate versus methotrexate

Volume of evidence

Four trials compared a TNF inhibitor (at licensed dose) combined with methotrexate to methotrexate alone in patients naïve to, or who had not previously failed methotrexate: PREMIER[102] ($n = 525$) for adalimumab; TEMPO[127] ($n = 459$) for etanercept; ASPIRE[135] ($n = 665$) for infliximab; Quinn 2005[141] ($n = 20$) for infliximab.

Direction of effect

A TNF inhibitor combined with methotrexate was significantly more effective than methotrexate monotherapy in controlling RA symptoms, improving physical function and slowing radiographic joint damage for all three TNF inhibitors. Fewer patients on combination therapy withdrew from treatment, but the difference was not statistically significant for the infliximab

TABLE 17 *Summary of the results of primary analyses for key outcomes included in this review*

TNF inhibitor and population	ACR20 RR[a]: (95% CI) (and NNT)	ACR70 RR[a]: (95% CI) (and NNT)	HAQ change Mean difference[b] (95% CI)	Modified Sharp score Mean difference[b] (95% CI)	Withdrawal for any reasons RR[c] (95% CI)	SAEs RR[c] (95% CI)	Serious infections RR[c] (95% CI) (and NNH)
Anti-TNF vs MTX							
Adalimuma (early RA)[b]	0.88 (0.75 to 1.03)	0.99 (0.75 to 1.30)	0.00 (–0.13 to 0.13)	**–2.70 (–4.74 to –0.66)/ 1 year, –4.90 ([Commercial-in-confidence information removed])/2 years**	1.14 (0.91 to 1.43)	**[Commercial-in-confidence information removed]**	**[Commercial-in-confidence information removed]**
Etanercept (early RA)	**1.22 (1.06 to 1.40) NNT 7.7 (4.5 to 25.0)**	1.23 (0.89 to 1.70)	–0.10 (–0.23 to 0.03)	**–0.97 (–1.65 to –0.29)/ 1 year**	**0.63 (0.48 to 0.84)**	NR	0.82 (0.31 to 2.15)
Etanercept (established RA)	**1.28 (1.06 to 1.54) NNT 8.3 (4.8 to 33.3)**	1.46 (1.00 to 2.14)	–0.10 (–0.23 to 0.03)	**–2.28 (–4.11 to –0.45)/ 1 year**	0.81 (0.65 to 1.00)	1.10 (0.75 to 1.61)	0.95 (0.85 to 1.06)
Anti-TNF versus placebo							
Adalimumab (established RA)	**2.11 (1.84 to 2.42) NNT 3.6 (3.1 to 4.2)**	**5.22 (3.45 to 7.89) NNT 7.7 (5.9, 11.1)**	**–0.31 (–0.36 to –0.26)**	**–2.20 (–3.33 to –1.07)/ 1 year**	**0.62 (0.53 to 0.73)**	1.05 (0.78 to 1.41)	2.35 (1.00 to 5.53)
Etanercept (established RA)	**3.59 (2.89 to 4.46) NNT 2.1 (1.9 to 2.4)**	**9.44 (3.98 to 22.38) NNT 7.7 (6.3 to 10.0)**	**–0.50 (–0.59 to –0.42)**	No data available	**0.37 (0.29 to 0.46)**	1.25 (0.75 to 2.08)	0.78 (0.37 to 1.62)
Infliximab (established RA)	**2.30 (1.90 to 2.78) NNT 3.2 (2.7 to 4.0)**	**3.16 (1.89 to 5.27) NNT 11.1 (7.7 to 20.0)**	**–0.27 (–0.35 to –0.19)**	**–5.70 (–8.58 to –2.82)/ 1 year**	0.76 (0.36 to 1.60)	0.84 (0.56 to 1.26)	0.61 (0.26 to 1.46)
Anti-TNF + MTX vs MTX							
Adalimumab + MTX (early RA)	**1.24 (1.08 to 1.42) NNT 7.7 (4.5 to 20.0)**	**1.64 (1.30 to 2.07) NNT 5.6 (3.8 to 10.0)**	–0.10 (–0.23 to 0.03)	**–4.40 (–6.14 to –2.66)/ 1 year [Commercial-in-confidence information removed]**	**0.71 (0.54 to 0.93)**	**[Commercial-in-confidence information removed]**	**[Commercial-in-confidence information removed]**
Etanercept + MTX (established RA)	**1.49 (1.25 to 1.77) NNT 4.5 (3.3 to 7.7)**	**2.53 (1.82 to 3.54) NNT 4.0 (3.0 to 5.9)**	**–0.40 (–0.52 to –0.28)**	**–3.34 (–5.12 to –1.56]/ 1 year**	**0.61 (0.48 to 0.77)**	1.25 (0.87 to 1.81)	0.86 (0.42 to 1.76)
Infliximab + MTX (early RA)	**1.17 (1.02 to 1.34) NNT 11.1 (5.9 to 100)**	**1.57 (1.20 to 2.05) NNT 8.3 (5.3 to 20.0)**	**–0.17 (–0.29 to –0.06)**	**–3.28 (–4.55 to –2.01]/ 1 year**	0.87 (0.64 to 1.19)	1.27 (0.84 to 1.92)	**2.74 (1.12 to 6.70) NNH 25 (16.7 to 100)**

Bold type indicates statistically significant results $p < 0.05$
[a] RR>1 favours anti-TNFs. [b] Negative value favours anti-TNFs. [c] RR<1 favours anti-TNFs.
NNH, number needed to harm.

combination, which was associated with nearly a three-fold increase in withdrawal owing to adverse events (RR 2.99, 95% CI 1.49 to 6.03) and serious infections (RR 2.74, 95% CI 1.12 to 6.70). Adalimumab combined with methotrexate was associated with a slight, but significant increase in **[Commercial-in-confidence information removed]**. Risks of serious infection (RR **[Commercial-in-confidence information removed]**) and withdrawal owing to adverse events (RR = 1.62, 95% CI 0.94 to 2.77) were also increased, compared with methotrexate alone, but these did not reach statistical significance. No significant differences in safety outcomes were found between etanercept combined with methotrexate and methotrexate alone. More malignancy occurred in the combination group but this did not reach statistical significance. All three TNF inhibitors, when combined with methotrexate, showed a trend towards increased SAEs, but again this was not statistically significant.

Additional information on effectiveness and safety

This section summarises additional evidence that is not included in the meta-analyses. Information cited in this section is collated from FDA reports, published reviews and observational studies, summaries of product characteristics, and submissions from the BSR and manufacturers of TNF inhibitor to NICE. Lack of appropriate, unbiased comparison groups is a major problem for the validity of comparative results from non-RCTs. This should be borne in mind when interpreting observational data. Issues related to tuberculosis and blood monitoring were discussed in the section 'Special precautions for use of TNF inhibitors' (p. 9) and are not described here.

Mortality

Mortality data from long-term follow-up programmes for patients treated with adalimumab and etanercept were reviewed by the FDA in 2003.[146] The observed death rates in the follow-up programmes, adjusted for age and gender, were lower than would be expected among US general populations and do not indicate a higher death rate with TNF inhibitor treatments.

Malignancies including lymphomas

A significant increase in the incidence of lymphoma compared with the general population was noted for all three TNF inhibitors in the 2003 FDA review.[146] Controversy remains with regard to whether the observed higher incidences indicate additional risk due to TNF treatment, or whether they are in line with the increased risk of lymphoma observed in RA patients with high inflammatory activity.[147–151] In general, the incidence of other types of malignancies in TNF inhibitor-treated patients was found to be similar to, or lower than that observed in the general population[146,152,153] and other RA populations.[85,151]

Congestive heart failure

Adalimumab and infliximab are contraindicated in moderate to severe heart failure (New York Heart Association class III or IV). Two RCTs (not included in this systematic review) that evaluated the use of etanercept in the treatment of congestive failure were terminated early owing to lack of efficacy, and data from one of these trials suggested a possible tendency towards worsening of congestive heart failure and increased all-cause mortality in patients treated with etanercept.[154,155] In another trial that evaluated the use of infliximab in congestive heart failure, no clinical benefit was observed and high-dose infliximab (10 mg kg^{-1} at 0, 2 and 6 weeks) was associated with an increased risk for a composite outcome that included death from any cause and hospitalisation for heart failure (hazard ratio 2.84, 95% CI 1.01 to 7.97).[156]

Pulmonary fibrosis

In an investigation of pulmonary fibrosis and associated death, BSRBR found that there was a two- to three-fold increase in mortality for patients with pulmonary fibrosis at baseline compared with those without it among all patients (including TNF-treated and control group) with 6 months' follow-up data.[85] As the vast majority of the patients with pulmonary fibrosis at baseline were in the TNF-treated groups and only one death associated with pulmonary fibrosis occurred in the control group, it was not possible to conclude whether there is a potential association between TNF treatment and death associated with pulmonary fibrosis.

Combination of TNF inhibitors with anakinra

Results from an RCT (not included in this systematic review, see Appendix 3) by Genovese and colleagues[157] suggest that combination therapy with etanercept plus anakinra provided no treatment benefit over etanercept alone, and was associated with an increased risk of serious infections (0% for etanercept alone and 3.7–7.4% for combination therapy). The combination of TNF inhibitors and anakinra is therefore not recommended.

Chapter 4

Health economics

Summary of review of existing economic evaluations

A comprehensive search for existing economic evaluations was undertaken. These were assessed for quality using the Consensus on Health Economic Criteria (CHEC) list.

Existing economic evaluations

Ten published economic evaluations and four unpublished economic evaluations, of which only three were available electronically, were identified and reviewed. All were of high quality meeting at least 15 of the 19 quality assessment criteria. All but one used a decision-analytic model. Most gave incremental cost-effectiveness ratios (ICERs) that suggested that the use of TNF inhibitors was under the threshold normally considered to be the limit for cost-effectiveness. Direct comparison of the ICERs between the studies is not possible because of their different approaches to modelling, time-horizons, comparators and perspective, country of origin, source of preference weights and effectiveness data used. Many of the estimates for effectiveness were derived from single trials, or a subset of trials rather than a systematic review and meta-analysis of relevant trial and observational data.

Although most were of high quality, none of them used all the appropriate parameters, effectiveness data, perspective and comparators required to make their results generalisable to the NHS context.

The aim of this section is to assess the cost-effectiveness of adalimumab, etanercept and infliximab for treating RA from an NHS perspective.

This section of the report has three components:

- a review of existing economic evaluations of the use of TNF inhibitors in RA
- a technical commentary on the decision-analytic models used in the economic analyses reported in the manufacturers' submissions to NICE
- a description of the BRAM and the economic analyses of TNF inhibitors used singly or sequentially in RA patients, undertaken by the authors.

Systematic review of economic evaluations

Method

Search strategy

The searches for clinical effectiveness were amplified to identify existing economic models and information on costs, cost-effectiveness and quality of life from the following sources:

- Bibliographic databases
  - MEDLINE (Ovid) 1966 to February 2005, EMBASE (Ovid) 1980 to week 9 2005
  - Cochrane Library (NHS EED) 2005 Issue 1
  - HEED February 2005
- Internet sites of national economic units
- Internet sites of regulatory authorities, e.g. FDA, EMEA.

Time and language limits were as for clinical effectiveness searches. Systematic reviews of DMARDs were sought to inform the economic analysis and provide a context for biological TNF inhibitors. The search strategy was based on the Aggressive Research Intelligence Facility (ARIF) search protocol for reviews, which includes the Cochrane Library, Clinical Evidence, MEDLINE, Bandolier, health technology assessment databases and in-house databases. Full details of search strategies are contained in Appendices 5–7.

Inclusion and exclusion criteria

The review is an update of a previous report.[1] Inclusion and exclusion criteria applied for economic searches are shown in *Table 18*.

TABLE 18 *Inclusion criteria for the review on cost-effectiveness*

Study design	Cost–consequence analysis, cost–benefit analysis, cost-effectiveness analysis, cost–utility analysis, cost studies (UK only), quality of life studies
Population	People with RA; other forms of arthritis are excluded
Intervention	Etanercept, infliximab or adalimumab
Comparator	DMARDs
Outcome	Quality of life estimates, cost estimates, cost-effectiveness

TABLE 19 *Summary of published economic analyses*

Study	TNF inhibitor(s) considered	Form of economic analysis	Model used	Time-horizon
Choi *et al.*, 2002[159]	Etanercept	Cost-effectiveness	Decision tree	6 months
Brennan *et al.*, 2004[160]	Etanercept	Cost–utility	Patient-level simulation	Lifetime
Wong *et al.*, 2002[161]	Infliximab	Cost–utility	Markov	Lifetime
Kobelt *et al.*, 2003[162]	Infliximab	Cost–utility	Markov	10 years
Jobanputra *et al.*, 2002[1]	Etanercept, infliximab	Cost–utility	Patient-level simulation	Lifetime
Kobelt *et al.*, 2004[163]	Etanercept, infliximab	Cost–utility	NA	NA
Chiou *et al.*, 2004[164]	Etanercept, infliximab, adalimumab	Cost–utility	Decision tree	1 year
Welsing *et al.*, 2004[165]	Etanercept	Cost–utility	Markov	5 years
Bansback *et al.*, 2005[166]	Etanercept, infliximab, adalimumab	Cost–utility	Patient-level simulation	Lifetime
Kobelt *et al.*, 2005[167]	Etanercept	Cost–utility	Markov	10 years

Study selection, data extraction, and quality assessment strategy

An experienced health economist applied the inclusion and exclusion criteria. Data were extracted by one reviewer using a predesigned data extraction form and were independently checked by a second reviewer. Data on the following were sought:

- study characteristics, such as form of economic analysis, population, interventions, comparators, perspective, time-horizon and modelling used
- effectiveness and cost parameters, such as effectiveness data, health state valuations (utilities), resource-use data, unit cost data, price year, discounting and key assumptions
- results and sensitivity analyses.

These characteristics and the main results of included economic evaluations are summarised in subsequent tables. The quality of included studies and industry submissions was assessed using the CHEC list.[158] The study question, selection of alternatives, form of evaluation, effectiveness data, costs, benefit measurement and valuation, decision modelling, discounting, allowance for uncertainty and presentation of results were all evaluated as part of this process.

Results of systematic review of economic evaluations

Ten published studies, including one by the current authors,[1] met the inclusion criteria. Given that Jobanputra[1] describes the initial version of BRAM which is updated in this report, it will not be further discussed here. Key features of the nine other studies are summarised in *Table 19*. In addition, all three manufacturers submitted economic analyses and models. These submissions are reviewed in detail in the section 'Review of industry cost-effectiveness submissions' (p. 80). Details of the nine studies are presented in Appendix 8, using a simplified version of the Drummond and Jefferson checklist. A summary of the ICERs for TNF inhibitors reported in published papers is provided in *Table 20*.

Four economic evaluations only considered etanercept compared with specified DMARDs or sequences of DMARDs (*Table 21*). Three studies were cost–utility analyses, with the cost-effectiveness ratio (ICER) reported as cost per QALY gained (*Table 21*). In addition to cost per QALY, Welsing and colleagues[165] considered cost per patient-year in three DAS28 states. Choi and colleagues[159] used the ACR20 response and a weighted average of proportions of patients achieving ACR70, ACR50 and ACR20 (ACR weighted response, ACR70WR) and reported the cost-effectiveness ratio as cost per ACR20 or ACR70WR. Brennan and colleagues[160] carried out the analysis from a healthcare perspective, whereas the other studies included direct and indirect costs. The four studies differed in how etanercept use was modelled: Choi and colleagues[159] considered etanercept alone over a short period of 6 months; Brennan and colleagues[160] placed etanercept as third line therapy in a DMARD sequence over a patient lifetime; Welsing and colleagues[165] considered three different etanercept pathways (etanercept first, then switch to conventional DMARDs if there

TABLE 20 *Summary of published ICERs for TNF inhibitor*[a]

Drug	Comparator	Study	Date	Time-horizon	ICER
Adalimumab	DMARD sequence	Bansback[166]	2005	Lifetime	ACR50/DAS28 good: €34,167 per QALY (MTX) €34,922 per QALY (MTX) (from pooled analysis) €41,561 per QALY (monotherapy) ACR20/DAS28 moderate: €40,875 per QALY (+ MTX) €44,018 per QALY (+ MTX) (from pooled analysis) €65,499 per QALY (monotherapy)
	Anakinra	Chiou[164]	2004	1 year	Adalimumab alone dominated Adalimumab + MTX dominated
Etanercept	Anakinra	Chiou[164]	2004	1 year	US $13,387 per QALY (monotherapy) US $7,925 per QALY (+ MTX)
	DMARD sequence	Brennan[160,168]	2004	Lifetime	£16,330 per QALY
	DMARD sequence	Bansback[166]	2005	Lifetime	ACR50/DAS28 good: €35,760 per QALY (+ MTX) €36,927 per QALY (monotherapy) ACR20/DAS28 moderate: €51,976 per QALY (+ MTX) €42,480 per QALY (monotherapy)
	Baseline level (failed at least two DMARDs, including methotrexate)	Kobelt[163]	2004	NA	After 3 months of treatment: €43,500 per QALY After 6 weeks of treatment: €36,900 per QALY
	MTX	Kobelt[167]	2005	10 years	Etanercept alone dominated. Treatment for 2 years, extrapolation to 10 years: Etan–MTX €37,331 per QALY Treatment for 2 years, extrapolation to 5 years: Etan–MTX €54,548 per QALY Treatment for 10 years: Etan–MTX €46494 per QALY Treatment for 5 years, extrapolation to 10 years. Etan–MTX €47,316 per QALY
	DMARD sequence	Jobanputra[1]	2002	Lifetime	£83,095 per QALY
	Usual treatment, leflunomide	Welsing[165]	2004	5 years	Etanercept monotherapy dominated by leflunomide/etanercept combinations Etanercept vs usual treatment: €163,556 per QALY for LEF–Etan €297,151 per QALY for Etan–LEF Etanercept vs leflunomide: €317,627 per QALY for LEF—Etan €517,061 per QALY for Etan–LEF
	Monotherapy leflunomide, MTX, SSZ, no second line agent	Choi[159b]	2002	6 months	Etanercept–SSZ: $41,900 per ACR20 Etanercept–MTX: $40,800 per ACR70WR
Infliximab	Placebo and MTX	Wong[161]	2002	Lifetime	$30,500 per QALY
	MTX	Kobelt[162]	2003	10 years	For 1 year of treatment: €3440 per QALY in Sweden €34,800 per QALY in UK

continued

TABLE 20 *Summary of published ICERs for TNF inhibitor[a] (cont'd)*

Drug	Comparator	Study	Date	Time-horizon	ICER
	Baseline level (failed at least two DMARDs, including MTX)	Kobelt[163]	2004	NA	After 3 months of treatment €43,500 per QALY After 6 weeks of treatment: €36,900 per QALY
	DMARD sequence	Bansback[166]	2005	Lifetime	ACR50/DAS28 good: €48,333 per QALY (+ MTX) ACR20/DAS28 moderate: €64,935 per QALY (+ MTX)
	DMARD sequence	Jobanputra[1]	2002	Lifetime	£115,937 per QALY
	Anakinra	Chiou[164]	2004	1 year	Infliximab + MTX dominated

[a] Industry-sponsored studies are highlighted in shaded cells.
[b] Cost-effectiveness analysis; all other studies are cost–utility analyses.
Etan, etanercept; LEF, leflunomide; QALY, quality-adjusted life-year.

is no response; leflunomide followed by etanercept if there is no response to leflunomide (LEF–Etan); and finally, etanercept switching to leflunomide with non-response (Etan–LEF)]. Kobelt and colleagues[167] considered etanercept alone and etanercept combined with methotrexate.

Two studies found high ICERs. Choi and colleagues[159] suggested that recommendations regarding use depended on whether an ICER over $40,000 per ACR20 or ACR70WR was considered acceptable. Welsing and colleagues[165] recommended use of etanercept following leflunomide after two other DMARDs (where the first is methotrexate) had failed. In contrast, Brennan and colleagues[160,168] reported a much lower ICER and suggested "etanercept was cost-effective when compared with non-biologic agents". Kobelt and colleagues[167] reported the ICER for etanercept in combination with methotrexate to be within the "acceptable range". Each study used a different modelling approach. Choi and colleagues[159] used a simple decision-tree structure and modelled costs and outcomes over 6 months. Welsing and colleagues[165] and Kobelt and colleagues[167] used a Markov model structure with a 5-year time-horizon and a 5- and 10-year time-horizon, respectively. Brennan and colleagues[160] developed an individual patient-level simulation model to calculate lifetime costs and outcomes. RCT data were used to model outcomes; it has been suggested that observational data are a more realistic representation of outcomes in practice and therefore more suitable for cost-effectiveness analyses.[169]

Each study took different approaches; for example, the evaluation undertaken (cost-effectiveness or cost–utility analysis), the treatment comparators and the time-horizon chosen (each used a different time-horizon, varying from 6 months to lifetime). Kobelt[167] used a cycle length of 1 year, which is not clinically relevant. A cycle length of around 4 months is more clinically relevant as decisions about the efficacy of DMARDs are generally made over this time. Three analyses were from a societal perspective, an approach that leads to a more favourable ICER. If a treatment is more effective, then patients are more able to work, thus leading to lower indirect costs. The Choi study[159] did not calculate cost per QALYs, therefore comparison with other results is not possible.

Two of the ten identified published studies report an economic analysis of infliximab in combination with methotrexate (*Table 22*), and were sponsored by the manufacturer Schering-Plough. Both studies were cost–utility analyses using a societal perspective and the comparator explored was methotrexate alone. The quality of life data used by Wong and colleagues[161] was based on self-reported global health using a visual analogue scale (VAS) from ATTRACT and the Arthritis, Rheumatism and Aging Medical Information System (ARAMIS) database. However, there are problems with VAS such as context bias and end-point aversion, and the method is not truly preference based. Other methods are more appropriate, for example using a utility measure such as EuroQol 5 Dimensions (EQ-5D). Therefore, results should be treated with some caution. Costs were obtained from the ARAMIS database, based on a North American population, and are not directly transferable to a UK

TABLE 21 *Published etanercept economic analyses*

Study	Sponsor	Patient group	Comparator(s)	Base-case ICER
Choi *et al.*, 2002[159]	Not stated	RA	Four monotherapy comparators: leflunomide, MTX, SSZ, no second line agent	Etanercept vs SSZ $41,900 per ACR20 Etanercept vs MTX $40,800 per ACR70WR
Welsing *et al.*, 2004[165]	Not stated (but used data from Wyeth)	RA	Two comparators: usual treatment, LEF	Etanercept alone was dominated by leflunomide/etanercept combinations Versus usual treatment €163,556 per QALY for LEF–Etan €297,151 per QALY for Etan–LEF Versus leflunomide: €317,627 per QALY for LEF–Etan €517,061 per QALY for Etan–LEF
Brennan *et al.*, 2004[160,168]	Not stated (but two authors from Wyeth)	RA	DMARD sequence	£16,330 per QALY
Kobelt *et al.*, 2005[167]	Wyeth Research	RA	MTX	Etanercept alone dominated. Treatment for 2 years, extrapolation to 10 years: Etan–MTX €37,331 per QALY Treatment for 2 years, extrapolation to 5 years: Etan–MTX €54,548 per QALY Treatment for 10 years: Etan–MTX €46,494 per QALY Treatment for 5 years, extrapolation to 10 years. Etan–MTX €47,316 per QALY

perspective, and the analysis was carried out from a societal perspective. The study authors concluded that infliximab with methotrexate was cost-effective, especially when including indirect costs of loss of productivity. However, cost-effectiveness is dependent on the ICER threshold of the decision-maker. The effectiveness data used by the Kobelt study[162] is from observational data only, and uses a societal perspective, therefore giving a more favourable ICER. This perspective also leads to a large difference in ICERs between the UK and Sweden as this difference was driven by indirect costs. Differences arose owing to higher average salary and more generous long-term illness benefits in Sweden, plus a lower proportion of UK patients in advanced HAQ states had taken early retirement compared with Sweden. A Markov model was used in both studies, with Wong[161] projecting 54-week results of an RCT to a lifetime horizon and Kobelt[162] producing results for a 10-year time-horizon. The latter uses a 1-year cycle length, which is not clinically appropriate as a patient may change DMARDs over a much shorter period.

The remaining four cost-effectiveness analyses considered more than one TNF inhibitor therapy (*Table 23*). Kobelt and colleagues[163] reported a cost–utility analysis using patient-level direct costs and effectiveness using data from a cohort of 160 patients. Patients received etanercept (n = 113) or infliximab (n = 47), but drug allocation was not randomised. Data were shown for use of a TNF inhibitor compared with resource use and quality of life for the year before treatment (baseline). Jobanputra and colleagues[1] considered etanercept and infliximab in comparison with a DMARD sequence. This work formed the economic evaluation of the previous NICE appraisal for TNF inhibitor drugs undertaken by the current authors and will therefore not be described further. Bansback and colleagues,[166] funded by Abbott Laboratories, used a patient-level simulation model to conduct cost–utility analyses

TABLE 22 *Published infliximab economic analyses*

Study	Sponsor	Patient group	Comparator(s)	Base case ICER
Wong *et al.*, 2002[161]	Schering-Plough, Centocor Corp., National Institutes of Health	RA	Placebo and MTX	$30,500 per QALY
Kobelt *et al.*, 2003[162]	Schering-Plough	RA	MTX	For 1 year of treatment: €3440 per QALY in Sweden €34,800 per QALY in UK

from a healthcare perspective. The model builds on two previous RA models.[1,160] Etanercept and adalimumab were considered as monotherapies and in combination with methotrexate, with two separate analyses for adalimumab plus methotrexate. The second analysis contained additional information from a larger adalimumab trial in a pooled analysis. Infliximab was only considered in combination with methotrexate. Results were presented as ICERs versus traditional DMARDs for two separate groups: an ACR50 response which corresponded to a good DAS28 response and an ACR20 response which corresponded to a moderate DAS28 response. Using such dichotomous data, unfortunately, does not reflect clinical reality, or practice, as many patients may continue, or cease, therapy despite such thresholds; actual drug continuation rates from observational studies are more appropriate for modelling. Chiou and colleagues[170] used a decision tree to carry out a cost–utility analysis of anakinra, adalimumab, etanercept and infliximab used alone or in combination with methotrexate during 1 year. Separate analyses were conducted for monotherapies and combination therapies. A preference weight was attached to each of the 16 health states representing a combination of the level of adverse effects and ACR response criteria. However, preference weights were derived from VAS, which is not ideal.

Kobelt and colleagues[163] reported QALYs within the generally accepted threshold of €50,000 per QALY; however, analysis was from a societal perspective, therefore results are not directly relevant to a UK healthcare perspective. Bansback and colleagues[166] suggested that adalimumab was cost-effective for the treatment of moderate to severe RA and was at least as cost-effective as etanercept or infliximab, but there was uncertainty about which drug was the most cost-effective. In addition, they concluded that with the exception of infliximab, the cost results were in a range normally considered cost-effective in Europe. Chiou and colleagues[170] found anakinra to be the least cost-effective option, and etanercept (as monotherapy and combined with methotrexate) was dominant over other TNF inhibitors. Compared with anakinra, both etanercept treatment regimens were below US $15,000 per QALY. However, the study is US based and uses US healthcare costs, therefore the results cannot be applied to the UK.

Direct comparison of these ICERs is inappropriate as the analyses are very different in terms of treatment comparators and time-horizons. The Kobelt analysis[167] is without modelling, Bansback and colleagues[166] conduct modelling over a patient's lifetime and Chiou and colleagues[170] model over 1-year. Modelling the response over a 1-year cycle is not clinically appropriate, especially as it is assumed that treatment will continue over this period with no switching of therapy. In reality, patients will switch from one drug to another in a period much shorter than 1 year owing to lack of response or adverse effects. In addition, Chiou[170] is the only study that does not use traditional DMARDs as the comparator, using anakinra monotherapy instead. However, anakinra was not recommended for routine use in the NHS by NICE in its November 2003 guidance (http://www.nice.org.uk/pdf/TA072guidance.pdf) because of its poor incremental cost-effectiveness, which was over £100,000 per QALY.[3]

Summary of review of existing economic evaluations

- Results of published economic evaluations vary: some analyses suggest that use of TNF inhibitors may fall within the usual acceptable cost-effectiveness ranges, whereas others report very high ICERs.
- A direct comparison of ICERs between studies is not possible because of different approaches to modelling, in particular time-horizon, cycle

TABLE 23 *Published economic analyses for more than one TNF inhibitor therapy*

Study	Sponsor	Patient group	Comparator(s)	Base case ICER
Etanercept, infliximab				
Jobanputra *et al.*, 2002[1]	NHS HTA Programme	RA	DMARD sequence	Etanercept £83,095 per QALY Infliximab £115,937 per QALY
Kobelt et al., 2004[163]	Österlund and Kock Foundations, King Gustav V 80 year fund, Reumatikerförbundet.	RA	Baseline level (failed at least 2 DMARDs, including MTX)	After 3 months of treatment: €43,500 per QALY After 6 weeks of treatment: €36,900 per QALY
Etanercept, infliximab, adalimumab				
Chiou *et al.*, 2004[170]	Not stated	RA	Anakinra	US $13,387 per QALY (Etanercept alone) Adalimumab alone dominated US $7925 per QALY (etanercept + MTX) Adalimumab + MTX and infliximab + MTX dominated
Bansback *et al.*, 2005[166]	Abbott Laboratories	RA	DMARD sequence	ACR50/DAS28 good: €34,167 per QALY (adalimumab+MTX) €34,922 per QALY (adalimumab+MTX)[a] €35,760 per QALY (etanercept + MTX) €48,333 per QALY (infliximab + MTX) €41,561 per QALY (adalimumab) €36,927 per QALY (etanercept) ACR20/DAS28 moderate: €40,875 per QALY (adalimumab+MTX) €44,018 per QALY (adalimumab+MTX)[a] €51,976 per QALY (etanercept+MTX) €64,935 per QALY (infliximab+MTX) €65,499 per QALY (adalimumab) €42,480 per QALY (etanercept)

[a] Including additional information from a larger adalimumab trial in a pooled analysis.

length, country of origin, perspective chosen, source of preference weights and comparator drugs.

- Many of the previous analyses are based on clinical estimates that are derived from single trials, or a small number of trials, rather than a formal systematic review, meta-analysis of evidence, or observational data of effectiveness in clinical practice.
- Drug manufacturers have sponsored four published analyses, with a further two having links with a drug company. Two studies do not state the sponsors of the study. The two remaining studies were not linked with any drug manufacturers.
- Each study was considered to be of adequate quality, in terms of criteria in the CHEC list, where at least 15 of 19 were met by all. All fulfilled criteria related to design and conduct; that is, each study was a cost-effectiveness evaluation addressing a clearly defined research question applied to a clearly defined population. An appropriate perspective was chosen in each and the outcomes identified were relevant and measured appropriately. Incremental analyses, to which appropriate sensitivity analyses had been applied, were reported without exception.
- Quality assessment criteria that were not met included failure to report the following: discounted future costs and benefits in two studies, potential conflicts of interest in five studies, competing interests in two studies; the generalisability of results in one study, and

TABLE 24 *Summary of methods used in industry economic analyses*

Submission features	Abbott Laboratories Adalimumab (Humira®)	Wyeth Etanercept (Enbrel®)	Schering-Plough Infliximab (Remicade®)
Choice of TNF inhibitor	Adalimumab in combination with MTX	Six-line drug sequence with etanercept/MTX combination 1st line, 2nd line or 3rd line	Infliximab in combination with MTX
Comparator	Three-line drug sequence without use of adalimumab	Six-line drug sequence without use of etanercept	MTX alone
Patient characteristics	Patients with RA, average age 55 years, 77% women, who have failed three DMARDs including MTX	Patients with RA, average age 53 years, (in line with patients in TEMPO)	Two patient groups: (1) active RA despite treatment with DMARDs; (2) severe active early RA
Form of analysis	Cost–utility analysis	Cost–utility analysis	Cost–utility analysis
Model used	Patient-based transition-state model with 10,000 patients	Markov model with 6-monthly cycles and 10,000 patients	Markov model with 6-monthly cycles, based on ARAMIS
Time-horizon of model	Lifetime	Lifetime	Lifetime
Base-case results	£17,860 per QALY	1st line: £16,000 per QALY 2nd line: £20,000 per QALY 3rd line: £18,000 per QALY	MTX experienced: £6228 per QALY MTX-naïve: £16,766 per QALY MTX-naïve with high CRP: £13,000 per QALY

ethical and distributional issues in any of the included studies.

- All but one economic analysis used a decision-analytic model. Published models vary in some important aspects; for example, the type of model used, whether switching of therapy is considered, drug combinations, comparator therapies, and time-horizon and cycle length.
- One study carried out a cost-effectiveness analysis using patient-level data on costs and outcomes from a patient cohort. However, results for two separate TNF inhibitors were combined.
- Six studies report costs that include both those from a healthcare perspective and indirect costs including losses of productivity; inclusion of these productivity costs improves the cost-effectiveness of TNF inhibitors.
- One study carried out a cost-effectiveness analysis, with the remaining nine conducting a cost–utility analysis. Two studies obtained preference weights from VAS, considered to be a less acceptable method for obtaining preference. The remaining seven studies used EQ-5D, in some cases using regression analysis to convert HAQ scores to EQ-5D.
- In model-based analyses, costs and benefits were modelled over a number of different time-horizons: 6 months (one study), 1 year (one study), 5 years (one study), 10 years (two studies) and lifetime (four studies). However, there was no association between ICER values and time-horizon used.

Review of industry cost-effectiveness submissions

A detailed summary of the economic analyses and models included in the company submissions to NICE for the appraisal of adalimumab, etanercept and infliximab carried out in 2005–6 is reported in this section. All three companies provided an electronic model.

The methods used in the economic analyses are presented in *Table 24*.

Abbott submission (adalimumab)

A patient-based, state-transition model was developed to assess the cost-effectiveness of adalimumab in combination with methotrexate compared with a sequence of traditional DMARDs in patients with moderate to severe RA. The main treatment sequences considered are shown in *Table 25*. Adalimumab monotherapy and other TNF

TABLE 25 *Treatment sequences: adalimumab*

Therapy line	Treatment sequence (fourth line)	Comparator sequence
Fourth	Adal + MTX	GST
Fifth	GST	LEF
Sixth	LEF	CyA + MTX
Seventh	CyA + MTX	Rescue
Eighth	Rescue	Rescue

Adal, adalimumab; CyA, ciclosporin A; GST, injectable gold.

TABLE 26 *HAQ changes by response type*

ACR improvement	Observed HAQ change	HAQ change given baseline of 1.6	New HAQ score for responders
<20%	–6.4%	–0.102	1.498
20–50%	–34.7%	–0.555	1.045
50–70%	–57.0%	–0.912	0.688
>70%	–64.6%	–1.034	0.566

inhibitors were also explored and results presented in the report. The first- to third-line therapies are not stated here as the analysis assumed that patients had failed three DMARDs including methotrexate.

The model used 6-monthly cycles in which patients can experience a number of events. In the first 6-month period on a therapy a patient can: have a positive response to treatment; have a negative response to treatment; suffer an SAE, or die. In subsequent periods a patient can: have continued efficacy; have a loss of efficacy; suffer an SAE; or die. Therefore, at the end of a cycle the patient can: continue on the same therapy; withdraw and proceed to the next therapy when a negative response, loss of efficacy or SAE has occurred; or die.

The model run was for 10,000 patients, and applied a single baseline profile rather than sampling individual patient characteristics. The baseline characteristics were set to reflect patients in adalimumab trials. Patients had a mean age of 54.7 years, 77% were women, with a baseline HAQ of 1.6 and a mean DMARD use of 3. However, assuming a fixed HAQ score at baseline ignores the heterogeneity of response.

Data used in the base-case analyses came from trials where the comparator was methotrexate, with the exception of the data for DMARDs. Here, an observational study (Geborek[171]) of leflunomide was used and was assumed to be representative of all DMARDs. It is inappropriate to use leflunomide data derived from populations that had failed two DMARDs to represent all DMARDs, particularly in early RA. This is because this observational study looks at RA patients who had failed at least two DMARDs before testing leflunomide, etanercept or infliximab. In addition, using annual withdrawal rates for leflunomide from this study and assuming that this applies to all DMARDs is inappropriate. No meta-analyses of biological trials were undertaken for their analysis, and main trial data for each of the TNF inhibitors were used instead.

ACR50 data were used in the base case to determine response rate on each therapy, with patient-level trial data used for adalimumab and published data for other DMARDs. Average improvement in HAQ for ACR20, ACR50 and ACR70 responders was available from the adalimumab trials. These data were not available for other DMARDs, therefore an assumption was made that HAQ improvement would be the same as for adalimumab and independent of treatment. The calculated HAQ change, categorised by response, is shown in *Table 26*. Long-term change in HAQ was obtained from a systematic review, assuming a slight progression of disability over time, with data for a successful response recalculated to account for the variation in patient numbers in the studies. However, to assume year-on-year decrease in HAQ response in early disease is problematic as HAQ is very labile in the first 5 years of disease. Withdrawal from treatment was assumed to change the HAQ score by the equivalent amount of the initial improvement, therefore giving a slightly higher HAQ score than at baseline, but due to gradual progression of

disability. Data for non-responders were based on an observational study by Young and colleagues.[46] This study does not report specifically on DMARD responders and non-responders and it is unclear how these data were obtained. In addition, the study is a hospital-based study of early RA patients where data were collected annually. As HAQ is especially labile in this population, single annual measurements have limited reliability.

Patient HAQ scores are updated every 6 months and the mean level of HAQ improvement was obtained from clinical trial data and published literature. HAQ scores are converted to QALYs by using regression of HAQ against utility from trial data. The relationship between HAQ and utility scores was given as $U = 0.76 - (0.28 \times \text{HAQ}) + 0.05 \times \text{Female}$. This relationship was derived from analysis of Health Utility Index (HUI) 3 data obtained from the adalimumab trials.

Data on the incidence of mild, moderate and serious adverse events were estimated from an observational study. The same study and a review provided data on long-term withdrawal; the limitations of using data from Geborek[171] are discussed above. Mortality risk for patients with RA was adjusted by HAQ score and Gompertz models were fitted, with the minimum age set at 50 years. The 6-monthly hazard rate was calculated in the model for patients' age and midpoint HAQ score during each therapy line. This simplification may be acceptable; however, exploratory analyses would be worthwhile to test this assumption.

Resource use and costs were derived from published data, costing BSR guidelines and expert clinical opinion. In addition, some healthcare resource use was estimated based on HAQ-DI scores. Costs and benefits were discounted at 6% and 1.5%, respectively. Costs were calculated from a healthcare perspective. Both simple one-way and probabilistic sensitivity analyses were undertaken.

The base-case results using ACR50 suggest that adalimumab is cost-effective as fourth line therapy, with an ICER of £17,860. In total, 32 one-way sensitivity analyses were conducted, all giving ICERs under £30,000 per QALY. Probabilistic sensitivity analysis showed adalimumab in combination with methotrexate to have a 99.8% probability of being cost-effective at a willingness-to-pay threshold of £30,000 per QALY. Comparison with etanercept gave a lower ICER of £14,388 and a 96% probability of being cost-effective at £30,000 per QALY.

Secondary analyses were also reported. Using an ACR20 response the cost per QALY for adalimumab plus methotrexate was £19,251. Cost-effectiveness ratios at different lines of entry were also explored for ACR50 and ACR20.

The ICERs for ACR50 are:
- first line: £19,095 per QALY
- second line: £18,166 per QALY
- third line: £18,479 per QALY.

The ICERs for ACR20 are:
- first line: £21,228 per QALY
- second line: £19,794 per QALY
- third line: £19,596 per QALY.

The study concluded that adalimumab "should be considered cost-effective when compared against conventional DMARDs" and on the basis of this "the cost-effectiveness of adalimumab is very similar to that of etanercept and infliximab".

Wyeth submission (etanercept)

A sequential model was developed whereby a simulated patient receives a given treatment until DMARD switching occurs as a result of either failure of effectiveness or SAEs. The main treatment sequences considered are shown in *Table 27*, but others were explored and are not presented in the report.

The submission indicates that "the aim of the economic model and treatment sequences was to demonstrate that etanercept + MTX is a cost-effective intervention when used earlier in the

TABLE 27 *Treatment sequences: etanercept*

Therapy line	Treatment sequence (1st line)	Comparator sequence
First	Etan + MTX	MTX
Second	MTX	SSZ
Third	SSZ	LEF
Fourth	LEF	GST
Fifth	GST	DMARD (non-specified)
Sixth	Salvage therapy	Salvage therapy

management of RA, i.e. 1st and 2nd line". Etanercept and methotrexate were used in combination as "the body of evidence suggests that combination therapy is more effective than monotherapy". Using combination data, however, will weigh ICERs in favour of etanercept since patients responding to combined therapy, if they are DMARD naïve, have the opportunity of responding to two agents and many may have responded to methotrexate alone.

The model uses 6-monthly cycles and allows patients to: experience changes in disease severity; enter a remission state; develop drug tolerance problems; experience an SAE; or die. At the end of each 6-month cycle the patient can:

- change disease severity
- experience an SAE
- switch treatment therapy
- die.

The model run consisted of 10,000 hypothetical patients, followed until death. Costs were calculated from the perspective of a healthcare provider. The main driver of the model result is the patient's disease severity. Disease severity determines several factors in the model, including the likelihood of switching therapy, health-related utility and mortality. HAQ was used to represent disease severity as it was not practical to measure both HAQ and DAS28 scores simultaneously. However, for the purpose of 'switching thresholds' a relationship between HAQ and DAS28 was required and changes in HAQ score were used as a proxy for changes in the DAS28. Perhaps here it would have been more appropriate to use actual switching rates from clinical observation rather than this conversion, which potentially introduces more uncertainty into the model. A baseline HAQ of 1.74 was obtained from TEMPO. Using a fixed HAQ at start of treatment has limitations and the heterogeneity of response is not taken into account. Patients' HAQ scores are updated every 6 months, with the changes based on evidence from clinical trials and other published sources (see *Table 28* for estimates).

A robust approach was applied, where distributions rather than point estimates were used to introduce a random element into HAQ change. The HAQ change estimates were derived from TEMPO for etanercept, methotrexate and combination therapy. The HAQ change for unspecified DMARD was based on the Tight Control for Rheumatoid Arthritis (TICORA). This is inappropriate since data for individual drugs are available. The initial HAQ change for sulfasalazine was assumed to be –0.29. This improvement is based on an ITT analysis of trial data, and HAQ improvement for those that continue the drug was –0.43. For the purposes of economic modelling, patients who continue treatment are of interest, since those who do not are accounted for elsewhere. Thus, a figure of –0.29 underestimated the benefit of continuing with sulfasalazine. Data from trials such as TEMPO represent ideal responses and the data may not reflect outcomes in routine care. For other therapies, the estimates were based on 'published sources', and where data were not available for 6-month changes, estimates were converted to 6-month rates using a simple formula. In all cases, the first 6 months' change was accounted for when calculating medium-term changes. Patients in remission were assumed to

TABLE 28 *HAQ change parameters*

	Etan	MTX	Etan+ MTX	SSZ	GST	Infl + MTX	DMARD	Adal	LEF	Salvage
Initial HAQ change	–0.690	–0.650	–0.890	–0.290	–0.430	–0.080	–0.270	–0.560	–0.500	–0.040
Medium-term non-remission: mean HAQ change	–0.005	–0.001	–0.052	0.075	0.045	–0.087	–0.080	–0.030	0.000	0.200
Remission: mean HAQ change	–0.0276	–0.0037	–0.0145	0.075	0.045	–0.087	–0.080	–0.030	0.000	0.200
Long-term: change per cycle	0.00	0.02	0.00	0.10	0.10	0.00	0.1	0.00	0.10	0.28

TABLE 29 *SAE parameters*

	Etan	MTX	Etan + MTX	SSZ	GST	Infl + MTX	DMARD	Adal	LEF	Salvage
Probability of SAE	0.07	0.07	0.05	0.07	0.06	0.10	0.06	0.07	0.08	0.10
Probability of switching if SAE	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33

experience different HAQ changes from those not in remission. However, the definition of remission is problematic, and the change in HAQ may have been sufficient to represent remission without assuming further treatment benefits in modelling.

SAEs in the model were dependent on the treatment received (*Table 29*). Their occurrence affected costs, utility and the likelihood of switching therapy. SAEs were assumed to occur for one cycle only. "Due to lack of reliable evidence for this parameter, it was assumed that one-third of patients who experience an SAE would switch therapies during that (6-month) period." This assumption would be unnecessary if actual data on switching were used, and the probability of switching may actually be much higher than one-third. In addition, SAEs and switching appear to be able to occur with salvage therapy, but is it unclear how or why this happens.

Switching occurs for one of two reasons: lack of effectiveness or occurrence of an SAE. The treatment switch criteria used in the model were:

- if a patient does not have an initial (i.e. first 6 months) improvement of 0.3468 in HAQ
- if, after an initial improvement, the patient's HAQ worsens by 0.3468 over 12 months or 0.3468 over a 6-month period.

Mortality rates for RA were assumed to be 1.63 times that of the general population of the same age. The change in mortality rate was adjusted taking change in HAQ into account. Inflating the already increased mortality on the basis of HAQ appears to introduce double-counting and is therefore inappropriate. Utility weights were assumed to vary linearly with HAQ score [i.e. $U = 0.76 + (\text{HAQ} \times -0.28)$]. This was further adjusted to consider SAEs, with a loss of 0.05 for each SAE experienced, but this assumption for a 6-month period for someone experiencing an SAE appears to be an underestimate.

Resource-use and cost data were taken from expert opinion and national sources. One blood test per year is assumed for those on TNF inhibitors and two for those on DMARDs. However, if those on TNF inhibitors are to receive methotrexate, then more frequent blood tests (e.g. monthly) are likely. This larger number of blood tests would apply to both arms. Rituximab is suggested for the salvage therapy, with a 6-month cost of almost £900. This is in contrast with the equivalent 'palliation' used in other analyses where costs are much lower, which may be a more accurate reflection of reality. For the base case, costs were discounted at 6% and QALYs at 1.5%. Simple one-way sensitivity analysis was undertaken on HAQ changes, mortality rate, SAE utility, cost, discount rates and switching threshold. The upper value for initial change in HAQ on etanercept of –1.3 appears to be rather high.

The base-case results suggest that etanercept is cost-effective first-line therapy. The ICERs indicate:

- first line: £16,000 per QALY
- second line: £20,000 per QALY
- third line: £18,000 per QALY.

Sensitivity analysis results are interpreted as showing that the results for all three models (first, second and third line) are "relatively robust to changes in key parameters".

Schering-Plough submission (infliximab)

The economic analysis presented in this submission assessed the cost-effectiveness of infliximab in combination with methotrexate compared with methotrexate alone in patients with severe RA. Data on effectiveness were drawn from ATTRACT and ASPIRE and so the patient populations seen in those trials were assumed for the modelling work: patients with active RA despite DMARD use and patients with severe active early RA. The perspective adopted was that of the NHS and Personal and Social Services (PSS).

To estimate the long-term consequences of RA and model the natural history of RA, a Markov model was used based on ARAMIS. This is not described in detail in the report. ARAMIS is a North American database consisting of 4258 prospectively enrolled patients with RA from nine centres followed for over 17,000 patient-years. The issue here is how a population of patients seen in private practices in the USA and Canada between 1981 and 1995 can reflect practice in the NHS in 2005. The model has states defined in terms of HAQ score (e.g. HAQ 0.1–1.0) and states defined in terms of treatments (e.g. methotrexate and one or more DMARD). Each health state, in terms of disability score and treatment, determines the transitional probability. During any cycle, patients may change or retain the same treatment, with the exception that the other treatments could not change to infliximab plus methotrexate. It is unclear why a change to infliximab and methotrexate is not permitted as this is a fairly common practice for people not doing well on a DMARD. An assumption was made that when infliximab was continued beyond the trial duration, the HAQ score would be preserved but not improved, and would be discontinued with worsening HAQ or side-effects. HAQ in RA or in the normal population tends to decline with age, therefore assuming that long-term stability is unreasonable.

Clinically significant radiographic progression was determined from cohort data using the smallest detectable difference (SDD) based on the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) definition. Although SDD is an important starting point for determining whether radiographic changes are clinically meaningful, it is by no means accepted that the two are the same. In addition, the SDD needs to be determined for each trial since it is a statistical concept and depends on the performance of two or more assessors in a particular setting, so SDDs from different settings vary considerably. Patients were divided into radiographic SDD progressors and non-progressors, with progressors having higher mean HAQ scores owing to physical disability from the progressing disease. Therefore, an absence of radiographic progression improved HAQ by 0.27 after 5–6 years. However, since there is a relationship between HAQ and radiographic change, and since HAQ changes are incorporated into the model, it appears that HAQ improvements are being double-counted.

Radiographic data were used in the model, such that evidence of radiographic stabilisation was applied to the Markov model as increasing the chance that a patient would remain in the same HAQ group, thereby decreasing the annual likelihood of HAQ progression. However, radiographic changes are likely to be greater in early RA and it is unreasonable to assume that similar changes could apply to the ATTRACT population. This analysis also calibrated the model to assume benefits 5 years from trial onset. Radiographic benefit was applied to patients treated for more than 6 weeks, so patients who discontinued infliximab where no ACR20 response was evident by week 14 did not receive this benefit. Most patients in trials do not show radiographic changes. Therefore, assuming this radiographic benefit several years later in patients with 6 weeks of treatment and an ACR20 response at 14 weeks is rather generous.

Estimates of the impact of infliximab on disease progression were obtained from the ATTRACT and from ASPIRE, with the likelihood of improved or worsened HAQ score estimated from the methotrexate and methotrexate/infliximab arms of the trials. However, using all arms of infliximab/methotrexate regardless of dose or dosing interval from ATTRACT may weigh in favour of infliximab as, although outcomes looked similar, patients on 10 mg kg^{-1} of infliximab did appear to be doing better. Health state values were based on a personal communication from G Kobelt to the company, as follows:

- HAQ 0 = 0.819
- HAQ 0.1–1.0 = 0.682
- HAQ 1.1–2.0 = 0.454
- HAQ 2.1–3.0 = 0.192.

UK-based sources for resource-use data and for unit costs were used (ERA study). Discount rates of 6% for costs and 1.5% for benefits were applied. A wide range of one-way and multiway sensitivity analyses was undertaken.

The base-case cost-effectiveness results are summarised in *Table 30*. The results are interpreted as yielding "costs per QALY that fall well within the range of such estimates for health care interventions typically funded in the UK. The high CRP subset has a better cost-effectiveness ratio because of faster radiological progression compared to the overall ASPIRE group."

The sensitivity analyses looked at stopping rules, discount rates, RA mortality assumptions, utility scores, resource use and radiographic

TABLE 30 *Base-case cost-effectiveness results (Schering-Plough)*

Population	Incremental cost (£)	Incremental QALYs	ICER
MTX experienced (ATTRACT)	17,370	2.79	6,228
MTX-naïve (ASPIRE)	23,808	1.42	16,766
MTX-naïve with high CRP (ASPIRE)[a]	23,926	1.84	13,000

[a] Represent early progressive RA.

stabilisation. ACR20 was used for the stopping rules in this analysis; however, the stopping rule recommended by NICE stipulates use of DAS28 scores only. Although the two are related, it is not clear that ACR20 can substitute for DAS28 changes in practice. Assumptions concerning the duration of radiographic benefit were shown to be a possible driver of the cost-effectiveness results.

Clinical advice recommended that strategies where dose escalation with infliximab occurred should be excluded owing to greatly increased cost while adding very little benefit. The analysis in this report also does not consider dose escalation, therefore the ICERs reported for infliximab will underestimate drug costs. In reality, dose escalation is common and ideally should be incorporated in cost-effectiveness analyses.

Summary of industry submissions

- The submission by Wyeth suggests that etanercept is highly cost-effective.
- The submission by Schering-Plough suggests that infliximab is highly cost-effective.
- The submission by Abbott suggests that adalimumab is highly cost-effective.
- All three submissions report a model-based cost–utility analysis with a lifetime horizon, and all three have undertaken extensive sensitivity analyses. The results of all sensitivity analyses broadly support the base-case findings of support for the use of the new therapy/product in question.
- Two of the three submissions (those from Wyeth and Abbott Laboratories) have considered drug sequences and the use of the new therapy as part of an existing sequence.

Economic analysis used in this report

Summary of the Birmingham economic evaluation

A simulation model, which considered improvements in quality of life and mortality, but assumed no effect of the TNF inhibitors on the need for joint replacement, was used.

For use in accordance with current NICE guidance, as the third DMARD in a sequence of DMARDs, the base-case ICER depended on whether the effectiveness data were taken from early RA or late RA patients, as shown in *Table 31* (in clinical practice there will be a mixture of both). Sensitivity analyses showed that the results were most sensitive to figures for HAQ progression on TNF inhibitors and the effectiveness of DMARDs, but not particularly sensitive to changes in mortality ratios used per unit HAQ.

When TNF inhibitors were used as the last active therapy, the equivalent results were as shown in *Table 32*.

TABLE 31 *TNF inhibitors in late and early RA*

		Cost per QALY (£)		Sensitivity analyses: late RA data (early RA data) (£)	
TNF inhibitor	Comparator	Late RA	Early RA	Lowest	Highest
Adal (no MTX)	Base strategy of	141,000	35,000	41,000 (21,000)	Dominated (55,000)
Etan (no MTX)	DMARDs with no	47,000	30,000	24,000 (19,000)	95,000 (46,000)
Adal (with MTX)	TNF inhibitors	64,000	30,000	30,000 (19,000)	150,000 (43,000)
Etan (with MTX)		50,000	29,000	25,000 (18,000)	96,000 (42,000)
Infl (with MTX)		139,000	30,000	39,000 (19,000)	Dominated (45,000)

TABLE 32 *TNF inhibitors as last active therapy*

TNF inhibitor	Comparator	Cost per QALY (£)	Sensitivity analyses (£)	
			Lowest	Highest
Adal (no MTX)	Base strategy of DMARDs with no TNF inhibitors	40,000	27,000	64,000
Etan (no MTX)		24,000	18,000	33,000
Adal (with MTX)		30,000	22,000	43,000
Etan (with MTX)		24,000	18,000	34,000
Infl (with MTX)		38,000	26,000	61,000

TABLE 33 *TNF inhibitors as first-line therapy*

TNF inhibitor	Comparator	Cost per QALY (£)	Sensitivity analyses (£)	
			Lowest	Highest
Adal (no MTX)	Base strategy of DMARDs with no TNF inhibitors	53,000	27,000	122,000
Etan (no MTX)		49,000	23,000	119,000
Adal (with MTX)		171,000	38,000	Dominated
Etan (with MTX)		78,000	28,000	Dominated
Infl (with MTX)		654,000	45,000	Dominated

Similarly, the results for first line therapy are shown in *Table 33*.

A limited analysis of sequential use was carried out, assuming that the properties of second or third TNF inhibitors were equivalent to the use of the same treatment as first TNF inhibitor. The results were similar to the results for the equivalent therapy as sole TNF inhibitor.

The main aim of the analysis was to assess the cost-effectiveness of adding a TNF inhibitor to an existing treatment pathway for RA compared with the same pathway without that TNF inhibitor. The costs are from an NHS perspective.

The analysis was conducted using an updated version of the BRAM,[2] which was further developed starting from the most recent previous version (used in the assessment of anakinra[3]).

The BRAM is an individual sampling model. The model was devised to reflect the typical real clinical patient pathway. A large number of virtual patient histories is simulated with the accumulation of costs and QALYs. The basic model structure is shown in *Figure 46*. A complete description of the model structure follows here.

Patients are assumed to follow a sequence of treatments (single or combination therapy), which involves: starting a treatment, spending some time on that treatment, quitting the treatment if it is toxic or ineffective, and starting the next treatment. The pattern is then repeated. Any patient who has started and had to quit all the active treatments moves on to palliation. Patients' HAQ scores are assumed to improve (decrease) on starting a treatment; this improvement is lost on quitting the treatment, which may be for reasons of either toxicity or loss of effectiveness. HAQ scores can range from 0 (best) to 3 (worst) and are constructed such that the smallest measurable change in disability is 0.125 (see Appendix 1 for further details of the HAQ). Reflecting observed data, while on any treatment, a patient's condition is assumed to decline slowly over time; this is modelled as periodic increases of 0.125 in HAQ score.

All patients are followed through to death. Mortality risk is assumed to depend on current HAQ score, as well as age and gender.

There are two important improvements from previous versions of the BRAM. First, there is individual variation in HAQ improvement on starting treatment. Secondly, time on treatment includes explicit consideration of early quitting, with early quitting owing to lack of effectiveness being correlated with poor HAQ improvement on starting treatment.

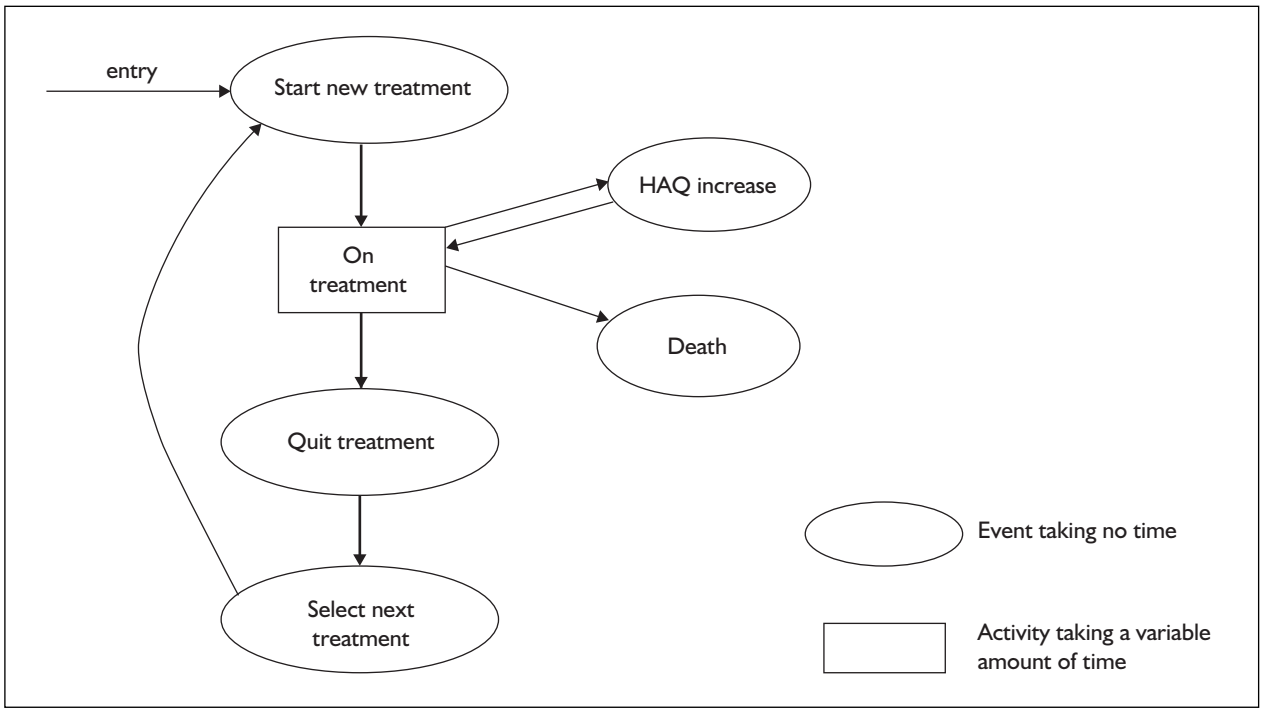

FIGURE 46 *Basic structure of the model*

Strategies compared using the BRAM

Baseline for comparison

Before considering how TNF inhibitors could be included in treatment strategies, it is convenient to describe the baseline strategy without TNF inhibitors.

The baseline strategy, based on a survey of rheumatology consultants in the UK,[25] starts with methotrexate as single therapy. If methotrexate is stopped on grounds of toxicity, it is followed by sulfasalazine as single therapy, otherwise by the combination of methotrexate plus sulfasalazine. Similarly, if this combination is quit on grounds of toxicity, it is followed by leflunomide. But, if the methotrexate–sulfasalazine combination lacks efficacy, hydroxychloroquine is added to the combination. These rules are shown in *Table 34* under the heading 'Moves dependent on toxicity'. For most other treatments, the choice of treatment next in sequence, and the move to the next agent, simply depend on drug cessation, for whatever reason. For example, sulfasalazine as single therapy, in *Table 34*, is always followed by leflunomide, as shown under the heading 'Always move to'. In the case of ciclosporin, the preferred next treatment is the combination of ciclosporin plus methotrexate. However, this combination cannot be offered if ciclosporin has just been quit on grounds of toxicity, nor can it be offered if methotrexate was earlier quit for toxicity. This is shown under 'Relevant toxicity'. Palliation is the treatment of last resort and therefore cannot be quit.

The structure as shown in *Table 34* is more general than the structure used in previous versions of the BRAM: all the previous strategies in the model can be described by tables of this form.

Comparisons

For clarity, the word 'comparison' is reserved for an analysis comparing two options. The term 'strategy set' is used for a collection of strategies (treatment sequences) with a common initial sequence and divergence point.

Single TNF inhibitors (versus no TNF inhibitor)

In these strategy sets only one TNF inhibitor is used. There are six options in each case: adalimumab alone; etanercept alone; each of the three TNF inhibitors combined with methotrexate; and the comparator option without TNF inhibitors. These produce a total of 15 possible comparisons: five ('major comparisons') relate to including each TNF inhibitor singly within a sequence without TNF inhibitors and ten ('minor comparisons') relate to comparisons between different TNF inhibitors.

Single TNF inhibitor at the start In this strategy set, the divergence point is at the start of the sequence, that is, patients are treated with a TNF inhibitor before any other DMARD (see *Table 35*,

TABLE 34 *Basic structure of the model*

			Moves dependent on toxicity	
Treatment	**Always move to**	**Relevant toxicity**	**If toxic, move to**	**Otherwise, move to**
MTX		MTX	SSZ	MTX+SSZ
SSZ	LEF			
MTX+SSZ		MTX+SSZ	LEF	MTX+SSZ+HCQ
MTX+SSZ+HCQ	LEF			
LEF	GST			
GST	AZA			
AZA	CyA			
CyA		CyA or MTX[a]	DPen	CyA+MTX
CyA+MTX	DPen			
DPen	Pall			

[a] It was assumed that toxicity of MTX+SSZ (± HCQ) would not preclude the use of the combination CyA+MTX.
AZA, azathioprine; DPen; penicillamine; GST, injectable gold; HCQ, hydroxychloroquine; Pall, palliation.

TABLE 35 *Strategy set with TNF inhibitors at the start*

			Moves dependent on toxicity	
Treatment	**Always move to**	**Relevant toxicity**	**If toxic, move to**	**Otherwise, move to**
Option 1	Adal			
Adal	MTX			
Option 2	Etan			
Etan	MTX			
Option 3	Adal+MTX			
Adal+MTX	SSZ			
Option 4	Etan+MTX			
Etan+MTX	SSZ			
Option 5	Infl+MTX			
Infl+MTX	SSZ			
Option 6	MTX			
MTX		MTX	SSZ	MTX+SSZ
SSZ	LEF			
MTX+SSZ		MTX+SSZ	LEF	MTX+SSZ+HCQ
MTX+SSZ+HCQ	LEF			
LEF	GST			
GST	AZA			
AZA	CyA			
CyA		CyA or MTX	DPen	CyA+MTX
CyA+MTX	DPen			
DPen	Pall			

options at the divergence point are shaded). Option 1 starts with adalimumab followed by methotrexate. Option 2 starts with etanercept followed by methotrexate. Option 3 starts with adalimumab in combination with methotrexate followed by sulfasalazine (it would be clinically inappropriate to use methotrexate as single therapy after failing this combination). Similarly, options 4 and 5 start with etanercept and infliximab, respectively, in combination with methotrexate. Option 6, the comparator, starts with methotrexate. Each of options 1, 2 and 6 continues with the complete baseline strategy, while options 3, 4 and 5 join this strategy from sulfasalazine, thus avoiding the early combinations with methotrexate. It is assumed that the

combination of ciclosporin with methotrexate would still be available in this case. When the model is run, initial characteristics for (virtual) patients are sampled from the starting distribution. Each patient is then run independently through each of the six options and differences in costs and QALYs between options are recorded. This process is repeated for a sufficiently large number of patients to produce a statistically stable comparison between each pair of options.

Single TNF inhibitor as third line therapy In this strategy set, TNF inhibitors are considered as third line therapy; that is, after two DMARDs including methotrexate have been tried, in accordance with current NICE guidance.

Each (virtual) patient is started on methotrexate. Patients who quit methotrexate on grounds of toxicity move to single-therapy sulfasalazine. Those who quit for any other reason move to the combination of methotrexate plus sulfasalazine. Any patient who dies while still on one of the treatments mentioned so far is discarded from the analysis and replaced by a new (virtual) patient starting again from the beginning with methotrexate. Any patient who fails on sulfasalazine (or methotrexate plus sulfasalazine) has reached the divergence point between the options (see *Table 36*; options after the divergence point are shaded). The patient's characteristics at this moment are stored for future use, and the patient is run through the rest of option 1, continuing with adalimumab and then leflunomide, and so on.

Costs and QALYs are counted only from the divergence point, and are discounted to the divergence point. The patient characteristics at the divergence point are retrieved, and the patient is run through option 2, starting with etanercept followed by leflunomide. Once the costs and QALYs for option 2 have been calculated, the patient characteristics at the divergence point are again retrieved, and the patient is run through option 3, starting this time with the combination adalimumab plus methotrexate, except that if methotrexate has

TABLE 36 *Strategy set with TNF inhibitors in third place*

			Moves dependent on toxicity	
Treatment	**Always move to**	**Relevant toxicity**	**If toxic, move to**	**Otherwise, move to**
MTX		MTX	SSZ	MTX+SSZ
SSZ	Divergence point			
MTX+SSZ	Divergence point			
Option 1	Adal			
Adal	LEF			
Option 2	Etan			
Etan	LEF			
Option 3		MTX	Adal	Adal+MTX
Adal+MTX	LEF			
Option 4		MTX	Etan	Etan+MTX
Etan+MTX	LEF			
Option 5	Infl+MTX[a]			
Infl+MTX	LEF			
Option 6	LEF			
LEF	GST			
GST	AZA			
AZA	CyA			
CyA		CyA or MTX	DPen	CyA+MTX
CyA+MTX	DPen			
DPen	Pall			

[a] The data set for this combination is used in the model, regardless of the reason for quitting MTX.

been quit on grounds of toxicity, adalimumab monotherapy is given instead. In either case, this therapy is followed by leflunomide. Option 4 is similar to option 3, with etanercept instead of adalimumab. In option 5, the combination infliximab plus methotrexate is given immediately after the divergence point.

In practice, patients who had quit methotrexate on grounds of toxicity would not be given a combination of infliximab and methotrexate (option 5). It was assumed that such patients would be given infliximab as single therapy, although the authors recognise that infliximab is often combined with other agents such as leflunomide or azathioprine in clinical practice. It was further assumed that the effectiveness of infliximab without methotrexate in these circumstances is similar to infliximab with methotrexate. To compensate for a bias in favour of infliximab introduced by this assumption, the cost for the combination is also used. (The cost of methotrexate forms only a small part of the cost of this combination.) Thus, in the model, the data set for the combination infliximab plus methotrexate is used regardless of the reason for quitting methotrexate. Option 5 continues with leflunomide, and so on. Finally, option 6 involves the use of leflunomide immediately after the divergence point. Differences between options are stored and the process is repeated for a sufficiently large number of patients.

Single TNF inhibitors as last active therapy In this strategy set, patients are run through the whole of the baseline strategy if necessary. Any patient who dies while still on active therapy is discarded from the analysis and replaced by a new patient. Any patient who fails on all the conventional DMARDs used in the baseline strategy reaches the divergence point (see *Table 37*, options at the divergence point are shaded). Thus, in this strategy TNF inhibitors are used are treatments of last resort. As before, the patient's characteristics at the divergence point are stored before the patient starts on option 1 (adalimumab followed by palliation). The patient is then restarted from the divergence point and run through each of the other options.

TABLE 37 *Strategy set with TNF inhibitors as last active therapy*

			Moves dependent on toxicity	
Treatment	**Always move to**	**Relevant toxicity**	**If toxic, move to**	**Otherwise, move to**
MTX		MTX	SSZ	MTX+SSZ
SSZ	LEF			
MTX+SSZ		MTX+SSZ	LEF	MTX+SSZ+HCQ
MTX+SSZ+HCQ	LEF			
LEF	GST			
GST	AZA			
AZA	CyA			
CyA		CyA or MTX	DPEN	CyA+MTX
CYA+MTX	DPen			
DPen	Divergence point			
Option 1	Adal			
Adal	Pall			
Option 2	Etan			
Etan	Pall			
Option 3		MTX	Adal	Adal+MTX
Adal+MTX	Pall			
Option 4		MTX	Etan	Etan+MTX
Etan+MTX	Pall			
Option 5	Infl+MTX[a]			
Infl+MTX	Pall			
Option 6	Pall			

[a] The data set for this combination is used in the model, regardless of the reason for quitting MTX.

Strategies including two TNF inhibitors consecutively

Here the relevant decision is, having used one TNF inhibitor, whether to use a second TNF inhibitor or to revert to conventional DMARDs. Only the case where the first TNF inhibitor is used as third line therapy is considered, and adalimumab and etanercept are considered only as single therapy. Any one of the three TNF inhibitors could be the first choice. Thus, there are three strategy sets to consider, each with three options.

The first of these strategy sets (*Table 38*) starts with methotrexate, followed by sulfasalazine (with or without methotrexate) and then adalimumab. The divergence point comes immediately after adalimumab. Options 1 and 2 are to treat with etanercept and infliximab, respectively, if adalimumab fails and then continue the baseline strategy from leflunomide onwards. In the comparator, option 3, adalimumab is followed by leflunomide and the baseline strategy. The equivalent strategy sets for other choices of first TNF inhibitor are shown in *Tables 87* and *88* (Appendix 9).

Strategies including all three TNF inhibitors consecutively

Here the relevant decision is, having used two TNF inhibitors, whether to use a third TNF inhibitor or to revert to conventional DMARDs. Again only the case where the first TNF inhibitor is used as third-line therapy is considered; that is, after sulfasalazine and methotrexate have been tried (according to current NICE guidance), and adalimumab and etanercept are considered only as single therapy. Any one of the three TNF inhibitors could be the first fixed choice, with either of the other two as the second fixed choice. Thus, there are six strategy sets to consider, each with two options.

The strategy set shown in *Table 39* starts with methotrexate, followed by sulfasalazine (with or without methotrexate) and then adalimumab followed by etanercept. The divergence point comes immediately after etanercept. Option 1 is to use infliximab after this and then continue the baseline strategy from leflunomide onwards; option 2 is to forgo infliximab and continue directly with leflunomide. The other five strategy sets, which are similar, are given in *Tables 89–93*, (Appendix 9).

Data used in the BRAM

The main source of data is the current review for TNF inhibitors and published literature for other data.

Initial patient data

Table 40 shows the initial age and sex distribution, based on UK data from Wiles *et al.*[172] The starting distribution of HAQ scores, shown in *Table 41*, is also based on Wiles.[172]

Starting treatments

In previous versions of the BRAM, the HAQ improvement (decrease) on starting any treatment

TABLE 38 *Strategy set with adalimumab followed by another TNF inhibitor*

			Moves dependent on toxicity	
Treatment	**Always move to**	**Relevant toxicity**	**If toxic, move to**	**Otherwise, move to**
MTX		MTX	SSZ	MTX+SSZ
SSZ	Adal			
MTX+SSZ	Adal			
Adal	Divergence point			
Option 1	Etan			
Etan	LEF			
Option 2	Infl+MTX			
Infl+MTX	LEF			
Option 3	LEF			
LEF	GST			
GST	AZA			
AZA	CyA			
CyA		CyA or MTX	DPen	CyA+MTX
CyA+MTX	DPen			
DPen	Pall			

TABLE 39 *Strategy set: adalimumab and etanercept possibly followed by infliximab*

			Moves dependent on toxicity	
Treatment	**Always move to**	**Relevant toxicity**	**If toxic, move to**	**Otherwise, move to**
MTX		MTX	SSZ	MTX+SSZ
SSZ	Adal			
MTX+SSZ	Adal			
Adal	Etan			
Etan	Divergence point			
Option 1	Infl+MTX			
Infl+MTX	LEF			
Option 2	LEF			
LEF	GST			
GST	AZA			
AZA	CyA			
CyA		CyA or MTX	DPen	CyA+MTX
CyA+MTX	DPen			
DPen	Pall			

was fixed as a multiple of 0.125. In this version, the HAQ improvement has been allowed to vary between individual patients in the model, and is modelled as a multiplier of the original HAQ. An example of the method used is shown here for the case of leflunomide.

Data available were baseline HAQ mean 1.03 (SD 0.62) and HAQ improvement mean 0.48 (SD 0.5).[173]

An Excel spreadsheet was set up to create a starting population of 10,000 virtual patients with HAQ scores drawn from a normal distribution with mean and standard deviation supplied by the user. Each generated HAQ score was converted to the nearest legitimate value (multiples of 0.125 in the range 0–3). The parameters supplied were adjusted to compensate for the effect of this conversion, so that the mean and standard deviation of the population generated correspond to the data.

A beta distribution was found to match the given mean and standard deviation for HAQ improvement. The parameters are shown in *Table 42*, while *Figure 47* displays the simulated population. Each square within the graph represents a possible pair of values of starting HAQ and HAQ on treatment: the darker the

TABLE 40 *Initial age and gender distribution*

	Age (years)							
	15–24	**25–34**	**35–44**	**45–54**	**55–64**	**65–74**	**75–84**	**Total**
Male	0.9	2.5	5.4	8.3	9.0	6.8	5.1	38
Female	1.5	4.0	8.8	13.7	14.7	10.9	8.4	62

TABLE 41 *Starting distribution of HAQ scores*

HAQ	0.125	0.25	0.375	0.5	0.625	0.75	0.875
%	3.1	6.7	6.7	5.8	5.3	4.9	4.8
HAQ	1	1.125	1.25	1.375	1.5	1.625	1.75
%	4.9	5.1	5.5	5.8	6.3	6.6	7.0
HAQ	1.875	2	2.125	2.25	2.375	2.5	Higher
%	6.9	6.2	4.7	2.7	0.9	0.1	0

TABLE 42 *Fitting beta distribution to HAQ change data for leflunomide*

	Mean	SD
Initial HAQ parameters	1.01	0.66
Initial HAQ sampled	1.03	0.62
HAQ improvement	0.48	0.50
	a	*b*
Beta parameters	0.57	0.65

square, the larger the number of simulated patients with that pair of HAQ values. It can be seen that there is a high proportion of patients with equal HAQ on treatment compared with before treatment. In this example, the sampled population contains a large number of zero initial HAQ values. These are omitted from the graphs, but included in the calculations relating to HAQ improvement.

Table 43 shows the parameters found for the beta distributions. Two sets of figures are given for each of the TNF inhibitors: one for early RA and one for late RA. The columns headed *a* and *b* are the actual parameters of the distribution, while the column headed Mean gives the mean value of the distribution. Since the distribution is for a multiplier giving HAQ improvement, the higher the mean, the more effective the treatment. Consider, for example, a patient with HAQ before treatment equal to 2.5. The effect of a treatment with mean 0.6 will lie somewhere between two extremes. One extreme is that all patients have HAQ reduced by $0.6 \times 2.5 = 1.5$, so that HAQ on treatment would be 1.0, while the other extreme is that 60% of patients have HAQ reduced to zero, while the other 40% have no change in HAQ. Where values of *a* and *b* are both less than 1, as is generally the case for the values used here, the distribution is close to the second of these cases.

Time on treatments

The model allows for two stages of early quitting of treatment. *Figure 48* shows the general shape for the survival curve assumed for a particular treatment. The first step represents cessation of treatment after 6 weeks, which is assumed to be

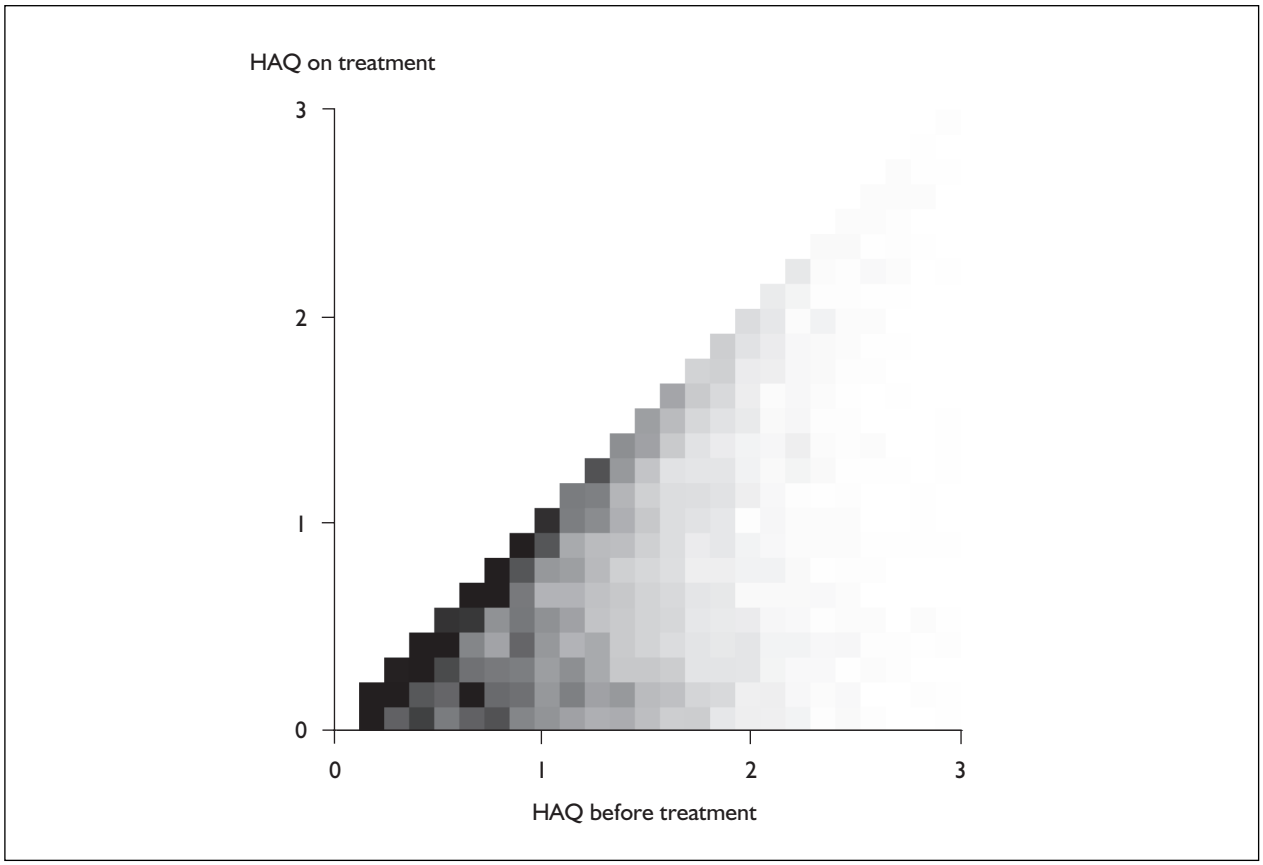

FIGURE 47 *Modelled distribution of HAQ change on starting leflunomide*

TABLE 43 *Beta distributions for HAQ multipliers*

Treatment	*a*	*b*	Mean	Source
Adal early RA	**[Commercial-in-confidence information removed]**	**[Commercial-in-confidence information removed]**	**[Commercial-in-confidence information removed]**	From PREMIER trial[102] (DE013); unpublished data (observed values) from trial report. MTX-naïve patients
Adal late RA	0.16	0.61	0.21	From van de Putte[113] (DE011), data with LOCF imputation, without concomitant MTX
Adal + MTX early RA	**[Commercial-in-confidence information removed]**	**[Commercial-in-confidence information removed]**	**[Commercial-in-confidence information removed]**	From PREMIER trial[102] (DE013); unpublished data (observed values) from trial report. MTX-naïve patients.
Adal + MTX late RA	1.08	1.36	0.44	Combined results from ARMADA trial[112] (DE009) and Keystone[114] (DE019)
AZA	0.20	0.80	0.20	Data assumed to be similar to anakinra using data from Bresnihan[174]
CyA	0.13	0.26	0.33	RCT of GST vs CyA in early RA,[175] Kvien[176]
Etan early RA	0.59	0.52	0.53	From ERA trial.[123] Unpublished data with LOCF imputation from trial report. MTX-naïve patients
Etan late RA	0.43	0.67	0.39	Combined results from Moreland,[122] Codreanu[103] and TEMPO.[127] Unpublished data with LOCF imputation from trial reports
Etan + MTX early RA	0.72	0.50	0.59	From TEMPO[127] (data from Wyeth submission)
Etan + MTX late RA	0.20	0.30	0.40	From Weinblatt.[125] Unpublished data with LOCF imputation from trial report
GST	0.45	0.70	0.39	As for CyA
HCQ	0.15	0.40	0.27	Trial of HCQ in early RA[177]
Infl (+MTX) early RA	0.76	0.67	0.53	From St Clair[135] (ASPIRE trial). MTX-naïve patients
Infl (+MTX) late RA	0.11	0.38	0.22	From ATTRACT[132] (unpublished data from trial report, observed values)
LEF	0.57	0.65	0.47	RCT of LEF vs MTX[173]
MTX	0.98	0.82	0.54	As for LEF
DPen	0.20	0.80	0.20	Assumed same as AZA
SSZ	0.70	0.84	0.45	Follow-up observations of patients involved in an RCT,[178] Smolen[179]
Combination CyA + MTX	0.80	0.45	0.64	Data from an RCT of CyA vs CyA combined with MTX in early RA[180]
Combination MTX+SSZ	0.70	0.84	0.45	Assumed as for SSZ
Combination MTX+SSZ+HCQ	0.15	0.40	0.27	Assumed as for HCQ

LOCF, last observation carried forward.

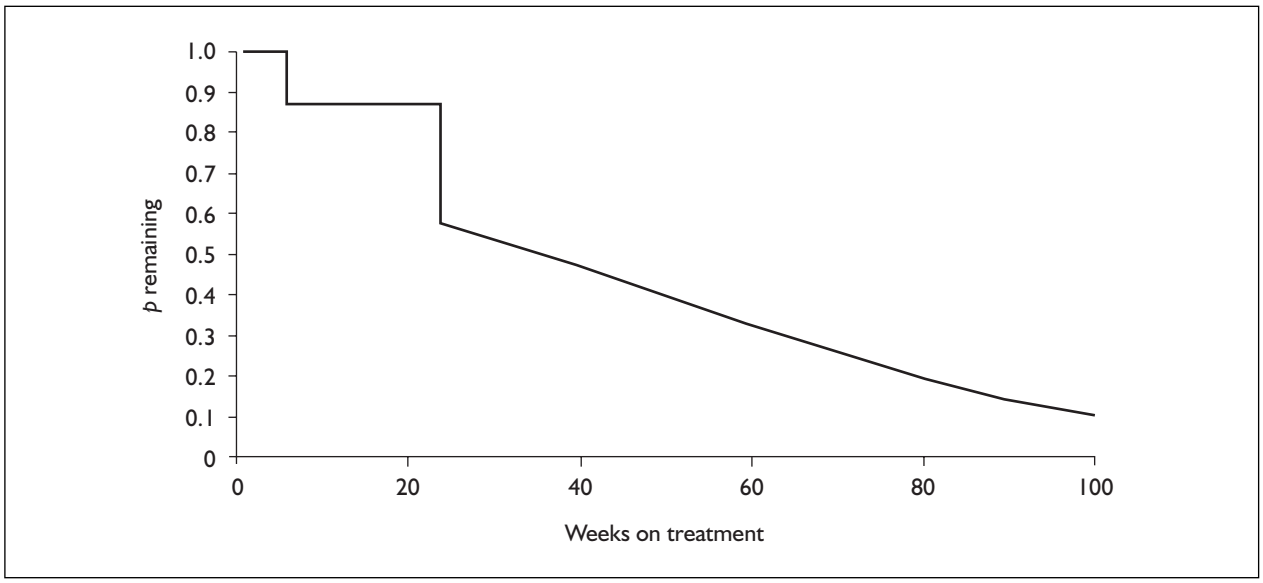

FIGURE 48 *Illustrative curve for survival time on a treatment (based on leflunomide data)*

TABLE 44 *Early cessation of DMARDs: data, sources and comments*

Drug	Cessation at ≤ 6 weeks[a]	Ceasing between 6 and 24 weeks	Comments and source
Adal (with or without MTX)	5%	10% (5% because of toxicity and 4% for inefficacy, 1% for other reasons)	No appropriate data found; assume same as infliximab
AZA	15%	25%	Data estimated from Willkens.[181] Reasons for cessation due to toxicity, inefficacy or other reasons are not available
CyA	8%	24% (12% because of inefficacy and 12% for toxicity)	Data estimated from Yocum[182] It is assumed that half of those ceasing between 6 and 24 weeks do so because of inefficacy and the other half because of toxicity; based on observations by Marra.[183]
Etan (with or without MTX)	4%	3% (1% because of toxicity and 2% for inefficacy)	Observational study by Geborek 2002[171] (see leflunomide). 84% of all patients remained on treatment at 12 months
GST	14%	27% (18% because of toxicity and 9% for inefficacy)	Figures estimated from Hamilton.[184] Estimated figures from Zeidler[175] are 10% within 6 weeks and 34% at 24 weeks
HCQ	3%	18% (4% because of toxicity and 14% for inefficacy)	Data estimated from Furst[185] using a cohort treated with 800 mg per day as this group provided the most complete data set
Infl + MTX	5%	10% (5% because of toxicity and 4% for inefficacy, 1% for other reasons)	Observational study by Geborek[171] (see leflunomide). 75% of all patients remained on treatment at 12 months
LEF	10% for drug toxicity and 3% for other reasons	30% (10% because of toxicity, 19% for inefficacy and 1% for other reasons)	Data estimated from Geborek.[171] These data are preferred to trial data because clinical experience indicates that continued drug use is less likely in practice than use in randomised trials.[186]
MTX	8.5%	19.5% (8.5% because of toxicity and 11% for inefficacy)	Estimates from Hamilton[184]

continued

TABLE 44 *Early cessation of DMARDs: data, sources and comments (cont'd)*

Drug	Cessation at ≤ 6 weeks[a]	Ceasing between 6 and 24 weeks	Comments and source
DPen	Assume same as AZA		No reliable data are available for use of penicillamine late in disease; late drug-use data are required by the modelling strategy
SSZ	10%	28% (9% because of toxicity, 10.5% for inefficacy and 8.5% for other reasons)	No ideal source identified. Data estimated from two clinical trials (Proudman[187] and Smolen[179]) that gave data from which inferences about early and late cessations were made
Combination (CyA and MTX)	0%	50%	No data source. The model assumes that patients will have tried both MTX and CyA monotherapy before trying this combination. Therefore, patients experiencing toxicity to either agent in the past would not be eligible for this combination. The use of this combination after failed monotherapy with CyA and MTX assumes a synergistic effect for efficacy, although there is no definitive evidence for this. In the absence of data, but based on an educated guess, it was assumed that 50% of patients cease therapy after 24 weeks owing to lack of efficacy
Combination (MTX and SSZ)	As for SSZ		As the model does not propose combination therapy from the outset with this combination, but proposes that SSZ is added when MTX is inefficacious (and not toxic), in a step-up strategy, it was assumed that patients respond, in terms of toxicity and drug continuation, as they would if SSZ alone had been used
Combination (MTX, SSZ and HCQ)	As for HCQ		As above, the model does not propose combination therapy from the outset but drugs are added in a step-up strategy. Thus, toxicity and drug continuation rates for this combination are assumed to be similar to HCQ alone, since patients only use HCQ in the combination if MTX and SSZ in combination have been inefficacious (and not toxic)

[a] It is assumed, unless stated otherwise, that patients ceasing by 6 weeks do so because of drug toxicity.

for toxicity. The second step represents cessation between 6 and 24 weeks after starting treatment, which could be for toxicity or inefficacy. *Table 44* shows the data used for early cessation of DMARDs. The implementation of this approach is illustrated in *Figure 49*. The variables $u1$ and $u2$ are drawn from a uniform distribution between 0 and 1. The value of $u1$ is used primarily to determine the HAQ improvement on starting treatment using the beta distribution with parameters as shown in *Table 43*, while $u2$ determines the time on treatment. The four zones in *Figure 49* represent the following:

A withdrawal within 6 weeks (assumed due to toxicity)
B withdrawal between 6 and 24 weeks for inefficacy
C withdrawal between 6 and 24 weeks for toxicity
D remaining on the treatment after 24 weeks.

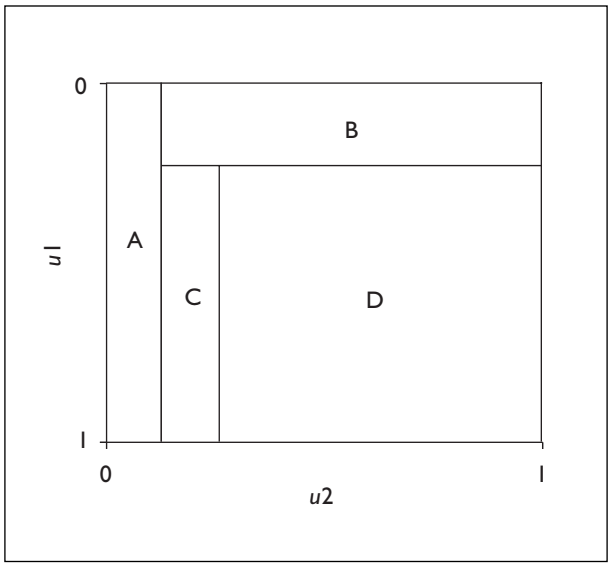

FIGURE 49 *Early cessation of treatment*

TABLE 45 *Times to quitting DMARD*

DMARD	*a*	*b* (years)	Mean (years)	Source
Adal	0.73	5.96	7.26	Assumed same as infliximab
AZA	0.39	4.35	15.53	GPRD database[188]
CyA	0.5	4.35	8.70	GPRD database[188]
Etan	0.73	12.34	15.03	Geborek[171]
GST	0.48	1.81	3.91	GPRD database[188]
HCQ	0.49	3.52	7.31	GPRD database[188]
Infl	0.73	5.96	7.26	Geborek[171]
LEF	1	5.98	5.98	GPRD database[188]
MTX	0.51	15.73	30.35	GPRD database[188]
DPen	0.57	2.60	4.20	GPRD database[188]
SSZ	0.46	4.66	11.01	GPRD database[188]
Combination CyA+MTX	1	1.74	1.74	Tugwell,[189] Gerards[190]
MTX+SSZ	0.46	4.66	11.01	As for SSZ alone
MTX+SSX+HCQ	0.49	3.52	7.31	As for HCQ alone

GPRD, General Practice Research Database.

In implementation, the values of $u1$ and $u2$ are compared with critical values calculated so that zones A, B and C in *Figure 49* have the appropriate areas to represent the probabilities given in *Table 44*. This method means that early withdrawal for inefficacy coincides with the minimum HAQ improvement.

For patients who remain on treatment after 24 weeks, the time on treatment is assumed to be independent of HAQ improvement. The value of $u2$ is converted to a value from a Weibull distribution, represented in the curved part of *Figure 48*.

A random variable X has a Weibull distribution with shape parameter a and scale parameter b if $\left(\frac{X}{b}\right)^a$ has an exponential distribution with unit mean. The Weibull distribution is more general than the constant-risk exponential distribution in that it reduces to the exponential distribution when $a = 1$. If $a < 1$, then the risk decreases over time, while if $a > 1$, the risk increases over time. Parameters a and b are shown in *Table 45*. For convenience, the mean of the distribution is also shown.

HAQ changes on treatment

The model assumes a constant risk of increase in HAQ score while in treatment and that an individual's HAQ score increases gradually and in steps of 0.125, apart from the effects of starting and ending treatment. While HAQ can change at any stage of disease, and is known to be more labile in early disease, the assumption of a gradual increase in HAQ is reasonable for the parts of the model where comparisons are being made, as the model applies to the later stages of the disease. The rate of increase in HAQ was chosen to reflect the empirically observed increase reported by Scott and Strand.[191]

Toxicity

Toxicity of treatments beyond 24 weeks was only an issue if it potentially affected later choices of treatment, as shown in *Table 44*. Thus, it was only an issue for methotrexate, ciclosporin and the combination methotrexate plus sulfasalazine. For other treatments, cessation because of toxicity or inefficacy has the same consequence in the model; that is, use of the treatment next in sequence. For ciclosporin it was assumed that drug cessation was due to toxicity with a probability of 0.8 regardless of time spent on drug.[192] For methotrexate, the probability p was set to depend on the time t years on the drug, by the formula $p = 0.362 + 0.115e^{-0.457t}$, which was derived from a comparison between the survival curves given in Maetzel.[193] For methotrexate plus sulfasalazine, it was assumed that the probability for methotrexate alone applies.

Costs

Costs are made up of drug costs plus monitoring costs. For all treatments, there are higher costs on starting than there are for continued use. The total cost for time on any treatment is modelled as a one-off starting cost followed by a steady annual usage cost. For completeness, all costs are shown. The price year is 2004 in each case. The unit costs of the various inputs are shown in *Tables 46* and *47*. The monitoring assumptions are listed in *Table 48*.

TABLE 46 *Unit costs for tests and visits*

Test	Cost (£)[a]	Source
FBC	3.98	Newchurch[194]
ESR	3.07	Newchurch[194]
BCP	3.84	Newchurch[194]
CXR	15.59	Newchurch[195]
Urinalysis	0.08	Newchurch[194]
Visit		
GP	24.00	Curtis and Netten[196]
Hospital outpatient	91.00	Curtis and Netten[196]
Hospital inpatient (per day)	202.00	Curtis and Netten[196]
Specialist nurse visit	45.50	Assumed half of outpatient visit

[a] Inflated to 2004 prices using Hospital and Community Health Services (HCHS) inflation index.[196]
BCP, biochemical profile; CXR, chest X-ray; FBC, full blood count.

TABLE 47 *Unit costs for drugs*

Treatment	Cost	Assumptions
Adal	£357.50 per dose	26 doses per year
AZA	53.4p per day	150 mg per day
CyA	£3.73 per day	225 mg per day
Etan	£178.75 per dose	52 doses of 50 mg per year
GST	£8.89 per dose	50-mg ampoule, administered at GP visit
HCQ	11.4p per day	300 mg per day
Infl	£419.62 per vial	70-kg patient, drug wastage if full vials not used, cost per administration £124
LEF	£1.70 per day	20 mg per day
MTX	11.7p per 2.5-mg tablet	15 mg per week
DPen	49.2p per day	500 mg per day
SSZ	32.9p per day	2.5 g per day

Source: BNF 50 (September 2005), accessed online at www.bnf.org[197]

TABLE 48 *Monitoring assumptions*

Treatment	Pretreatment	On treatment
Palliation		Outpatient visit every 3 months
Adal	FBC, ESR, BCP, CXR	FBC, ESR, BCP at weeks 2, 4, 8, 12, then every 3 months
AZA	FBC, ESR, BCP	FBC and BCP weekly for 6 weeks, then every 2 weeks for 3 visits, then monthly
CyA	FBC, 2 × BCP, ESR, urinalysis	FBC, BCP every 2 weeks for 4 months, then BCP monthly
Etan	FBC, ESR, BCP, CXR	FBC, ESR, BCP at weeks 2, 4, 8, 12, then every 3 months
GST	FBC, ESR, BCP, urinalysis	FBC, BCP, urinalysis every week for up to 21 injections, then every 2 weeks for 3 months, then every 3 weeks for 3 months, then monthly. Treatment given by i.m. injections
HCQ	FBC, ESR, BCP	FBC, ESR, BCP every 3 months
Infl	FBC, ESR, BCP, CXR	FBC, ESR, BCP at weeks 2, 6 and every 8 weeks (at time of infusions)
LEF	FBC, ESR, BCP, urinalysis	FBC every 2 weeks for 6 months, every 8 weeks thereafter. BCP monthly for 6 months, every 8 weeks thereafter
MTX	FBC, ESR, BCP, CXR	FBC, BCP every 2 weeks for 4 months then monthly
SSZ	FBC, ESR, BCP	FBC every 2 weeks and BCP every 4 weeks for 12 weeks, then FBC and BCP every 3 months

TABLE 49 *Treatment costs*

Treatment	Start-up (£)	Annual usage (£)
Palliation	0.00	364.00
Adal	515.88	9714.84
Adal+MTX	515.88	9751.34
AZA	694.81	1380.26
CyA	350.37	2482.08
Etan	515.88	9714.84
Etan+MTX	515.88	9751.34
GST	2765.24	1581.48
HCQ	101.89	448.97
Infl	1676.14	9333.54
LEF	986.91	1211.72
MTX	512.76	1222.34
DPen	476.94	1401.77
SSZ	584.47	514.88
Combination CyA+MTX	350.37	2566.34
MTX+SSZ	584.47	1341.94
MTX+SSZ+HCQ	101.89	1346.85

All costs discounted at 6% per annum from divergence point.

Combining the above information leads to the model inputs shown in *Table 49*. It should be noted that palliation does not include hospitalisation. Hospital admissions may be higher for RA patients with no DMARD options, but no data were available as a guide.

The base model does not include costs for hospitalisation as a result of RA. This is because of wide variation in rates dictated by local facilities and practice. The ERA study shows a large range of hospitalisation for RA, but there are no data for the impact of DMARDs on hospital admission rates.[46] The effects of DMARDs on joint replacement have also not been included in the base model. Again, this is because of the absence of data on the effects of DMARDs on joint replacement rates. These uncertainties are explored later in a sensitivity analysis.

Basic mortality comes from standard life tables. A relative risk of 1.33 per unit HAQ is applied.[198] More recently, Sokka and colleagues[199] reported a risk of 2.73 per unit HAQ. The present analysis maintained the relative risk of 1.33 for the base case, but used the range from 1 to 2.73 for sensitivity analysis.

In the base case, the following assumptions were made concerning HAQ increases over time. It was assumed that patients remaining on TNF inhibitors experience a worsening (increase) in HAQ equivalent to the general population. Based on the study by Krishnan and colleagues,[200] this was set a progression of 0.03 per year, making a mean time of 4 years between each 0.125 unit increase in HAQ. It was assumed that TNF inhibitors halve the general worsening in HAQ, so that patients on palliation have a progression rate of 0.06 per year, a mean time of 2 years between each 0.125 unit increase in HAQ. For conventional DMARDs, an intermediate progression rate of 0.045 per year was assumed, a mean time of 2.7 years between each 0.125 unit increase in HAQ. These assumptions were varied in sensitivity analysis.

On quitting any treatment, it is assumed that the HAQ improvement (reduction) obtained on starting treatment is exactly reversed. For example, if the HAQ score improves from 1.25 to 0.875 on starting treatment, and the HAQ score is 1 before quitting treatment, then the HAQ score will be 1.375 after quitting. If applying this rule would take the post-treatment HAQ score above 3, then the post-treatment HAQ score is set to 3.

Quality of life (QoL) scores

Conversion from HAQ to QALYs is by the formula QoL = 0.862 – 0.327HAQ calculated from the data set supplied by Hurst, and reported in Hurst and colleagues.[201] It was assumed that start and end effects can be modelled as one-off deductions equal to 0.2 years times the change in QoL score.

QALYs are discounted at 1.5% per annum from the divergence point between strategies.

Results

The model was run for each of the strategy sets shown above. A fixed random number seed was used, and the model was run for at least 10,000 (virtual) patients. Comparisons between each pair of options can be found in the form of an ICER with a quasi-confidence interval, reflecting the sampling in running the model, not parameter uncertainty. Fixed stopping rules were used to determine whether the quasi-confidence interval was sufficiently precise, or whether the run-length needed to be increased. The definition of 'sufficiently precise' used was as follows. In cases of dominance (north-west or south-east quadrants), 95% quasi-confidence intervals for cost difference and QALY difference each had to avoid zero. In other cases, a quasi-confidence interval [lower (L), upper (U)] for the ICER had to satisfy the

following properties, according to the values of L and U:

- U < 5000 or L > 200,000: U/L < 2.5
- U < 10,000 or L > 100,000: U/L < 2.0
- U < 20,000 or L > 50,000: U/L < 1.5
- U < 30,000 or L > 30,000: U/L < 1.2
- L < 30,000 and U > 30,000: U/L < 1.1.

In cases where there were more than two options to compare, the more important comparisons are those between an option including a TNF inhibitor and the baseline without that TNF inhibitor. These are referred to as 'major comparisons'. Comparisons between different strategies including TNF inhibitors are referred to as 'minor comparisons'. Results are given for the following minor comparisons:

- effect of adding methotrexate (adalimumab plus methotrexate versus adalimumab alone, etanercept plus methotrexate versus etanercept alone)
- comparison between monotherapies (adalimumab versus etanercept alone)
- comparison between combinations with methotrexate (adalimumab plus methotrexate versus etanercept plus methotrexate versus infliximab plus methotrexate).

The model was first run with 10,000 patients. If any major comparison gave insufficiently precise results, then the number of patients was increased to 20,000, then to 40,000, then to 100,000, then to 200,000, and so on as necessary until all major comparisons gave sufficiently precise results. If any quoted minor comparison was insufficiently precise at this stage, the number of patients was increased once more. The actual number of patients modelled in each case is stated.

Base case-results

Results were obtained with base-case parameters for each of the strategy sets described above.

Single TNF inhibitor use

The base-case ICERs are summarised in *Table 50*. The full individual results for each single TNF inhibitor, used alone or with methotrexate, for each strategy are given in *Tables 51–54*.

For the HAQ improvement on starting a TNF inhibitor, the 'early RA' values were used for the strategy set involving TNF inhibitors at the start, both sets of values were used for single TNF inhibitors in third place, and the 'late RA' values were used for all other cases. When interpreting these results, it should be borne in mind that the distinction between early RA and late RA is rather arbitrary and is not always practical. Of note, patients' response to a drug or to a combination of drugs depends on their previous experience with these therapies. Patients' previous experience with methotrexate is particularly relevant here: the early RA data used in our model represent the benefit that would be expected if the patients were naïve to methotrexate or had not previously failed methotrexate treatment. The analyses using early RA data in the strategies involving TNF inhibitors combined with methotrexate as third line therapy are therefore better interpreted as sensitivity analyses that incorporated treatment benefit that is unlikely to be seen in current practice (as most patients, if not all, would have failed methotrexate before starting a TNF inhibitor as the third line treatment, according to current guidance). For TNF inhibitors used alone, the cost-effectiveness of current practice probably lies between the results in which early RA data and late RA data were used.

TABLE 50 *Summary of base-case ICERs for each TNF inhibitor (alone and with MTX)*

TNF inhibitor	Comparator	Cost per QALY (£)			First-line use (early RA)
		Usage consistent with 2002 NICE guidance			
		Third line (late RA data)	Last in strategy	Third line (using early RA data)	
Adalimumab (no MTX)	Base strategy of DMARDs with no TNF inhibitors	140,000	40,000	35,000	53,000
Etanercept (no MTX)		47,000[a]	24,000	30,000[a]	49,000
Adalimumab (with MTX)		64,000	30,000	30,000	170,000
Etanercept (with MTX)		50,000[a]	24,000	28,000	78,000
Infliximab (with MTX)		140,000[a]	38,000	30,000	650,000

[a] Reflecting current practice.

TABLE 51 *Base case: TNF inhibitors third (late RA values) (40,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	47,442	154	5.6365	0.0234
Etan	60,341	188	6.3415	0.0246
Adal+MTX	47,963	155	5.9053	0.0232
Etan+MTX	60,329	188	6.2974	0.0250
Infl+MTX	47,278	148	5.6380	0.0235
Base	16,509	36	5.4169	0.0218
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	30,934	150	0.2196	0.0224
Etan – Base	43,832	181	0.9246	0.0237
Ad+M – Base	31,454	151	0.4884	0.0226
Et+M – Base	43,821	182	0.8805	0.0241
In+M – Base	30,770	145	0.2212	0.0224
Ad+M – Adal	520	204	0.2688	0.0288
Etan – Et+M	12	243	0.0441	0.0252
Etan – Adal	12,899	225	0.7050	0.0238
Et+M – Ad+M	12,367	225	0.3920	0.0242
Ad+M – In+M	684	200	0.2673	0.0228
Et+M – In+M	13,051	221	0.6593	0.0241
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	141,000		117,000 to 177,000	
Etan – Base	47,400		45,100 to 50,000	
Ad+M – Base	64,400		58,900 to 71,000	
Et+M – Base	49,800		47,200 to 52,700	
In+M – Base	139,000		116,000 to 174,000	
Ad+M – Adal	1,940		382 to 3,490	
Etan – Et+M		Comparison is inconclusive		
Etan – Adal	18,300		17,000 to 19,800	
Et+M – Ad+M	31,500		27,900 to 36,200	
Ad+M – In+M	2,560		999 to 4,120	
Et+M – In+M	19,800		18,300 to 21,500	

QSE, quasi-standard error.
Ad, adalimumab; Et, etanercept; In, infliximab; M, methotrexate.

Sequential use of TNF inhibitors

Sequential use of TNF inhibitors was modelled with the TNF inhibitors starting as third line therapy and using the 'late RA' values for the TNF inhibitors. Base-case ICERs are summarised in *Table 55* and the individual results for the sequential use of TNF inhibitors are given in *Tables 56–64*. The results are similar to those using the 'Following TNF inhibitor' as the sole TNF inhibitor in third place as shown in *Table 51*, except that the two other TNF inhibitors are somewhat less cost-effective if used after etanercept. Similar results were obtained for TNF inhibitors as the third in the sequence.

Sensitivity analysis

Extensive sensitivity analysis has been carried out for all strategy sets involving use of a single TNF inhibitor. As in the base case, for the HAQ improvement on starting a TNF inhibitor, the early RA values were used for the strategy set involving TNF inhibitors at the start, the late RA values were used for TNF inhibitors last, and both sets of values were used for TNF inhibitors in third place. Full details of the sensitivity analysis are given in Appendix 10. Summarised forms are given in *Tables 65–68*.

Summary of model results

When the effectiveness values for early RA were used for TNF inhibitors in third place, the results for the three TNF inhibitors were broadly similar. They are sensitive to assumptions about HAQ progression while on treatment, and to assumptions about effectiveness and long-term survival on conventional DMARDs. When the effectiveness values for late RA were used instead, the results were considerably less favourable.

TABLE 52 *Base case: TNF inhibitors third (early RA values) (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	48,264	98	6.3183	0.0150
Etan	60,948	119	6.8617	0.0159
Adal+MTX	48,536	99	6.4613	0.0149
Etan+MTX	61,254	119	6.9715	0.0160
Infl+MTX	48,173	94	6.4405	0.0149
Base	16,494	23	5.3995	0.0138
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	31,770	96	0.9188	0.0148
Etan – Base	44,454	116	1.4623	0.0157
Ad+M – Base	32,042	96	1.0619	0.0148
Et+M – Base	44,761	116	1.5720	0.0157
In+M – Base	31,679	92	1.0410	0.0147
Ad+M – Adal	272	131	0.1430	0.0154
Et+M – Etan	306	155	0.1097	0.0169
Etan – Adal	12,684	144	0.5434	0.0162
Et+M – Ad+M	12,719	144	0.5101	0.0163
Ad+M – In+M	362	128	0.0208	0.0154
Et+M – In+M	13,081	142	0.5310	0.0162
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	34,600		33,500 to 35,700	
Etan – Base	30,400		29,700 to 31,100	
Ad+M – Base	30,200		29,300 to 31,100	
Et+M – Base	28,500		27,900 to 29,100	
In+M – Base	30,400		29,600 to 31,300	
Ad+M – Adal	1,900		23 to 3,780	
Et+M – Etan	Etan+MTX more effective than Etan alone; diff. cost not significant			
Etan – Adal	23,300		21,900 to 24,900	
Et+M – Ad+M	24,900		23,400 to 26,700	
In+M – Ad+M	Adal+MTX more costly than Infl+MTX; diff. QALY not significant			
Et+M – In+M	24,600		23,100 to 26,300	

When the effectiveness values for early RA were used for TNF inhibitors at the start, the results were somewhat less favourable than the results obtained using early RA values for TNF inhibitors in third place. The results for combinations with methotrexate were much worse than for monotherapy. This reflects the definition of the strategy options, in that starting with a TNF inhibitor in combination with methotrexate precludes the later use of methotrexate alone.

An important limitation of this work is the poor quality of the data on effectiveness of conventional DMARDs. It has not been possible to find data that would support quantification of a reduction in effectiveness with disease duration.

TABLE 53 *Base case: TNF inhibitors first (400,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	49,538	51	8.9674	0.0084
Etan	63,892	62	9.3005	0.0088
Adal+MTX	49,650	52	8.5176	0.0080
Etan+MTX	64,079	62	8.9408	0.0085
Infl+MTX	49,079	49	8.3682	0.0080
Base	15,331	11	8.3166	0.0079
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	34,207	50	0.6508	0.0085
Etan – Base	48,561	60	0.9839	0.0087
Ad+M – Base	34,319	51	0.2010	0.0083
Et+M – Base	48,748	61	0.6242	0.0086
In+M - Base	33,748	48	0.0516	0.0083
Ad+M – Adal	112	69	–0.4498	0.0085
Et+M – Etan	187	82	–0.3597	0.0090
Etan – Adal	14,354	76	0.3332	0.0088
Et+M – Ad+M	14,429	77	0.4232	0.0086
Ad+M – In+M	571	68	0.1493	0.0083
Et+M – In+M	15,000	75	0.5726	0.0086
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	52,600		51,200 to 54,000	
Etan – Base	49,400		48,500 to 50,300	
Ad+M – Base	171,000		158,000 to 186,000	
Et+M – Base	78,100		76,000 to 80,300	
In+M – Base	654,000		495,000 to 962,000	
Ad+M – Adal	Adal alone more effective than Adal+MTX; diff. cost not significant			
Et+M – Etan	Etan alone dominates Etan+MTX			
Etan – Adal	43,100		40,900 to 45,500	
Et+M – Ad+M	34,100		32,700 to 35,600	
Ad+M – In+M	3,830		2,820 to 4,830	
Et+M – In+M	26,200		25,400 to 27,100	

TABLE 54 *Base case: TNF inhibitors last (20,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	36,176	215	1.8631	0.0218
Etan	49,208	262	2.9877	0.0267
Adal+MTX	36,420	216	2.1607	0.0223
Etan+MTX	49,390	263	2.9836	0.0271
Infl+MTX	36,430	209	1.9166	0.0225
Base	2,857	11	1.0317	0.0182
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	33,319	213	0.8314	0.0159
Etan – Base	46,352	260	1.9560	0.0228
Ad+M – Base	33,563	214	1.1290	0.0171
Et+M – Base	46,534	260	1.9519	0.0234
In+M - Base	33,574	207	0.8848	0.0169
Ad+M – Adal	244	294	0.2976	0.0204
Et+M – Etan	182	348	–0.0041	0.0297
Etan – Adal	13,033	323	1.1246	0.0251
Et+M – Ad+M	12,970	325	0.8229	0.0264
In+M – Ad+M	11	290	–0.2442	0.0212
Et+M – In+M	12,960	318	1.0670	0.0261
Comparison	**ICER (£/QALY)**		**Quasi-CI**	
Adal – Base	40,100		38,500 to 41,800	
Etan – Base	23,700		23,100 to 24,300	
Ad+M – Base	29,700		28,800 to 30,700	
Et+M – Base	23,800		23,200 to 24,500	
In+M – Base	37,900		36,500 to 39,500	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Et+M – Etan	Comparison is inconclusive			
Etan – Adal	11,600		10,800 to 12,400	
Et+M – Ad+M	15,800		14,600 to 17,200	
In+M – Ad+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant			
Et+M – In+M	12,100		11,300 to 13,000	

TABLE 55 *Summary ICERs for sequential use of two TNF inhibitors*

First TNF inhibitor used	Following TNF inhibitor	ICER (£ per QALY)
Adal (alone)	Etan	52,000
	Infl	240,000
Etan (alone)	Adal	240,000
	Infl	190,000
Infli (with MTX)	Adal	140,000
	Etan	47,000

TABLE 56 *Second TNF inhibitor following adalimumab (40,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Etan	58,871	184	5.7622	0.0235
Infl	46,036	146	5.0558	0.0224
Base	15,972	36	4.9302	0.0206
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Etan – Base	42,899	179	0.8320	0.0231
Infl – Base	30,064	142	0.1256	0.0220
Etan – Infl	12,835	216	0.7064	0.0234
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Etan – Base	51,600		48,800 to 54,600	
Infl – Base	239,000		177,000 to 368,000	
Etan – Infl	18,200		16,900 to 19,600	

TABLE 57 *Second TNF inhibitor following etanercept (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	45,666	95	4.8230	0.0138
Infl	45,424	91	4.8559	0.0139
Base	15,653	23	4.6988	0.0129
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	30,013	93	0.1242	0.0136
Infl – Base	29,773	89	0.1571	0.0137
Adal – Infl	240	122	–0.0329	0.0138
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	242,000		198,000 to 310,000	
Infl – Base	190,000		161,000 to 230,000	
Adal – Infl	Infl more effective than Adal; diff. cost not significant			

TABLE 58 *Second TNF inhibitor following infliximab (40,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	46,365	152	5.1019	0.0223
Etan	58,844	185	5.7985	0.0237
Base	15,994	36	4.8872	0.0206
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	30,371	148	0.2147	0.026
Etan – Base	42,850	179	0.9113	0.0232
Etan – Adal	12,479	221	0.6966	0.0234
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	141,000		118,000 to 177,000	
Etan – Base	47,000		44,700 to 49,600	
Etan – Adal	17,900		16,700 to 19,400	

TABLE 59 *Third TNF inhibitor following adalimumab and etanercept (100,000 patients)*

Option	**Cost (£)**	**QSE**	**QALYs**	**QSE**
Infl	44,122	90	4.3990	0.0133
Base	15,134	23	4.3289	0.0123
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Infl – Base	28,988	87	0.0701	0.0133
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Infl – Base	414,000		300,000 to 667,000	

TABLE 60 *Third TNF inhibitor following adalimumab and infliximab (20,000 patients)*

Option	**Cost (£)**	**QSE**	**QALYs**	**QSE**
Etan	56,640	256	5.2256	0.0318
Base	1,391	50	4.4743	0.0279
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Etan – Base	41,250	248	0.7513	0.0319
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Etan – Base	54,900		50,600 to 60,100	

TABLE 61 *Third TNF inhibitor following etanercept and adalimumab (100,000 patients)*

Option	**Cost (£)**	**QSE**	**QALYs**	**QSE**
Infl	44,299	90	4.4228	0.0133
Base	15,130	23	4.3222	0.0123
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Infl – Base	29169	88	0.1006	0.0134
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Infl – Base	290,000		229,000 to 395,000	

TABLE 62 *Third TNF inhibitor following etanercept and infliximab (100,000 patients)*

Option	**Cost (£)**	**QSE**	**QALYs**	**QSE**
Adal	44,497	94	4.3904	0.0131
Base	15,130	23	4.3231	0.0123
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	29,367	92	0.0673	0.0132
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	437,000		313,000 to 720,000	

TABLE 63 *Third TNF inhibitor following infliximab and adalimumab (20,000 patients)*

Option	**Cost (£)**	**QSE**	**QALYs**	**QSE**
Etan	56,788	257	5.2257	0.0318
Base	15,434	50	4.4850	0.0280
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Etan – Base	41,354	248	0.7407	0.0319
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Etan – Base	55,800		51,400 to 61,100	

TABLE 64 *Third TNF inhibitor following infliximab and etanercept (10,000 patients)*

Option	**Cost (£)**	**QSE**	**QALYs**	**QSE**
Adal	44,336	66	4.3794	0.0093
Base	15,122	16	4.3218	0.0087
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	29,214	64	0.0577	0.0093
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	506,000		383,000 to 749,000	

TABLE 65 *Sensitivity analyses: TNF inhibitors at the start*

Scenario	Adal – Base	Etan – Base	Adal+MTX – Base	Etan+MTX – Base	Infl+MTX – Base
Base case	52,600	49,400	171,000	78,100	654,000
No HAQ progression on TNF inhibitors	27,000	23,500	37,600	28,000	46,100
Slow HAQ progression on all DMARDs	108,000	89,500	Base	613,000	Base
Slow HAQ progression on all treatments	122,000	109,000	Base	645,000	Base
Fast HAQ progression on all treatments	92,500	99,500	Base	343,000	Base
No effect of HAQ on mortality	50,500	46,500	211,000	80,700	1,910,000
Mortality ratio 2.73 per unit HAQ	62,300	55,300	125,000	77,400	433,000
Effectiveness of conventional DMARDs down 50%	34,700	30,400	39,300	32,100	44,600
Effectiveness of conventional DMARDs up 50%	115,000	119,000	Base	Base	Base
Survival times on conventional DMARDs down 50%	40,300	36,900	104,000	55,600	227,000
Survival times on conventional DMARDs up 50%	60,500	56,900	151,000	86,800	605,000
Survival times on TNF inhibitors down 50%	53,400	48,300	Base	177,000	Base
Survival times on TNF inhibitors up 50%	54,900	50,700	92,300	66,800	166,000
Review at 12 weeks	53,500	48,900	195,000	81,500	2,190,000
Short-term quitters on TNF inhibitors down 50%	56,000	50,400	167,000	79,600	833,000
Short-term quitters on TNF inhibitors up 50%	50,500	48,100	161,000	75,700	518,000
Short-term quitters on conventional DMARDs down 50%	53,400	49,500	139,000	74,700	345,000
Short-term quitters on conventional DMARDs up 50%	50,800	47,000	198,000	79,800	2,950,000
Include offset costs	53,100	48,100	166,000	77,900	827,000

Base: baseline option dominates option with TNF inhibitor.

TABLE 66 *Sensitivity analyses: TNF inhibitors in third place, early RA values*

Scenario	Adal – Base	Etan – Base	Adal+MTX – Base	Etan+MTX – Base	Infl+MTX – Base
Base case	34,600	30,400	30,200	28,500	30,400
No HAQ progression on TNF inhibitors	21,200	18,700	19,100	17,800	19,500
Slow HAQ progression on all DMARDs	43,000	38,800	36,300	36,000	39,000
Slow HAQ progression on all treatments	54,600	45,600	43,200	42,000	45,300
Fast HAQ progression on all treatments	49,400	45,200	40,500	41,000	42,100
No effect of HAQ on mortality	32,200	29,200	28,400	27,400	29,200
Mortality ratio 2.73 per unit HAQ	36,100	31,400	31,000	29,400	31,200
Effectiveness of conventional DMARDs down 50%	26,600	22,600	23,100	22,100	24,300
Effectiveness of conventional DMARDs up 50%	49,600	43,400	40,200	39,000	41,300
Survival times on conventional DMARDs down 50%	27,800	24,900	25,100	23,800	25,200
Survival times on conventional DMARDs up 50%	39,200	34,400	34,300	33,400	34,300
Survival times on TNF inhibitors down 50%	36,700	32,000	32,200	29,600	33,400
Survival times on TNF inhibitors up 50%	33,200	29,800	28,200	27,700	28,800
Review at 12 weeks	33,700	30,400	29,700	28,500	30,300
Short-term quitters on TNF inhibitors down 50%	35,300	30,800	30,700	29,000	31,300
Short-term quitters on TNF inhibitors up 50%	33,800	30,500	29,200	28,300	30,200
Short-term quitters on conventional DMARDs down 50%	34,100	30,800	29,900	28,300	30,900
Short-term quitters on conventional DMARDs up 50%	32,500	29,100	28,600	27,300	28,900
Include offset costs	32,400	28,900	28,100	27,100	28,400

TABLE 67 *Sensitivity analyses: TNF inhibitors in third place, late RA values*

Scenario	Adal – Base	Etan – Base	Adal+MTX – Base	Etan+MTX – Base	Infl+MTX – Base
Base case	141,000	47,400	64,400	49,800	139,000
No HAQ progression on TNF inhibitors	41,500	24,400	30,200	24,600	39,400
Slow HAQ progression on all DMARDs	535,000	68,500	101,000	69,600	462,000
Slow HAQ progression on all treatments	Base	90,200	150,000	93,300	Base
Fast HAQ progression on all treatments	Base	95,400	147,000	96,100	Base
No effect of HAQ on mortality	97,700	43,300	53,800	43,900	92,900
Mortality ratio 2.73 per unit HAQ	680,000	53,000	84,400	53,400	329,000
Effectiveness of conventional DMARDs down 50%	58,400	31,200	40,500	31,600	56,900
Effectiveness of conventional DMARDs up 50%	Base	87,500	136,000	90,700	Base
Survival times on conventional DMARDs down 50%	66,700	34,200	42,300	35,000	61,900
Survival times on conventional DMARDs up 50%	324,000	57,900	84,600	59,700	246,000
Survival times on TNF inhibitors down 50%	120,000	46,400	62,300	46,600	124,000
Survival times on TNF inhibitors up 50%	149,000	47,700	63,200	48,900	130,000
Review at 12 weeks	145,000	47,000	62,800	48,200	125,000
Short-term quitters on TNF inhibitors down 50%	134,000	45,800	64,200	48,800	115,000
Short-term quitters on TNF inhibitors up 50%	151,000	47,100	59,400	48,100	135,000
Short-term quitters on conventional DMARDs down 50%	165,000	48,900	60,700	48,700	132,000
Short-term quitters on conventional DMARDs up 50%	99,200	42,800	55,600	43,800	94,600
Include offset costs	135,000	45,400	60,300	46,600	116,000

Base: baseline option dominates option with TNF inhibitor.

TABLE 68 *Sensitivity analyses: TNF inhibitors in last place*

Scenario	Adal – Base	Etan – Base	Adal+MTX – Base	Etan+MTX – Base	Infl+MTX – Base
Base case	40,100	23,700	29,700	23,800	37,900
No HAQ progression on TNF inhibitors	27,100	18,100	22,100	18,000	25,700
Slow HAQ progression on all DMARDs	39,500	24,400	30,500	24,900	37,600
Slow HAQ progression on all treatments	64,100	33,400	43,000	34,000	60,500
Fast HAQ progression on all treatments	58,300	30,300	39,400	30,000	53,300
No effect of HAQ on mortality	40,100	23,200	30,000	23,400	38,600
Mortality ratio 2.73 per unit HAQ	37,500	23,000	29,500	23,100	34,900
Effectiveness of conventional DMARDs down 50%	39,500	23,900	29,800	23,800	37,400
Effectiveness of conventional DMARDs up 50%	38,900	23,600	29,400	23,900	38,200
Survival times on conventional DMARDs down 50%	38,500	23,700	28,900	24,000	37,700
Survival times on conventional DMARDs up 50%	39,500	23,700	30,300	23,600	38,800
Survival times on TNF inhibitors down 50%	43,800	24,700	32,800	25,700	43,500
Survival times on TNF inhibitors up 50%	37,200	22,800	28,900	23,000	36,600
Review at 12 weeks	39,700	23,300	29,400	23,900	37,800
Short-term quitters on TNF inhibitors down 50%	40,800	23,900	30,200	24,100	38,400
Short-term quitters on TNF inhibitors up 50%	39,000	23,400	29,400	23,700	37,400
Short-term quitters on conventional DMARDs down 50%	39,300	23,500	29,500	23,800	37,400
Short-term quitters on conventional DMARDs up 50%	38,300	23,900	29,800	24,000	36,500
Include offset costs	38,400	22,300	27,900	22,400	36,100

Chapter 5

Implications for other parties

The substantial economic impact of RA in terms of direct and indirect costs has been highlighted elsewhere in this report. Studies indicate a great range of potential costs that cannot readily be explained by socioeconomic or clinical factors. However, it is apparent that a minority of patients may account for a great proportion of the direct medical costs. Costs incurred by individuals, in a cohort of early arthritis patients, are similar to costs incurred by healthcare services. Costs incurred by family and friends in terms of forgone paid work, forgone leisure time and other factors greatly exceed costs incurred by individuals and healthcare services. Clearly, this could have an impact on the quality of life of patients and carers. Further, physical disability resulting in difficulties in self-care, and work disability has implications for PSS.

Chapter 6

Factors relevant to the NHS

Since the last NICE guidance the use of TNF inhibitors to treat RA has become established practice in rheumatology in the UK. Use of infliximab requires day-case facilities by rheumatology departments because it is given intravenously. At present, there is great variation in use of day-case facilities by rheumatologists, determined in part by local resources of inpatient and outpatient facilities. Widespread use of adalimumab and etanercept places a greater demand on outpatient facilities and requires greater involvement of outpatient nurses in order that patients and carers may be taught to self-administer injections, and to provide back-up in case of difficulties and disease and drug monitoring services. Again, there are great variations in use of nurse specialists in rheumatology and relatively few training opportunities for nurses wishing to specialise in this area. However, increasing use of DMARDs has led to an increasing requirement for specialised nurses.

The long-term impact of TNF inhibitors on joint failure and the likelihood of orthopaedic surgery cannot be demonstrated directly at present because the agents are still relatively new. Surrogate end-points such as radiographic change suggest potentially important benefits, and potentially a reduced demand for surgery, but the clinical relevance of reported radiographic changes is debated.[45]

Finally, issues of equity have been highlighted by the wide variation in availability of TNF inhibitors across the UK, and these have continued despite NICE guidance.

Chapter 7
Discussion

Summary

Effectiveness: principal findings

- All the TNF inhibitors were effective treatments for patients with RA.
- For patients who were naïve to methotrexate, adalimumab monotherapy was marginally less effective and etanercept monotherapy was marginally more effective than methotrexate.
- Combination of a TNF inhibitor with methotrexate was more effective than methotrexate alone in patients naïve to methotrexate.
- An increased risk of serious infections cannot be ruled out for infliximab and adalimumab plus methotrexate.

Cost-effectiveness: principal findings

- Last active therapy in sequence:
  - TNF inhibitors are most cost-effective when used last
  - the ICER for etanercept used last is £24,000 per QALY and substantially lower than the ICERs for adalimumab (£30,000 per QALY) or infliximab (£38,000 per QALY).
- Third-line use (as recommended in the 2002 NICE guidance):
  - gives ICERs around £30,000 per QALY using early RA effectiveness data
  - gives ICERs of around £50,000 per QALY for etanercept (with or without methotrexate) using late RA data
  - ICERs for adalimumab and infliximab are somewhat higher using late RA data.
- First-line use:
  - gives ICERs around £50,000 per QALY for adalimumab and etanercept monotherapy
  - much higher ICERs for combinations including methotrexate as first-line therapy.
- Sequential use:
  - similar results to use of the equivalent TNF inhibitor as sole TNF inhibitor in the sequence
  - ICERs for adalimumab and infliximab increased somewhat if used after etanercept.

Principal findings

The key findings of this review were as follows.

Quality and quantity of evidence

Twenty-nine RCTs (nine adalimumab, 11 etanercept and nine infliximab), including ten trials reviewed in the previous assessment report,[1] were included in this review. The trials were generally of high quality and recruited a total of 9939 patients. Five of the trials[102,123,135,140,141] recruited exclusively RA patients with short disease duration (≤ 3 years). In addition, the BeSt study is described and discussed in this review in view of its novel approach and clinical relevance, although it does not strictly meet the inclusion criteria.

Head-to-head comparisons

Only a small number of included RCTs looked at head-to-head comparisons of TNF inhibitors with methotrexate: ERA[123] and TEMPO[127] for etanercept and PREMIER[102] for adalimumab. No identified RCT directly compared a TNF inhibitor with a conventional DMARD other than methotrexate. BeSt is the only RCT that compares different sets of sequential treatments in early RA patients.

In the PREMIER trial,[102] adalimumab alone (at licensed dose) was marginally less effective than methotrexate in controlling the symptoms of RA in patients who were naïve to methotrexate, and was associated with slight, but not significant, increase in SAEs (RR **[Commercial-in-confidence information removed]**). The only advantage of adalimumab monotherapy over methotrexate was a reduction in radiographic joint damage. The results are reflected in the extension of marketing authorisation for adalimumab recently issued by the EMEA,[67] which recommended the use of adalimumab in combination with methotrexate, rather than adalimumab alone, in early RA patients.

Etanercept alone (at licensed dose) was as effective or slightly more effective than methotrexate in controlling RA symptoms and retarding joint damage in patients who were naïve to or who had no treatment failure with methotrexate in the ERA[123] and TEMPO[127] trials. Although the mean disease duration for the patients was only 1 year in the ERA trial, compared with over 6 years in the TEMPO, the results from these two studies are remarkably similar, with no statistical

heterogeneity found between the studies in any of the outcomes being meta-analysed. Subgroup analyses within TEMPO also indicated that treatment effects do not vary substantially between early RA and late RA patients.

TEMPO was unique in that it was the only trial that allowed head-to-head comparison between a TNF inhibitor and methotrexate, in a population that included both early RA and established RA. While it provides useful insight in many aspects, the generalisability of the results, at least in the UK, is not clear. In this trial half of the patients were reported as having previously received methotrexate without toxicity or lack of efficacy and yet these patients had not been treated with methotrexate for at least 6 months before the study. Such patients are uncommon in real practice. Consequently, the use of results from this trial in the economic model to give an estimate of improvement with the use of the combination of etanercept plus methotrexate in established RA, would exaggerate the treatment benefit as most real patients would have failed treatment with methotrexate at this stage.

TNF inhibitors versus placebo

The majority of RCTs included in this review compared TNF inhibitors with placebo. Adalimumab, etanercept and infliximab are all effective treatments, compared with placebo, in terms of improving symptoms of the disease and preventing radiographic damage due to disease. The relative risk for ACR20 for etanercept versus placebo showed a decreasing pattern in trials in which patients: (1) were not receiving any concurrent DMARDs; (2) were receiving concurrent DMARDs which had failed to provide adequate disease control; and (3) were receiving concurrent, newly initiated methotrexate (see *Figure 24*, p. 48). This reflects increasing response rates in the control (placebo) arms rather than differential response rates in the intervention (etanercept) arms. Statistically significant differences were found in most of the efficacy outcomes (but not necessarily safety outcomes) between (3) and the other two analyses. This confirmed the importance of separating comparisons in which newly initiated methotrexate was involved. The difference between (1) and (2), however, was only marginal (test for heterogeneity $p = 0.10$). This is consistent with the suggestion that the presence or absence of concurrent DMARDs that had failed to provide adequate control of disease activity does not have a significant influence on the treatment effect of adalimumab or etanercept. Further observations from direct comparison within etanercept trials, in Codreanu[103] (replacing ongoing sulfasalazine with etanercept or adding etanercept to ongoing sulfasalazine) and ADORE[107] (replacing ongoing methotrexate with etanercept or adding etanercept to ongoing methotrexate) are also consistent with this interpretation: there were generally no significant differences between etanercept-alone arms and combination arms in efficacy and safety outcomes in these two trials. No adalimumab trial allowed such observation, and the current licence stipulates that adalimumab should be given in combination with methotrexate unless it is not tolerated, possibly on the basis that the absolute improvement observed in adalimumab trials was larger when adalimumab was given with methotrexate.

The pooled risk of malignancies for adalimumab compared with placebo approached statistical significance in the meta-analysis. Malignancies were also observed more frequently in infliximab-treated patients in placebo-controlled trials. While these findings were based on a small number of cases and do not appear to be supported by observational studies, continuous vigilance regarding this potential adverse effect is warranted. Observational studies published to date have compared the incidence of malignancies for TNF inhibitor-treated patients with either the incidence observed in general population or that observed in cohorts of RA patients. Comparisons have ignored the well-known 'healthy patient' effect of trials and, indeed, patients who entered trials of TNF inhibitors or who received TNF treatment in practice were a subgroup of RA patients in which patients with risk factors associated with malignancies (such as past history of malignancy; chronic obstructive pulmonary disease, viral hepatitis and HIV infection) were excluded. The patients who received TNF inhibitors in observational studies were therefore likely to have a lower risk of malignancies (with the exception of lymphoma) compared with general population or general RA population. Future observational studies should attempt to adjust for such potential confounding.

TNF inhibitor plus methotrexate versus methotrexate

Four trials[102,127,135,141] compared the combination of a TNF inhibitor plus methotrexate with methotrexate alone in patients naïve to methotrexate or patients who did not have a history of treatment failure with methotrexate. The combinations were significantly more effective than methotrexate alone for all three TNF

inhibitors, although the incremental benefits were significantly smaller (with the exception of joint damage) than those observed in comparisons between TNF inhibitors and placebo. Combination of infliximab and methotrexate in this context was associated with increased risk of serious infection, and a similar, non-significant trend (which may be due to insufficient statistical power) was observed for adalimumab. No trials have compared a combination of methotrexate with a conventional DMARD to the combination of methotrexate with a TNF inhibitor.

Overall effectiveness and safety

At the licensed dose the NNTs (95% CI) required to produce an improvement in ACR20 response in comparison with placebo are: adalimumab 3.6 (3.1 to 4.2), etanercept 2.1 (1.9 to 2.4), infliximab 3.2 (2.7 to 4.0). While these are favourable NNTs for medical interventions, they also emphasise the importance of direct comparisons between DMARDs in estimating the ICER of new treatments for RA.

The NNT figures appear to be slightly in favour of etanercept. Indirect comparisons of agents should be interpreted with caution, however, given the potential differences in patient populations, study design and method of analysis across trials. This is particularly the case when using NNTs with a metric like the ACR response. Not only do ACR responses have a ceiling effect, but the absolute health gain obtained from achieving a positive ACR response is a function of the baseline health status of patients. Truly fair and unbiased comparisons can only be made through direct comparisons of TNF inhibitors in trials and these are urgently needed.

An important clinical difference between the included trials is whether patients recruited were concurrently receiving newly initiated methotrexate in both intervention and control arms. The relative risks of achieving ACR response (TNF inhibitor plus methotrexate versus methotrexate alone) were, perversely, larger in trials in which patients were no longer responding to methotrexate than in trials where patients had not previously received methotrexate or had not failed to respond previously. For example, pooled RRs for ACR70 for methotrexate plus TNF inhibitor versus methotrexate alone range from 3.16 (infliximab) to 9.44 (etanercept) in trials of methotrexate partial or non-responders; these are reduced to a range from 1.57 (infliximab) to 2.53 (etanercept) in trials of methotrexate-naïve patients or responders. This is largely due to the fact that the response rates in the methotrexate arm were much higher in the latter trials. When interpreting these results, it is important to take into account the absolute risk differences between treatment groups, which are reflected in NNTs.

Methodology

In this systematic review, results were pooled from the end of trials irrespective of the duration of follow-up. This was done to maximise the number of studies and to increase the statistical power of meta-analyses. The authors acknowledge that it may, on occasion, be preferable to pool results with similar duration of follow-up when there is evidence that the effect size of the treatment varies over time. Nevertheless, statistical heterogeneity in the end-of-trial results between studies was not found for the majority of analyses that were carried out. Where heterogeneity was observed, the differences in the duration of follow-up do not usually explain the heterogeneity, except for the single case of Keystone[129] in the analysis of etanercept versus placebo. This 8-week study is the only trial included in the meta-analyses with a duration of less than 12 weeks. Its short duration might explain the smaller RR observed for ACR50 and ACR70 compared with other etanercept trials.

As the duration of trial increases, the influence of imputation methods used to deal with missing data (e.g. last observation carried forward or assuming that all withdrawals were non-responders) becomes greater. This is because losses to follow-up and withdrawals increase as study length increases. The impact is difficult to assess, however, as results obtained using different analytical methods are rarely reported together.

The differential withdrawal and follow-up between treatment groups, particularly in placebo-controlled trials, makes the assessment of adverse events difficult. The quality of reporting adverse events in published papers needs to be improved but, commonly, cause and effect relationships are difficult to determine.[35] Skin carcinomas, for example, were omitted from the reporting of malignancy in several trials. Trials lack power to identify potentially important toxicities, and although postmarketing surveillance through databases such as the BSRBR can be useful in detecting rarer adverse events, such large-scale studies are resource intensive, depend on the goodwill of many specialists and raise important concerns about data quality and ownership.

Results of modelling

The results of the economic evaluation using BRAM generally reflect the patterns observed in the review of clinical effectiveness. The estimated ICER for etanercept used as third-line treatment compared with base case, is somewhat more favourable than the previous estimate (£48,000 per QALY and £83,000 per QALY, respectively). This is because the model now gives some lasting benefit to effective treatments after their withdrawal. The additional evidence available and improvements in the economic model mean that the ICER for infliximab as a third-line agent has changed from £115,000 per QALY to £139,000 per QALY. In particular, an estimated mean HAQ improvement of 0.6 (derived from a personal communication) was used in the first evaluation, whereas a mean improvement of 0.4, based on empirical data from ATTRACT, was used in this evaluation. This outweighs the incorporation of some lasting benefit to infliximab treatment.

When used alone as third-line treatment, the modelling results for adalimumab and etanercept using 'early RA' data are much more favourable than the results using 'late RA' data. The evidence about whether HAQ improvements tend to be smaller in patients with longer disease duration was inconsistent in the trials. Nevertheless, given equal change in absolute HAQ score on treatment, the improvement in early RA patients (who tend to have better HAQ scores to start with) will give a larger relative improvement. This effect is reflected in the current version of the BRAM, which modelled HAQ improvement using a multiplier for each treatment and the individual patient's baseline HAQ score, rather than using a fixed average HAQ change for all patients.

Compared with etanercept alone, concurrent use of methotrexate makes little difference in cost-effectiveness when etanercept is used as third-line treatment. Concurrent use of methotrexate improved the cost-effectiveness of adalimumab as third-line treatment.

The modelling results for TNF inhibitors combined with methotrexate as third-line therapy using 'early RA' data demonstrate that use of inappropriate estimates of treatment effect (assuming that the HAQ improvement for combination therapy in patients who were naïve to methotrexate or who had not failed methotrexate can be applied to patients who had failed methotrexate treatment) can produce ICERs that are misleadingly low.

The BRAM produces ICERs in the region of £50,000 per QALY for monotherapy with a TNF inhibitor as first-line treatment. Combination with methotrexate makes the results less favourable to TNF inhibitors in cost-effectiveness terms. This appears to be because, although the combination has better effectiveness than monotherapy in itself, the use of the combination precludes subsequent use of methotrexate (which is cheap).

The more favourable ICERs for TNF inhibitors used as last active therapy (compared with palliation) and less favourable ICERs for TNF inhibitors used as first-line treatment (compared with methotrexate) highlight the importance of using appropriate comparators in economic evaluation. Such comparators should reflect treatment options relevant to a patient's disease stage.

Assumptions, limitations and uncertainties

Strengths

Strengths of this review include:

- A comprehensive search strategy to identify all relevant evidence already within the public domain was undertaken.
- Additional information, not previously available, was provided by industry and lead researchers.
- There was a substantial number of trials for each agent, which generally showed consistent results.
- Trials were mainly well conducted.
- Clinical expert input at an early stage ensured that a clinically relevant perspective was maintained throughout.
- Data were available from the BSRBR and GPRD that were not available in the first review.
- The BRAM has been in the public domain for some time and subject to scrutiny and a number of improvements. A meeting was held with all three manufacturers before undertaking the report to ensure that there were no concerns about fundamental errors within the model and general agreement about the direction of proposed further development.

Limitations and uncertainties include:

- There is a potential for bias through unblinding in TNF inhibitor studies, as infusion and injection-related adverse events are more frequent with active therapy. Unblinding of physician or patient has been demonstrated to

introduce bias which generally exaggerates the treatment effect.
- This review primarily focuses on evidence from RCTs, which, so far, have insufficient numbers of patients and follow-up time to detect rare but potentially SAEs. Some of the non-statistically significant trends in adverse events identified in this review therefore warrant close monitoring when new trial evidence becomes available. For example, for all three TNF inhibitors, a similar non-significant trend for increased SAEs was found for TNF inhibitors combined with methotrexate compared with methotrexate alone in patients who were naïve to methotrexate. Pooling the data for all three agents showed that SAEs just approached statistical significance (RR **[Commercial-in-confidence information removed]**). Using methods specific for analysing data of sparse events, Bongartz and colleagues demonstrated a statistically significant increase in the risk of malignancies associated with higher doses of adalimumab and infliximab.[202] The analysis was based on similar (but fewer) trials to those included in this review. Data from adalimumab and infliximab trials in both early and late RA patients were combined in this analysis.
- It is commendable that all the manufacturers made available the clinical study reports of their major trials in the technology appraisal process. This allowed the reviewers to include unpublished data. Substantial information from adalimumab trials and some information from infliximab trials, however, was regarded by manufacturers as confidential, despite repeated requests to reconsider. Therefore, important data on SAEs had to be removed from this report, and readers are urged to interpret data in the relevant sections with care.

Assumptions relating to the economic analyses are described in detail in the section 'Economic analysis used in this report' (p. 86). However, key limitations include:

- The BRAM assumes that if patients continue on a DMARD it remains effective. Patients and clinicians are aware of the limitations and flaws of such an assumption.[203]
- The evidence concerning how long patients remain on treatment is uncertain and data were used from observational cohorts studying drug survival with particular DMARDs to determine when lack of effectiveness or toxicity causes a change in treatment.
- The evidence about how long patients remain on TNF inhibitors is also uncertain. Data from the BSRBR about drug-survival for the different TNF inhibitors were not used because of uncertainty about their validity: constraints imposed by national guidance on the use of TNF inhibitors mean that data may not be accurately recorded and there has been no audit or validation of the registry data.
- The drug survival curves for 6, 12 and 18 months in the BSRBR show different patterns of patients remaining on each TNF inhibitor during the first 6 months of treatment, suggesting a cohort effect, possibly caused by changing use of these drugs, which needs to be investigated and explained and which adds to the uncertainty about how long patients will remain on treatment.
- This report explored the strategies of using either TNF inhibitor alone or combination therapy (TNF inhibitor plus methotrexate) as the first-line treatment for early RA patients and incorporated data on HAQ improvement from relevant clinical trials. There were insufficient data to distinguish survival on treatment between these two strategies and thus a common data set for withdrawal was used. This may potentially underestimate the treatment benefit of combination therapy, if the combination therapy is better than monotherapy. The impact is probably greater for adalimumab than for etanercept: in the PREMIER trial the combination therapy was better than adalimumab alone, whereas in TEMPO continuation on the drug appeared to be similar between these two strategies.
- Adalimumab was only modelled at 40 mg every other week using associated costs. In the PREMIER trial the dose could be increased (dosing interval reduced) to 40 mg weekly. Since the data from PREMIER were used in the 'early RA' scenario in the model, the treatment benefit may have been overestimated and the costs underestimated.
- By using an NHS and PSS perspective, as required by NICE, the BRAM significantly underestimates the potential economic advantages of effective disease control since costs incurred by families and carers are substantial.
- Strategies for treating RA are potentially very complex. For reasons of feasibility only the most common strategies were modelled. The model is based on the saw-tooth strategy, in which there is continued or serial use of one or multiple DMARDs. While this approach appears to reflect and be effective in clinical practice,[38] there are limited long-term data on optimum strategies for treating RA, although recent data,

for example from BeSt, described in this report, suggest that alternative approaches may be more effective.

Implications for research

- Direct comparative RCTs of TNF inhibitors against each other and against other DMARDs are needed.
- Trials of different anti-TNFs in patients who have failed a previous TNF inhibitor are also needed.
- Longer term studies of the QoL in patients with RA and the impact of DMARDs and other interventions on QoL are needed.
- Longer term studies or follow-up, directly assessing the impact of DMARDs, including TNF inhibitors, on joint replacement, other disease and drug-related morbidity, and mortality, are required.
- Continued vigilance about the potential harms of TNF inhibitors is necessary and work is needed to improve the assessment of cause and effect relationships in patients who experience adverse effects, especially as RA itself can cause multisystem disease.[35]

Chapter 8
Conclusions

Adalimumab, etanercept and infliximab are effective treatments compared with placebo for RA patients who are not well controlled by conventional DMARDs, improving control of symptoms, improving physical function and slowing radiographic changes in joints. When used alone, adalimumab is marginally less effective and etanercept is marginally more effective than methotrexate, in methotrexate-naïve patients. The combination of a TNF inhibitor with methotrexate was more effective than methotrexate alone in this population, although the clinical relevance of this additional benefit is yet to be established, particularly in view of the well-established effectiveness of methotrexate alone. In addition, an increased risk of serious infection cannot be ruled out for the combination of methotrexate with adalimumab and infliximab.

Results of published economic evaluations vary: some analyses suggest that the use of TNF inhibitors may fall within the usual acceptable cost-effectiveness ranges, whereas others report very high ICERs. Although most are of high quality, none of them used all of the appropriate parameters, effectiveness data, perspective and comparators required to make their results generalisable to the NHS context. The societal perspective generates more favourable ICERs. All economic evaluations submitted by the manufacturers report ICERs that fall within the currently accepted thresholds of cost-effectiveness. However, these models make assumptions and use data that favour the TNF inhibitor being evaluated, the appropriateness of which can be questioned.

The results of the economic evaluation based on BRAM are consistent with the observations from the review of clinical effectiveness, including the ranking of treatments. TNF inhibitors are most cost-effective when used as last active therapy, with the ICER for etanercept (£24,000 per QALY) being significantly lower than the ICERs for adalimumab (£30,000 per QALY) or infliximab (£38,000 per QALY). Other things being equal, etanercept would be, therefore, the TNF inhibitor of choice. However, the most appropriate choice of TNF inhibitor may also depend on patient preference as to route of administration.

The next most cost-effective use of TNF inhibitors is third line, as recommended in the 2002 NICE guidance, which gives ICERs around £30,000 per QALY using early RA effectiveness data. Using data for late RA, however, gives an ICER of around £50,000 per QALY for etanercept, with higher figures for adalimumab and infliximab. First-line use gives ICERs around £50,000 per QALY for adalimumab and etanercept as monotherapies, with much higher figures for combinations with methotrexate.

This study only modelled sequential use of TNF inhibitors with the TNF inhibitors starting as third-line therapy and using the late RA values for the TNF inhibitors. The results are similar to those using the given TNF inhibitor as the sole TNF inhibitor in third place, except that the two other TNF inhibitors are somewhat less cost-effective if used after etanercept.

Direct head-to-head trials of DMARDs and the TNF inhibitors are needed to establish with more certainty the relative values of the different agents. Longer term follow-up and postmarketing surveillance are needed to ascertain the true risk of adverse events.

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Contribution of authors

Pelham Barton (Lecturer in Mathematical Modelling) constructed and analysed the new version of the Birmingham Rheumatoid Arthritis Model (BRAM), drafted the section of the report relating to the BRAM, responded to peer review, and read and edited the draft report. Stirling Bryan (Professor in Health Economics) selected studies from the searches for published economic analyses, contributed to the economics review, review of submissions from industry, development of model structure and unit cost data collection, and edited the report. Amanda Burls (Senior Clinical Lecturer in Public Health and Epidemiology) was the senior reviewer on this report and provided project management and advice on all aspects of the report, participated in data extraction and analyses, drafted the results section, summary and discussion, compiled and edited the draft report, and takes final responsibility for the whole report. Yen-Fu Chen (Systematic Reviewer) was the main reviewer on this report and maintained day-to-day running of the review. He compiled the study protocol, carried out study selection and data extraction (mainly for etanercept and infliximab), and conducted meta-analyses. He also drafted the following sections: methods, narratives for included trials, and part of the results and discussion, and edited the report. Wendy Clark (Information Pharmacist) applied the inclusion and exclusion criteria, was involved in data extraction principally for adalimumab, and commented on the draft report. Anne Fry-Smith (Information Specialist) devised and implemented search strategies for bibliographic databases, drafted the searching methods section and commented on the draft report. Paresh Jobanputra (Consultant Rheumatologist) drafted the introduction, assisted with study selection, extracted data from some studies, contributed to the development of the economic model, identified data sources for parameters for the model, edited the report and responded to peer-review comments. Sue Jowett (Health Economist) wrote the review of existing economic evaluations.

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Appendix 1

Details of key outcomes used in RA trials

The Health Assessment Questionnaire (HAQ)

The HAQ now comprises a family of questionnaires designed to assess the functional capacity of patients with musculoskeletal complaints and specifically RA. The most widely used HAQ is derived from the Stanford Health Assessment Questionnaire[204] and consists of two or three questions in eight categories:

- Dressing and grooming: dress yourself, including doing shoelaces, and shampoo your hair
- Rising: from an armless chair and in and out of bed
- Eating: being able to cut meat, lift a full cup or glass to the mouth, and open a new carton of milk
- Walking: outdoors on flat ground and climb five steps
- Hygiene: wash and dry entire body, take a bath, get on and off the toilet
- Reaching: reach and get down a 5-lb object, bend down and pick up clothing
- Grip: open car doors, open previously unopened jars, turn taps on and off
- Activities: run errands and shop, get in and out of car, do chores.

The score from the most limited activity in each category is obtained. Each category is scored 0 (without any difficulty), 1 (with some difficulty), 2 (with much difficulty) or 3 (unable to do). Use of aids or devices to help with function is taken into account, so that the need for such assistance automatically scores 2 (unless 3 has been ticked). The maximum score in each of the eight categories is added to give a maximum possible score of 24. This total score may be divided by 8 to give an average value in the range 0–3.

HAQ has several modifications:[205]

- Modified HAQ (MHAQ): a shortened version of HAQ which uses only one question in each of the eight categories and does not consider the use of aids and devices to assist function. It is simpler to score and has the same range as HAQ (0–3).
- RA-HAQ: another shortened version of HAQ designed to overcome some of the metric limitations of MHAQ. .
- DHAQ: uses the original eight categories of HAQ, but is based on the most difficult items in each of the categories. Neither the RA-HAQ nor DHAQ has been widely used, unlike MHAQ.

American College for Rheumatology response criteria[206]

To achieve an ACR20 response a 20% improvement in the score for tender joints and a 20% improvement in swollen joints is necessary, and 20% improvement in at least three of the following:

- global disease activity assessed by observer
- global disease activity assessed by patient
- patient assessment of pain
- physical disability score (e.g. HAQ)
- acute-phase response (e.g. ESR or CRP).

Responses may also be defined as ACR50 (50%) or ACR70 (70%) depending on the degree of benefit.

ACR-N is an extension of the ACR response criteria, and is defined as the lowest of the following three values:

- percentage change in the number of swollen joints
- percentage change in the number of tender joints
- the median of the percentage change in the other five measures listed above.

It is thus a continuous variable. For example, an ACR-N of 38 means an improvement of at least 38% in tender and swollen joint counts and an improvement of at least 38% in three of the five other parameters.[207] The ACR-N has been adopted in some clinical trials, such as the ERA study[123] without prior validation; its advantages and disadvantages have recently been debated.[207,208]

Disease Activity Score (DAS)

Original DAS

DAS = $0.54(\sqrt{\text{RAI}}) + 0.065$(total number of swollen joints out of 44) + 0.33(ln ESR) + 0.0072 (patient general health score where 0=best, 100=worst)

where RAI refers to a graded score of joint tenderness for 53 joints, known as the Ritchie Articular Index.

DAS based on 28 joint evaluations

DAS 28-4 = $0.56(\sqrt{\text{TJC28}}) + 0.28(\sqrt{\text{SJC28}}) + 0.7\ln(\text{ESR}) + 0.014$ (patient general health score where 0=best, 100=worst)

where TJC is tender joint count and SJC is swollen joint count. Where scores for general health are not available, or not measured, the following formula is used:

DAS 28-3 = $[0.56(\sqrt{\text{TJC28}}) + 0.28(\sqrt{\text{SJC28}}) + 0.7\ln(\text{ESR})]1.08 + 0.16$

Radiographic assessment methods[209]

Sharp score

The simplified Sharp system,[210] which evaluates hand and wrist images, assesses 17 areas for erosions and 18 areas for joint space narrowing. Each joint is scored on a six-point scale as follows: 0 = no erosion; 1 = discrete erosion; 2 = two separate quadrants with erosions or 20–40% joint involvement; 3 = 3 separate quadrants with erosions or 41–60% joint involvement; 4 = all four quadrants with joint erosion or 61–80% joint involvement; and 5 = extensive destruction with over 80% joint involvement. The range of erosion scores for a patient with two hands and wrists is 0–170. For joint space narrowing each joint is scored using a five-point scale as follows: 0 = no narrowing; 1 = up to 25% narrowing; 2 = 26–65% narrowing; 3 = 66–99% narrowing; and 4 = complete narrowing. The range for joint space narrowing is therefore 0–144. This gives a total joint score in the range 0–314.

Van der Heijde modified Sharp score

In this case 16 joints are assessed in each hand and wrist and six joints in each foot. Erosions are scored 0–5 and depending on the affected surface area and 0–10 in the feet, yielding possible erosion scores of 0–160 for hands/wrists and 0–120 for feet (total 0–280). Joint space narrowing is assessed in 15 joints for each hand/wrist and six joints in each foot on a scale of 0–4. The range of possible joint space narrowing scores is in the range 0–168. This yields a possible total score in the range 0–448.[211]

Larsen score

In this method standard films are used to classify each joint into one of six possible categories (0 = normal, 5 = severely damaged). Any joint may be scored, but the focus is on hands and feet. In the hands each proximal interphalangeal joint and each metacarpophalangeal joint scores 0–5; each wrist joint scores 0–25 (the basic score is multiplied by 5): this gives a maximum score of 150 for two hands and wrists. In the feet each metatarsophalangeal joint is scored 0–5, giving a total score of 50 for two feet. This yields a possible total score in the range 0–200.

Scott-modified Larsen[212]

Scott and colleagues suggested minor modifications to the scale to improve correlation between scorers. It was proposed that grade 1 included erosions and cysts of less than 1 mm diameter and grade 2 included one or more erosions of more than 1 mm diameter.

Appendix 2

Searches: clinical effectiveness

Cochrane Library (CENTRAL)

2005 Issue 1

#1 rheumatoid NEXT arthritis in All Fields in all products
#2 MeSH descriptor Arthritis, Rheumatoid, this term only in MeSH products
#3 (#1 OR #2)
#4 "tumor necrosis factor*" in All Fields in all products
#5 "tumour necrosis factor*" in All Fields in all products
#6 MeSH descriptor Receptors, Tumor Necrosis Factor, this term only in MeSH products
#7 "anti tnf" in All Fields in all products
#8 antitnf in All Fields in all products
#9 infliximab in All Fields in all products
#10 remicade in All Fields in all products
#11 enbrel in All Fields in all products
#12 etanercept in All Fields in all products
#13 adalimumab in All Fields in all products
#14 humira in All Fields in all products
#15 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)
#16 (#3 AND #15)

Ovid MEDLINE(R)

1966 to February week 2 2005

1 arthritis rheumatoid/
2 tumo?r necrosis factor.mp.
3 exp receptors tumor necrosis factor/
4 anti TNF.mp.
5 infliximab.mp.
6 remicade.mp.
7 enbrel.mp.
8 etanercept.mp.
9 or/2-8
10 rheumatoid arthritis.mp.
11 1 or 10
12 9 and 11
13 randomized controlled trial.pt.
14 controlled clinical trial.pt.
15 randomized controlled trials.sh.
16 random allocation.sh.
17 double blind method.sh.
18 single blind method.sh.
19 or/13-18
20 (animals not human).sh.
21 19 not 20
22 clinical trial.pt.
23 exp clinical trials/
24 (clin$ adj25 trial$).ti,ab.
25 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
26 placebo$.ti,ab.
27 random$.ti,ab.
28 placebos.sh.
29 research design.sh.
30 or/22-29
31 30 not 20
32 31 not 21
33 21 or 32
34 12 and 33
35 limit 34 to yr=2001 - 2005
36 adalimumab.mp.
37 humira.mp.
38 or/36-37
39 1 and 38 and 33
40 35 or 39

EMBASE (Ovid)

1980 to week 8 2005

1 arthritis rheumatoid/
2 tumo?r necrosis factor.mp.
3 exp receptors tumor necrosis factor/
4 anti TNF.mp.
5 infliximab.mp.
6 remicade.mp.
7 enbrel.mp.
8 etanercept.mp.
9 or/2-8
10 rheumatoid arthritis.mp.
11 1 or 10
12 9 and 11
13 adalimumab.mp.
14 humira.mp.
15 or/13-14
16 randomized controlled trial/
17 exp clinical trial/
18 exp controlled study/
19 double blind procedure/
20 randomization/
21 placebo/

22 single blind procedure/
23 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp.
24 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp.
25 (placebo$ or matched communities or matched schools or matched populations).mp.
26 (comparison group$ or control group$).mp.
27 (clinical trial$ or random$).mp.
28 (quasiexperimental or quasi experimental or pseudo experimental).mp.
29 matched pairs.mp.
30 or/16-29
31 12 and 30
32 limit 31 to yr=2001 - 2005
33 15 and 11 and 30
34 32 or 33

Science Citation Index (Web of Science)

1981–2005

#1 TS=(rheumatoid arthritis AND (infliximab OR remicade OR enbrel OR etanercept OR tumor necrosis factor OR tumour necrosis factor OR tnf))
#2 TS=(rheumatoid arthritis AND (infliximab OR remicade OR enbrel OR etanercept))
#3 TS=(rheumatoid arthritis AND (infliximab OR remicade OR enbrel OR etanercept) AND (trial* OR random* OR control*))
#4 TS=(rheumatoid arthritis AND (adalimumab OR humira) AND (trial* OR random* OR control*))
#5 TS=(rheumatoid arthritis AND (adalimumab OR humira) AND (trial* OR random* OR control*))
#6 #3 OR #4
#7 #3 OR #5

Appendix 3

List of excluded studies for clinical effectiveness review

TABLE 69 *Studies excluded from clinical effectiveness review*

Citation	Reason for exclusion/comment
No appropriate comparison between TNF inhibitors and other active comparators or placebo	
Fleischmann *et al*., 2003[213]	This was a retrospective analysis which compared the efficacy and safety of etanercept between age ≥65 group and age <65 group using data from etanercept trials. No data from placebo groups or other active comparator groups were included
Genovese *et al*., 2004[157]	This study compared the combination of anakinra and etanercept with etanercept alone. It was thus an assessment of the efficacy and safety of anakinra versus placebo. The results indicated that adding anakinra to etanercept provided no treatment benefit, but was associated with increased risk of adverse events
Goekoop-Ruiterman *et al*., 2004,[143] BeSt	This is an ongoing RCT which compares four treatment strategies for RA. As all strategies included infliximab treatment at some point, the effectiveness and safety of infliximab compared with other agents cannot be appropriately assessed. Although not meeting inclusion criteria, because of its importance this study is described in detail in the section 'Infliximab' (p. 46) of this report
van Riel *et al*., EULAR 2005,[107] ADORE	This was an open-label RCT which compared two treatment strategies in RA patients inadequately controlled by methotrexate therapy: adding etanercept to methotrexate or replacing methotrexate with etanercept. No comparison of etanercept with placebo or other active treatment can be made
Neither full paper nor trial report available	
Schattenkirchner *et al*., 1998[106]	This was a small (n = 24), double-blind, Phase I RCT which compared adalimumab 0.5 mg kg^{-1} s.c. weekly with placebo, with follow-up of 8–12 weeks
Not including outcomes of interest (clinically important outcomes)	
Smeets *et al*., 2003[214]	This was an RCT which studied the effect of single dose of infliximab compared with placebo on cell infiltration in synovial tissues in 24 patients
St Clair *et al*., 2002[215]	This was a pharmacokinetic study of infliximab using data from ATTRACT
Schotte *et al*., 2001[216]	This appears to be a study of the effect of etanercept on the production of proinflammatory cytokine mononuclear cells in the blood. Unable to obtain the paper (citation may be incorrect)
Interventions do not include adalimumab, etanercept or infliximab	
Grigor *et al*., 2004,[217] TICORA	This was a single-blind RCT which compared two treatment strategies (intensive outpatient management and routine care) in RA patients. Neither strategy included TNF inhibitors as part of the treatment
Lukina *et al*., 2001[218]	This was an RCT which compared intramuscular injections of anti-interferon-γ, anti-TNF-α, and placebo in 30 RA patients. The identity of the anti-TNF-α is not clear and it does not appear to be one of the three TNF inhibitors of interest
Sigidin *et al*., 2001[219]	This appears to be a duplicate publication of Lukina *et al*., 2001[218] listed above. The identity of the anti-TNF-α is not clear and it does not appear to be one of the three TNF inhibitors of interest
Not RCTs	
Brocq *et al*., 2002[220]	Non-randomised study describing outcomes from consecutive use of etanercept and infliximab and vice versa
Buch *et al*., 2004[72]	Observational study of ceasing and restarting TNF inhibitors with no control group
Capria *et al*., 2004[221]	Non-randomised study investigating TNF inhibition and endothelial dysfunction
Cohen *et al*., 2004[222]	Observational study of adding methotrexate to partial responders to etanercept monotherapy with no control group

continued

TABLE 69 *Studies excluded from clinical effectiveness review (cont'd)*

Citation	Reason for exclusion/comment
Ferraro-Peyret *et al*., 2004[223]	Non-randomised study investigating infliximab treatment and autoantibodies in RA and ankylosing spondylitis patients
Genovese *et al*., 2001[224]	Three-year outcomes from the extension of etanercept ERA trial in which patient no longer remained on randomised treatment. Abstract
Genovese *et al*., 2002[225]	Four-year outcomes from the extension of etanercept ERA trial in which patient no longer remained on randomised treatment. Abstract
Genovese *et al*., 2003[226]	Five-year outcomes from the extension of etanercept ERA trial in which patient no longer remained on randomised treatment. Abstract
Gomez-Puerta *et al*., 2004[227]	Observational study of using etanercept after treatment failure with infliximab with no control group
Korczowska *et al*., 2003[228]	Non-randomised study investigating infliximab treatment and bone turnover
Kucharz *et al*., 2003[229]	Non-randomised study investigating infliximab treatment and serum endostatin level
Osborn, 2002[230]	Abstract. Double-blind controlled study of single injection of intra-articular etanercept versus saline in RA patients. No mention of randomisation
Saadeh *et al*., 2002[231]	Non-randomised study investigating infliximab treatment and asthma control in RA patients. Abstract
Smith *et al*., 2004[232]	Case report of treating renal amyloidosis complicating RA with etanercept
Yazici *et al*., 2001[233]	Non-randomised study comparing the efficacy of etanercept with infliximab. Abstract
Review articles	
Breedveld, 2001[234]	Review of TNF blockade in RA
Calin, 2003[235]	Review of infliximab
Muhlhauser, 2003[236]	Review of etanercept (German)
Pugsley, 2001[237]	Review of etanercept
Rashmi and Ujala, 2004[238]	Review of novel therapeutic approach for RA
Rau, 2002[239]	Review of adalimumab treatment in RA
Sautner, 2005[240]	Review of adalimumab (German)
Vervaeren, 2002[241]	Review of new treatment in RA (French)
Winning, 2001[242]	Review of infliximab treatment in RA
Yung, 2001[243]	Review of etanercept
News articles/commentaries/editorials	
Anonymous, 2003[244]	Summary of adalimumab DE019 (German)
Anonymous, 2004[245]	News on Genovese *et al*., 2004[157] listed above, which compared the combination of anakinra and etanercept and etanercept alone
Bain and Brazil, 2003[246]	Commentary on adalimumab
Becker, 2004[247]	News article on adalimumab (German)
Boers, 2001[248]	Letter. Commentary on ATTRACT
Bruhn, 2002[249]	Commentary on adalimumab (German)
Bruhn, 2004[250]	News article on TEMPO (German)
Choy, 2004[251]	Editorial on combination therapy
Cutolo, 2001[252]	Commentary on an etanercept RCT
Czajka, 2001[253]	News article on ATTRACT (German)
Haneveld, 2004[254]	News article on TEMPO (Dutch)
Hellwig, 2003[255]	Commentary on adalimumab (German)
Masche, 2003[256]	Commentary on adalimumab (German)
Matucci-Cerinic, 2004[257]	Commentary on ARMADA
Moreland, 2004[258]	Commentary on an infliximab RCT
Moreland, 2004[259]	Commentary on an adalimumab RCT
Rothschild, 2002[260]	Conference news report regarding TNF therapies

continued

TABLE 69 *Studies excluded from clinical effectiveness review (cont'd)*

Citation	Reason for exclusion/comment
Irrelevant (conference news reports; cost studies)	
Braddock, 2004[261]	Conference news report
Croasdell, 2003[262]	Conference news report
Evans, 2003[263]	Conference news report
Levy *et al*., 2004[264]	Conference news report
Oelke, 2002[265]	Conference news report
Trepman *et al*., 2003[266]	Conference news report
Yung, 2002[267]	Conference news report
van de Putte *et al*., 2002[268]	Cost study for an adalimumab trial. Abstract

EULAR, European League Against Rheumatism.

Appendix 4

Additional tables for clinical effectiveness review

Adalimumab

Adalimumab versus placebo: sensitivity analyses

TABLE 70 *Meta-analyses: adalimumab licensed dose (40 mg every other week or equivalent) and above versus placebo (with or without ongoing conventional DMARDs), end of trial*

Comparison or outcome	Studies	*N* included in analysis	Statistical method	Effect size (95% CI)
ACR20 responder	5[112–115,119]	2172	RR (fixed)	2.23 (1.94 to 2.56)*
ACR50 responder	5[112–115,119]	2172	RR (fixed)	3.73 (2.91 to 4.77)*
ACR70 responder	5[112–115,119]	2172	RR (fixed)	5.28 (3.49 to 8.00)*
RD ACR20 responder	5[112–115,119]	2172	RD (fixed)	0.30 (0.26 to 0.34)*
RD ACR50 responder	5[112–115,119]	2172	RD (fixed)	0.24 (0.21 to 0.27)*
RD ACR70 responder	5[112–115,119]	2172	RD (fixed)	0.14 (0.11 to 0.16)*
SJC, mean change from baseline	5[112–115,119]	2169	WMD (fixed)	–5.52 (–6.39 to –4.64)*
Patient's global assessment, mean change from baseline	5[112–115,119]	2168	WMD (fixed)	–1.76 (–2.01 to –1.50)*
HAQ, mean change from baseline	5[112–115,119]	2168	WMD (fixed)	–0.33 (–0.38 to –0.28)*
DAS28, mean change from baseline	2[113,119]	721	WMD (random)	–1.30 (–1.69 to –0.92)*
Modified van de Heijde–Sharp score, mean change from baseline	1[114]	551	WMD (fixed)	–2.20 (–3.33 to –1.07)*
Withdrawal for any reasons	5[112–115,119]	2179	RR (random)	0.60 (0.40 to 0.88)*
Withdrawal due to lack of efficacy	5[112–115,119]	2179	RR (fixed)	0.35 (0.28 to 0.43)*
Withdrawal due to adverse events	5[112–115,119]	2179	RR (fixed)	1.41 (0.90 to 2.21)
Death	5[112–115,119]	2179	RR (fixed)	1.76 (0.45 to 6.86)
SAEs	5[112–115,119]	2179	RR (fixed)	1.08 (0.81 to 1.44)
Malignancy: all	5[112–115,119]	2179	RR (fixed)	2.99 (0.93 to 9.66)
Malignancy: skin cancer excluding melanoma	5[112–115,119]	2179	RR (fixed)	1.97 (0.53 to 7.27)
Malignancy: all cancer excluding non-melanoma skin cancer	5[112–115,119]	2179	RR (fixed)	2.52 (0.56 to 11.47)
Serious infection	5[112–115,119]	2179	RR (fixed)	2.35 (1.03 to 5.34)*
Any infection	4[112–115]	1895	RR (fixed)	1.19 (1.08 to 1.31)*

* Statistically significant result ($p < 0.05$).

TABLE 71 *Meta-analyses: adalimumab (s.c. or i.v. all doses) versus placebo (with or without ongoing conventional DMARDs), end of trial*

Comparison or outcome	Studies	*N* included in analysis	Statistical method	Effect size (95% CI)
ACR20 responder	8[112–119]	2581	RR (fixed)	2.27 (1.99 to 2.60)*
ACR50 responder	8[112–119]	2581	RR (fixed)	3.78 (2.96 to 4.83)*
ACR70 responder	5[112–115,119]	2347	RR (fixed)	5.09 (3.36 to 7.71)*
RD ACR20 responder	8[112–119]	2581	RD (fixed)	0.30 (0.27 to 0.34)*
RD ACR50 responder	8[112–119]	2581	RD (random)	0.23 (0.18 to 0.28)*
RD ACR70 responder	5[112–115,119]	2347	RD (fixed)	0.13 (0.11 to 0.15)*
SJC, mean change from baseline	8[112–119]	2578	WMD (fixed)	–5.37 (–6.11 to –4.64)*
Patient's global assessment, mean change from baseline	8[112–119]	2577	WMD (fixed)	–1.74 (–1.97 to –1.51)*
HAQ, mean change from baseline	8[112–119]	2577	WMD (fixed)	–0.31 (–0.35 to –0.27)*
DAS28, mean change from baseline	2[113,119]	827	WMD (fixed)	–1.23 (–1.44 to –1.02)*
Modified van de Heijde–Sharp score, mean change from baseline	1[114]	551	WMD (fixed)	–2.20 (–3.33 to –1.07)*
Withdrawal for any reasons	8[112–119]	2588	RR (random)	0.62 (0.46 to 0.84)*
Withdrawal due to lack of efficacy	8[112–119]	2588	RR (fixed)	0.39 (0.32 to 0.47)*
Withdrawal due to adverse events	8[112–119]	2588	RR (fixed)	1.44 (0.93 to 2.24)
Death	8[112–119]	2588	RR (fixed)	1.53 (0.44 to 5.26)
SAEs	8[112–119]	2588	RR (fixed)	1.06 (0.80 to 1.40)
Malignancy: all	6[112–115,118,119]	2414	RR (fixed)	2.84 (0.90 to 8.97)
Malignancy: skin cancer excluding melanoma	6[112–115,118,119]	2414	RR (fixed)	2.00 (0.55 to 7.24)
Malignancy: all cancer excluding non-melanoma skin cancer	6[112–115,118,119]	2414	RR (fixed)	2.23 (0.50 to 9.91)
Serious infection	7[112–115,117–119]	2468	RR (fixed)	2.27 (1.00 to 5.18)
Any infection	4[112–115]	2070	RR (fixed)	1.19 (1.08 to 1.31)*

* Statistically significant result ($p < 0.05$).

Etanercept

Etanercept versus sulfasalazine in sulfasalazine partial responders/non-responders

TABLE 72 *Summary of 24-week results from Codreanu:[103] etanercept (25 mg s.c. twice weekly) versus sulfasalazine in sulfasalazine partial responders/non-responders*

Comparison or outcome	*N* included in analysis	Statistical method	Effect size (95% CI)
ACR20 responder	153	RR (fixed)	2.64 (1.67 to 4.17)*
ACR50 responder	153	RR (fixed)	3.33 (1.62 to 6.82)*
ACR70 responder	153	RR (fixed)	10.68 (1.48 to 76.99)*
RD ACR20 responder	153	RD (fixed)	0.46 (0.31 to 0.61)*
RD ACR50 responder	153	RD (fixed)	0.33 (0.19 to 0.46)*
RD ACR70 responder	153	RD (fixed)	0.19 (0.11 to 0.28)*
SJC, end of study result	153	WMD (fixed)	–5.90 (–9.54 to –2.26)*
Patient's global assessment, end of study result	153	WMD (fixed)	–2.40 (–2.94 to –1.86)*
HAQ, end of study result	153	WMD (fixed)	–0.40 (–0.58 to –0.22)*
DAS, end of study result	153	WMD (fixed)	–1.50 (–1.87 to –1.13)*
Modified van de Heijde–Sharp score, mean change from baseline	0	Not estimable	Not assessed
Withdrawal for any reasons	153	RR (fixed)	0.26 (0.12 to 0.54)*
Withdrawal due to lack of efficacy	153	RR (fixed)	0.04 (0.01 to 0.30)*
Withdrawal due to adverse events	153	RR (fixed)	0.97 (0.25 to 3.72)
Death	153	RR (fixed)	1.47 (0.06 to 35.48)
SAEs	153	RR (fixed)	2.43 (0.29 to 20.23)
Malignancy: all	153	RR (fixed)	2.45 (0.12 to 50.13)
Malignancy: skin cancer excluding melanoma	153	RR (fixed)	1.47 (0.06 to 35.48)
Malignancy: all cancer excluding non-melanoma skin cancer	153	RR (fixed)	1.47 (0.06 to 35.48)
Serious infection	153	RR (fixed)	2.45 (0.12 to 50.13)
Any infection	153	RR (fixed)	1.76 (1.05 to 2.93)*

* Statistically significant result ($p < 0.05$).

TABLE 73 *Meta-analyses: etanercept s.c. all doses (including sublicence doses) versus placebo (with or without ongoing conventional DMARDs), end of trial*

Comparison or outcome	Studies	*N* included in analysis	Statistical method	Effect size (95% CI)
ACR20 responder	7[103,121,122,125,126,129,130]	1672	RR (fixed)	3.48 (2.78 to 4.35)*
ACR50 responder	7[103,121,122,125,126,129,130]	1672	RR (fixed)	4.97 (3.40 to 7.27)*
ACR70 responder	6[103,122,125,126,129,130]	1492	RR (fixed)	8.55 (3.59 to 20.37)*
RD ACR20 responder	7[103,121,122,125,126,129,130]	1672	RD (fixed)	0.43 (0.38 to 0.47)*
RD ACR50 responder	7[103,121,122,125,126,129,130]	1672	RD (fixed)	0.26 (0.22 to 0.30)*
RD ACR70 responder	6[103,122,125,126,129,130]	1492	RD (fixed)	0.11 (0.08 to 0.14)*
SJC, end of study result	7[103,121,122,125,126,129,130]	1689	WMD (random)	–5.78 (–8.12 to –3.43)*
Patient's global assessment, end of study result	7[103,121,122,125,126,129,130]	1689	WMD (fixed)	–2.33 (–2.56 to –2.10)*
HAQ, end of study result	6[103,122,125,126,129,130]	1440	WMD (fixed)	–0.49 (–0.57 to –0.40)*
DAS, end of study result	1[103]	150	WMD (fixed)	–1.50 (–1.89 to –1.11)*
Modified van de Heijde–Sharp score, mean change from baseline	0	0	Not estimable	No data available
Withdrawal for any reasons	7[103,104,121,122,125,126,129]	2168	RR (fixed)	0.43 (0.36 to 0.51)*
Withdrawal due to lack of efficacy	6[103,104,121,122,125,126]	1748	RR (fixed)	0.28 (0.21 to 0.36)*
Withdrawal due to adverse events	7[103,104,121,122,125,126,129]	2168	RR (fixed)	0.87 (0.54 to 1.38)
Death	7[103,104,121,122,125,126,129]	2168	RR (fixed)	1.44 (0.44 to 4.69)
SAEs	5[103,104,122,125,129]	1429	RR (fixed)	1.25 (0.76 to 2.06)
Malignancy: all	6[103,104,122,125,126,129]	1988	RR (fixed)	0.47 (0.13 to 1.67)
Malignancy: skin cancer excluding melanoma	6[103,104,122,125,126,129]	1988	RR (fixed)	0.64 (0.15 to 2.77)
Malignancy: all cancer excluding non-melanoma skin cancer	6[103,104,122,125,126,129]	1988	RR (fixed)	0.34 (0.07 to 1.74)
Serious infection	7[103,104,122,125,126,129,130]	2046	RR (fixed)	0.75 (0.37 to 1.48)
Any infection	6[103,104,122,125,126,129]	1988	RR (random)	1.01 (0.83 to 1.24)

* Statistically significant result ($p < 0.05$).

Infliximab

Infliximab alone versus placebo or methotrexate

TABLE 74 *Meta-analyses: infliximab i.v. (all doses) without MTX versus control (placebo or MTX) in MTX partial responders/ non-responders, end of trial*

Comparison or outcome	Comparator	Studies	*N* included in analysis	Statistical method	Effect size (95% CI)
Paulus 20 responder	vs placebo	1[136]	73	RR (fixed)	7.35 (1.91 to 28.21)*
	vs MTX	1[137]	58	RR (fixed)	2.86 (0.40 to 20.67)
Paulus 50 responder	vs placebo	1[136]	73	RR (fixed)	5.14 (1.31 to 20.15)*
	vs MTX	1[137]	58	RR (fixed)	4.33 (0.26 to 72.44)
ACR70 responder	–	0	0	Not estimable	Data not available
RD Paulus 20 responder	vs placebo	1[136]	73	RD (fixed)	0.53 (0.35 to 0.70)*
	vs MTX	1[137]	58	RD (fixed)	0.13 (–0.05 to 0.31)
RD Paulus 50 responder	vs placebo	1[136]	73	RD (fixed)	0.35 (0.17 to 0.52)*
	vs MTX	1[137]	58	RD (fixed)	0.14 (0.00 to 0.27)
RD ACR70 responder	–	0	0	Not estimable	Data not available
SJC, end of study result	vs placebo	1[136]	73	WMD (fixed)	–12.20 (–17.17 to –7.23)*
Patient's global assessment, end of study result	vs placebo	1[136]	73	WMD (fixed)	–1.00 (–1.39 to –0.61)*
HAQ, mean change from baseline	–	0	0	Not estimable	Data not available
DAS28, end of study result	–	0	0	Not estimable	Data not available
Modified van de Heijde–Sharp score, mean change from baseline	–	0	0	Not estimable	Data not available
Withdrawal for any reasons	vs MTX	1[137]	58	RR (fixed)	0.48 (0.25 to 0.93)*
Withdrawal due to lack of efficacy	vs MTX	1[137]	58	RR (fixed)	0.32 (0.15 to 0.69)*
Withdrawal due to adverse events	vs MTX	1[137]	58	RR (fixed)	3.00 (0.17 to 52.53)
Death	–	0	0	Not estimable	Data not available
SAEs	–	0	0	Not estimable	Data not available
Malignancy	vs MTX	1[137]	58	Not estimable	No events
Serious infection	vs MTX	1[137]	58	Not estimable	No events
Any infection	vs placebo	1[136]	73	RR (fixed)	2.94 (0.37 to 23.06)

* Statistically significant result ($p < 0.05$).

Infliximab versus placebo (with concomitant, ongoing methotrexate)

TABLE 75 *Meta-analyses: infliximab i.v. licensed dose and above versus placebo with ongoing MTX in MTX partial responders/ non-responders, end of trial*

Comparison or outcome	Studies	*N* included in analysis	Statistical method	Effect size (95% CI)
ACR20 responder	4[111,133,137,140]	1513	RR (fixed)	2.50 (2.10 to 2.99)*
ACR50 responder	4[111,133,137,140]	1513	RR (fixed)	3.73 (2.75 to 5.07)*
ACR70 responder	2[111,133]	1448	RR (fixed)	3.79 (2.34 to 6.15)*
RD ACR20 responder	4[111,133,137,140]	1513	RD (fixed)	0.34 (0.30 to 0.39)*
RD ACR50 responder	4[111,133,137,140]	1513	RD (fixed)	0.25 (0.21 to 0.29)*
RD ACR70 responder	2[111,133]	1448	RD (fixed)	0.12 (0.09 to 0.14)*
SJC, mean change from baseline	2[111,133]	1401	WMD (fixed)	–5.28 (–6.27 to –4.29)*
Patient's global assessment, mean change from baseline	2[111,133]	1400	WMD (fixed)	–1.60 (–1.91 to –1.29)*
HAQ, mean change from baseline	2[111,133]	1381	WMD (fixed)	–0.29 (–0.36 to –0.23)*
DAS28, end of study result	1[140]	24	WMD (fixed)	–1.80 (–2.68 to –0.92)*
Modified van de Heijde–Sharp score, mean change from baseline	2[133,140]	373	WMD (fixed)	–6.79 (–9.19 to –4.39)*
Withdrawal for any reasons	3[111,133,137]	1553	RR (random)	0.48 (0.17 to 1.33)
Withdrawal due to lack of efficacy	2[133,137]	471	RR (fixed)	0.28 (0.19 to 0.41)*
Withdrawal due to adverse events	4[111,133,137,140]	1577	RR (fixed)	1.65 (0.97 to 2.81)
Death	2[111,133]	1510	RR (fixed)	0.55 (0.16 to 1.81)
SAEs	2[111,133]	1510	RR (fixed)	0.92 (0.67 to 1.27)
Malignancy: all	3[111,133,137]	1553	RR (fixed)	2.64 (0.62 to 11.26)
Malignancy: skin cancer excluding melanoma	3[111,133,137]	1553	RR (fixed)	1.68 (0.31 to 9.04)
Malignancy: all cancer excluding non-melanoma skin cancer	3[111,133,137]	1553	RR (fixed)	2.30 (0.40 to 13.17)
Serious infection	3[111,133,137]	1553	RR (fixed)	1.32 (0.74 to 2.35)
Any infection	2[111,132]	1510	RR (fixed)	**[Commercial-in-confidence information removed]***

* Statistically significant result ($p < 0.05$).

TABLE 76 *Meta-analyses: infliximab i.v. all doses versus placebo with ongoing MTX in MTX partial responders/non-responders, end of trial*

Comparison or outcome	Studies	*N* included in analysis	Statistical method	Effect size (95% CI)
ACR20 responder	5[111,133,137,138,140]	1555	RR (fixed)	2.50 (2.10 to 2.99)*
ACR50 responder	5[111,133,137,138,140]	1555	RR (fixed)	3.68 (2.72 to 4.98)*
ACR70 responder	2[111,133]	1448	RR (fixed)	3.79 (2.34 to 6.15)*
RD ACR20 responder	5[111,133,137,138,140]	1555	RD (fixed)	0.34 (0.29 to 0.39)*
RD ACR50 responder	5[111,133,137,138,140]	1555	RD (fixed)	0.24 (0.21 to 0.28)*
RD ACR70 responder	2[111,133]	1448	RD (fixed)	0.12 (0.09 to 0.14)*
SJC, end of study result	2[111,133]	1401	WMD (fixed)	–5.28 (–6.27 to –4.29)*
Patient's global assessment, end of study result	2[111,133]	1400	WMD (fixed)	–1.60 (–1.91 to –1.29)*
HAQ, mean change from baseline	2[111,133]	1381	WMD (fixed)	–0.29 (–0.36 to –0.23)*
DAS28, end of study result	1[140]	24	WMD (fixed)	–1.80 (–2.68 to –0.92)*
Modified van de Heijde–Sharp score, mean change from baseline	2[133,140]	373	WMD (fixed)	–6.79 (–9.19 to –4.39)*
Withdrawal for any reasons	4[111,133,137,138]	1595	RR (random)	0.45 (0.16 to 1.28)
Withdrawal due to lack of efficacy	3[133,137,138]	513	RR (fixed)	0.27 (0.18 to 0.40)*
Withdrawal due to adverse events	5[111,133,137,138,140]	1619	RR (fixed)	1.66 (0.97 to 2.82)
Death	2[111,133]	1510	RR (fixed)	0.55 (0.16 to 1.81)
SAEs	2[111,133]	1510	RR (fixed)	0.92 (0.67 to 1.27)
Malignancy: all	3[111,133,137]	1567	RR (fixed)	2.64 (0.62 to 11.26)
Malignancy: skin cancer excluding melanoma	3[111,133,137]	1567	RR (fixed)	1.68 (0.31 to 9.04)
Malignancy: all cancer excluding non-melanoma skin cancer	3[111,133,137]	1567	RR (fixed)	2.30 (0.40 to 13.17)
Serious infection	4[111,133,137,138]	1595	RR (fixed)	1.29 (0.72 to 2.31)
Any infection	2[111,133]	1510	RR (random)	**[Commercial-in-confidence information removed]**

* Statistically significant result ($p < 0.05$).

Infliximab plus MTX versus MTX

TABLE 77 *Meta-analyses: combination of infliximab (i.v. all doses) plus MTX versus MTX alone in MTX-naïve patients, end of trial*

Comparison or outcome	Studies	Participants	Statistical method	Effect size (95% CI)
ACR20 responder	2[135,141]	1000	RR (fixed)	1.20 (1.07 to 1.36)*
ACR50 responder	2[135,141]	1000	RR (fixed)	1.51 (1.26 to 1.82)*
ACR70 responder	2[135,141]	1000	RR (fixed)	1.67 (1.31 to 2.13)*
RD ACR20 responder	2[135,141]	1000	RD (fixed)	0.11 (0.04 to 0.18)*
RD ACR50 responder	2[135,141]	1000	RD (fixed)	0.16 (0.10 to 0.23)*
RD ACR70 responder	2[135,141]	1000	RD (fixed)	0.14 (0.08 to 0.20)*
SJC, mean change from baseline	1[135]	846	WMD (fixed)	–3.00 (–4.76 to –1.24)*
Patient's global assessment, mean change from baseline	1[135]	842	WMD (fixed)	–0.70(–1.18 to –0.22)*
HAQ, mean change from baseline	2[135,141]	1016	WMD (fixed)	–0.17 (–0.28 to –0.07)*
DAS28, end of study result	2[135,141]	838	WMD (fixed)	–0.82 (–1.08 to –0.55)*
Modified van de Heijde–Sharp score, mean change from baseline	1[135]	1004	WMD (fixed)	–3.23 (–4.43 to –2.03)*
Withdrawal for any reasons	1[135]	1040	RR (fixed)	0.93 (0.71 to 1.21)
Withdrawal due to lack of efficacy	1[135]	1040	RR (fixed)	0.28 (0.16 to 0.49)*
Withdrawal due to adverse events	2[135,141]	1060	RR (fixed)	3.02 (1.55 to 5.88)*
Death	1[135]	1040	RR (fixed)	0.39 (0.05 to 2.75)
SAEs	1[135]	1040	RR (fixed)	1.25 (0.86 to 1.82)
Malignancy: all	1[135]	1040	RR (fixed)	**[Commercial-in-confidence information removed]**
Malignancy: skin cancer excluding melanoma	1[135]	1040	RR (fixed)	**[Commercial-in-confidence information removed]**
Malignancy: all cancer excluding non-melanoma skin cancer	1[135]	1040	RR (fixed)	3.50 (0.19 to 64.88)
Serious infection	1[135]	1040	RR (fixed)	2.59 (1.11 to 6.04)*
Any infection	1[135]	1040	RR (fixed)	**[Commercial-in-confidence information removed]***

* Statistically significant result ($p < 0.05$).

Appendix 5

Searches: economic evaluations

Ovid MEDLINE(R)

1966 to February week 3 2005

1 arthritis rheumatoid/
2 tum?r necrosis factor.mp.
3 exp receptors tumor necrosis factor/
4 anti tnf.mp.
5 infliximab.mp.
6 remicade.mp.
7 enbrel.mp.
8 etanercept.mp.
9 or/2-8
10 1 and 9
11 economics/
12 exp "costs and cost analysis"/
13 cost of illness/
14 exp health care costs/
15 economic value of life/
16 exp economics medical/
17 exp economics hospital/
18 economics pharmaceutical/
19 exp "fees and charges"/
20 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.
21 (expenditure$ not energy).tw.
22 (value adj1 money).tw.
23 budget$.tw.
24 or/11-23
25 10 and 24
26 limit 25 to yr=2001-2005
27 adalimumab.mp.
28 humira.mp.
29 or/27-28
30 29 and 24
31 26 or 30
32 quality of life/
33 life style/
34 health status/
35 health status indicators/
36 value of life/
37 quality of wellbeing.tw.
38 or/32-37
39 1 and 38
40 limit 39 to yr=2001-2005
41 31 or 40

EMBASE (Ovid)

1980 to week 9 2005

1 arthritis rheumatoid/
2 tum?r necrosis factor.mp.
3 exp receptors tumor necrosis factor/
4 anti tnf.mp.
5 infliximab.mp.
6 remicade.mp.
7 enbrel.mp.
8 etanercept.mp.
9 or/2-8
10 1 and 9
11 cost benefit analysis/
12 cost effectiveness analysis/
13 cost minimization analysis/
14 cost utility analysis/
15 economic evaluation/
16 (cost or costs or costed or costly or costing).tw.
17 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
18 (technology adj assessment$).tw.
19 or/11-18
20 10 and 19
21 limit 20 to yr=2001-2005
22 adalimumab.mp.
23 humira.mp.
24 or/22-23
25 24 and 19
26 21 or 25
27 exp quality of life/
28 health status/
29 27 or 28
30 1 and 29
31 limit 30 to yr=2001 - 2005

Cochrane Library (NHSEED)

2005 Issue 1

See search strategy for Cochrane Library under Clinical Effectiveness, page 141.

HEED

February 2005

A series of searches were done using the following terms: anti tnf; infliximab; remicade, enbrel, etanercept, adalimumab, humira and references which included rheumatoid arthritis were selected.

Appendix 6

Searches: decision-analytic models

Ovid MEDLINE(R)

1966 to February week 2 2005

1 arthritis rheumatoid/
2 tum?r necrosis factor.mp.
3 exp receptors tumor necrosis factor/
4 anti tnf.mp.
5 infliximab.mp.
6 remicade.mp.
7 enbrel.mp.
8 etanercept.mp.
9 or/2-8
10 1 and 9
11 decision support techniques/
12 markov.mp.
13 exp models economic/
14 decision analysis.mp.
15 cost benefit analysis/
16 or/11-15
17 10 and 16
18 limit 17 to yr=2001 - 2005
19 adalimumab.mp.
20 humira.mp.
21 or/19-20
22 1 and 21 and 16
23 18 or 22

EMBASE (Ovid)

1980 to week 8 2005

1 arthritis rheumatoid/
2 tum?r necrosis factor.mp.
3 exp receptors tumor necrosis factor/
4 anti tnf.mp.
5 infliximab.mp.
6 remicade.mp.
7 enbrel.mp.
8 etanercept.mp.
9 or/2-8
10 1 and 9
11 decision support techniques/
12 markov.mp.
13 exp models economic/
14 decision analysis.mp.
15 cost benefit analysis/
16 or/11-15
17 10 and 16
18 limit 17 to yr=2001-2005
19 adalimumab.mp.
20 humira.mp.
21 or/19-20
22 1 and 21 and 16
23 18 or 22

Appendix 7

Searches: systematic reviews of DMARDs

Ovid MEDLINE(R)

1999 to March week 4 2005

1 arthritis rheumatoid/
2 (hydroxychloroquine or ciclosporine or gold or methotrexate or leflunomide or penicillamine or sulfasalazine or azathioprine).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3 dmard$.mp.
4 1 and (2 or 3)
5 (systematic adj review$).mp.
6 (data adj synthesis).mp.
7 (published adj studies).ab.
8 (data adj extraction).ab.
9 meta-analysis/
10 meta-analysis.ti.
11 comment.pt.
12 letter.pt.
13 editorial.pt.
14 animals/
15 human/
16 14 not (14 and 15)
17 4 not (11 or 12 or 13 or 16)
18 or/5-10
19 17 and 18
20 limit 19 to yr=2001 - 2005
21 from 20 keep 5-6,9,12

EMBASE (Ovid)

1996 to week 14 2005

1 (systematic adj review$).mp.
2 meta-analysis.ti.
3 meta-analysis/
4 arthritis rheumatoid/
5 (hydroxychloroquine or ciclosporine or gold or methotrexate or leflunomide or penicillamine or sulfasalazine or azathioprine).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
6 dmard$.mp.
7 or/1-3
8 4 and (5 or 6)
9 7 and 8
10 limit 9 to yr=2001 - 2005
11 from 10 keep 1,3,6,13,22,32,59

Cochrane Library

2005 Issue 1

#1 dmard* in All Fields in all products
#2 hydroxychloroquine OR ciclosporine OR gold OR methotrexate in All Fields in all products
#3 leflunomide OR penicillamine OR sulfasalazine OR azathioprine in All Fields in all products
#4 "rheumatoid arthritis" in All Fields in all products
#5 MeSH descriptor Arthritis, Rheumatoid, this term only in MeSH products
#6 (#1 OR #2 OR #3)
#7 (#4 OR #5)
#8 (#6 AND #7)

Appendix 8

Existing economic evaluations: appraisal and data extraction

TABLE 78 *Choi* et al., *2002*[159]

Authors	Choi, Seeger, Kuntz
Date	2002
Type of economic evaluation	Cost-effectiveness analysis
Country of origin	USA
Currency used	US dollars
Year to which costs apply	1999
Perspective	Societal
Study population	Patients with MTX-naïve RA
Intervention 1	Etanercept
Intervention 2	LEF
Intervention 3	MTX (up to 15 mg weekly)
Intervention 4	SSZ
Intervention 5	No second line agent
Source of effectiveness data	Clinical trial data used: ACR20 response criteria and a weighted outcome measure of ACR responses relative to a full weight of ACR70 responses (ACR70 response: ACR70 WR) by calculating a weighted average of proportions achieving ACR70, ACR50 and ACR20. A weight of 1 was assigned to ACR70, a weight of 50/70 to ACR50 and a weight of 20/70 to ACR20
Cost data handled appropriately	Yes. Direct and indirect costs were considered. Medication costs were averaged wholesale prices and monitoring costs were based on published estimates where available. If unavailable, costs were derived from the cost of the components recommended by ACR for each DMARD which were summed, or by monitoring guidelines in the package insert of leflunomide The cost of no second-line treatment was calculated by subtracting ophthalmological monitoring cost (once over the 6-month period) from the monitoring cost of the least expensive DMARD costs. Monitoring costs of etanercept were assumed to be the same as the monitoring costs of the no second-line treatment. Toxicity cost associated with MTX therapy was estimated to be $259 (1999 prices). Toxicity cost of SSZ was assumed to be the same as MTX. It was assumed that there were no toxicity costs for leflunomide or etanercept Inpatient surgical costs were included to capture potential savings associated with improvement of RA from each option. An exponential relationship between HAQ score and inpatient surgery costs for each treatment strategy was developed. Medical admission costs were assumed to be largely due to toxicity of DMARDs Indirect costs were included to capture the potential savings associated with improvement of RA for each treatment. An HAQ indirect cost assignment was used, using the same HAQ efficacy estimates used for the surgical costs. A linear relationship was assumed to exist between work capacity and HAQ score to infer indirect cost savings associated with HAQ improvement. This was based on a published cost-effectiveness analysis in a Swedish RA population. The average wage was multiplied by work capacity achieved in each option to estimate the cost of lost work capacity
Modelling summary	A decision-analytic model was constructed and analysed using Data software (version 3.5; TreeAge Software, Williamstown, MA, USA). The decision tree with a time-horizon of 6 months was used in the model (this was considered to represent the usual duration of clinical trials of RA)

continued

TABLE 78 *Choi* et al., *2002*[159] *(cont'd)*

Outcome measures used in economic evaluations	The occurrence of toxicity related to each therapy and ACR response criteria (ACR20 or ACR70). ICERs were for per patient achieving ACR20 or ACR70WR
Direction of result with appropriate quadrant location	In the base-case analysis using either ACR20 or ACR70WR for MTX-naïve RA, MTX and SSZ both cost less and were more effective (SE quadrant: cost saving) than no second-line therapy. SSZ compared with MTX at ACR20 was in the NE quadrant (more costly but also more effective). Using ACR70, SSZ compared with MTX cost more but was less effective (NW quadrant). LEF was also ruled out by simple dominance when compared with MTX (i.e. NW quadrant). Compared with MTX and SSZ, etanercept was both more expensive and more effective (i.e. NE quadrant): etanercept vs SSZ: $41,900 per ACR20 etanercept vs MTX: $40,800 per ACR70WR
Statistical analysis for patient-level stochastic data	Not undertaken
Appropriateness of statistical analysis	NA
Uncertainty around cost-effectiveness expressed	Not undertaken
Appropriateness of method dealing with uncertainty around cost effectiveness	NA
Sensitivity analysis	Yes: sensitivity analyses were performed to determine the robustness of the base-case results to variations of baseline estimates. Three-way sensitivity analyses were also done to determine robustness of base-case results to variations of more than one key variable, including the main variable of triple therapy efficacy
Modelling inputs and techniques appropriate	Yes
Authors' conclusions	MTX is cost-effective (cost savings vs the no second-line treatment option) for MTX-naïve RA in achieving ACR20 or ACR70WR over a 6-month period. The relative cost-effectiveness between SSZ and MTX cannot be determined with reasonable certainty, but SSZ therapy appears to be as cost-effective as MTX (cost saving) in achieving ACR outcomes over a 6-month period. The most efficacious option, etanercept, incurs higher incremental costs per ACR20 or ACR70WR than other options analysed. Whether etanercept compared with MTX is cost-effective depends on whether >$40,000 per ACR20 or ACR70WR over a 6-month period is considered acceptable

NE, north-east; NW, north-west; SE, south-east.

TABLE 79 *Wong* et al., *2002*[161]

Authors	Wong, Singh, Kavanaugh
Date	2002
Type of economic evaluation	Cost–utility analysis
Country of origin	USA
Currency used	US dollars
Year to which costs apply	1998
Perspective	Societal
Study population	Patients with active, refractory RA
Intervention 1	Placebo + MTX
Intervention 2	Infliximab + MTX
Source of effectiveness data	Data were extrapolated from ATTRACT and ARAMIS. Quality of life data were assessed as self-reported global health using a VAS: for the first year data from ATTRACT were used and after the first year estimates were based on ARAMIS
Cost data handled appropriately	Yes. Drug costs were based on the average wholesale price of infliximab, infusion administration costs and pretreatment evaluation. Direct costs were taken from ATTRACT and included all non-protocol-related medical care costs. For a societal perspective, indirect cost estimates from ATTRACT were also used for the first year for the subset of patients who were employed at the time of enrolment. Indirect costs beyond the first year were estimated to be between one and three times the costs in year 1. Costs from ARAMIS included self-reported hospitalisation, emergency room visits, outpatient surgeries, home care and non-traditional treatments, as well as those for physicians, therapists and nurse practitioners, laboratory tests, radiological studies, drugs and nursing home, rehabilitation or hospitalisation
Modelling summary	Markov model consisting of 21 health states to project the 54-week results of RCTs to lifetime economic and clinical outcomes. A cycle length of 6 months was used
Outcome measures used in economic evaluations	Life expectancy and QALYs (based on VAS) to calculate cost per QALY
Direction of result with appropriate quadrant location	NE quadrant. $30,500 per QALY
Statistical analysis for patient-level stochastic data	Not undertaken
Appropriateness of statistical analysis	NA
Uncertainty around cost-effectiveness expressed	Not undertaken
Appropriateness of method dealing with uncertainty around cost effectiveness	NA
Sensitivity analysis	Yes. Sensitivity analyses were conducted to examine the impact of varying the values used, with and without indirect costs related to productivity losses from disability
Modelling inputs and techniques appropriate	Yes
Authors' conclusions	Infliximab plus MTX for 54 weeks for RA should be cost-effective, with its clinical benefit providing good value for the drug cost, especially when including productivity losses. Although infliximab beyond 54 weeks will be likely to be cost-effective, the economics and clinical benefit remain uncertain and will depend on long-term results of clinical trials

TABLE 80 *Kobelt* et al.*, 2003*[162]

Authors	Kobelt, Jonsson, Young, Eberhardt
Date	2003
Type of economic evaluation	Cost–utility analysis
Country of origin	France, Sweden, UK
Currency used	Euros, Swedish Kronor, pounds sterling
Year to which costs apply	Not stated
Perspective	Societal
Study population	Patients with RA not responding to at least two DMARDs (including MTX)
Intervention 1	Infliximab + MTX
Intervention 2	MTX alone
Source of effectiveness data	Clinical data from two RA cohorts, followed for up to 15 years, in Sweden and the UK (ERAS), in which average HAQ scores were calculated and used to inform the effectiveness data and the transition probabilities within the model
Cost data handled appropriately	Direct costs included hospitalisation, surgical interventions, ambulatory and community care and RA medication. Non-medical direct costs and informal care costs were excluded. The cost of hospitalisation was based on the number of inpatient days in different wards and ward-specific costs; the cost of surgical interventions was based on the type of intervention and its duration multiplied by the cost per minute of operating theatre use. Outpatient costs were based on the number of visits to different healthcare professionals. The cost of RA drugs was calculated from the number of months of use and the cost associated with standard drug monitoring protocols in place in the rheumatology departments of participating study centres. Unit cost data were taken from hospital accounting data and official price lists. Indirect costs were calculated as the loss of work capacity of patients in the more advanced disease states. For patients in disease state 1 (i.e. HAQ < 0.6) only short-term sick leave was considered. The human capital approach was used, in which an individual's productivity is valued at market price. The total number of productive years lost at each stage (of the model) was compared with the number in state 1, and the difference multiplied by the average gross annual income. The cost of infliximab was calculated using the official list price and the doses prescribed in clinical practice (in Sweden and in the UK, respectively)
Modelling summary	Markov model with a cycle length of 1 year (in line with the annual follow-up of epidemiological studies). A time-horizon of 10 years was used
Outcome measures used in economic evaluations	Incremental QALYs (based on EQ-5D) and ICERs
Direction of result with appropriate quadrant location	NE quadrant. For 1 year of treatment, €3440 per QALY in Sweden and €34,800 per QALY in the UK. The only exception is with the 'alternative model' comparing total costs at 1 year (unadjusted) and total costs at 1 year (adjusted for the effect loss at discontinuation) for Sweden. The direction of results in these two cases is the SE quadrant (cost saving)
Statistical analysis for patient-level stochastic data	Not undertaken
Appropriateness of statistical analysis	NA
Uncertainty around cost-effectiveness expressed	Not undertaken
Appropriateness of method dealing with uncertainty around cost effectiveness	NA
Sensitivity analysis	A sensitivity analysis was undertaken by way of an 'alternative model', in which a loss of treatment effect was assumed in the year after discontinuation, expressed as a faster disease progression than that reported in the cohorts. Differences in HAQ scores between infliximab and MTX groups in the clinical trials were applied to the cohorts for the treatment arm for the first year. Thus, treatment was compared directly with that of the cohorts. A sensitivity analysis was also undertaken on the price of infliximab

continued

TABLE 80 *Kobelt* et al.*, 2003*[162] *(cont'd)*

Modelling inputs and techniques appropriate	Yes
Authors' conclusions	1 or 2 years of treatment with infliximab reduced direct and indirect resource consumption in Sweden and the UK, thereby partly offsetting the treatment costs. In the base-case analysis, including direct and indirect costs, the cost per QALY gained was SEK32,000 in Sweden (€3440) and £21,600 in the UK (€34,800) for 1 year of treatment. The respective QALY gains were 0.248 and 0.298. With 2 years of treatment, the cost per QALY gained was SEK150,000 in Sweden (€16,100) and £29,900 in the UK (€48,200). The results suggest that 1–2 years of treatment with infliximab and MTX, compared with MTX alone, will lead to savings in both direct and indirect costs. Savings in direct costs are €1500–2000 in Sweden and up to 800 in the UK. These savings will not offset the cost of infliximab. The majority of savings will come from maintaining the patients' ability to work. However, when only direct costs are included, the cost-effectiveness ratios remain within the usual range for treatments to be recommended for use

TABLE 81 *Welsing* et al.*, 2004*[165]

Authors	Welsing, Severens, Hartman, van Riel, Laan
Date	2004
Type of economic evaluation	Cost–utility analysis
Country of origin	Netherlands
Currency used	Euros
Year to which costs apply	Not stated
Perspective	Societal
Study population	Patients with RA who satisfy the indication for TNF inhibitors in the Netherlands
Intervention 1	Usual treatment
Intervention 2	Treatment with leflunomide, in the case of non-response after 3 months switch to usual treatment
Intervention 3	Treatment with etanercept, in the case of non-response after 3 months switch to usual treatment
Intervention 4	Treatment with leflunomide, in the case of non-response after 3 months switch to etanercept, in the case of non-response switch to TNF-blocking agent, switch to usual treatment
Intervention 5	Treatment with etanercept, in the case of non-response after 3 months switch to leflunomide, in the case of non-response switch to leflunomide switch to usual treatment
Source of effectiveness data	The following sources of effectiveness data were used: 1. QoL data from a 48-week multicentre trial involving 411 patients were assigned to the health states within the Markov model 2. Follow-up data of patients from an open longitudinal study of early RA (disease duration <1 year with no prior use of DMARDs), underway since 1985 at the University Medical Centre Nijmegen, the Netherlands. These patients stopped treatment with SSZ and MTX owing to insufficient effect or toxicity and had high disease activity. These data were used to calculate transition probabilities for usual treatment 3. Effectiveness data from a data set, made available by Wyeth Pharmaceuticals (Madison, NJ, USA), from clinical trials of monotherapy with etanercept in patients who failed DMARD treatment (one to four DMARDs) and of combination therapy with MTX in patients with insufficient response to MTX alone. Patients with high disease activity at baseline and a good or moderate response to etanercept (EULAR criteria) after 3 months were selected. These data were used to calculate transition probabilities. Published ACR20, ACR50 and ACR70 response criteria after 1 and 2 years of treatment were used to represent Markov states for moderate disease activity, low disease activity and remission, respectively. Expected patient-years were calculated in each of the different Markov states

continued

TABLE 81 *Welsing* et al.*, 2004*[165] *(cont'd)*

Cost data handled appropriately	Yes. Costs were assigned from a 48-week multicentre trial with MTX that included 411 patients. Medical and non-medical (absence from paid work, travel expenses) costs were collected
Modelling summary	A Markov model consisting of health states defined by the DAS. A cycle length of 3 months was used. Markov states from remission (DAS <1.6), low disease activity (1.6< DAS >2.4), moderate disease activity (2.4< DAS >3.7) and high disease activity (DAS28>3.7) were used. A time limit of 5 years (20 cycles) was applied. A specific Markov model was used with the same structure and the same costs and utility values of the Markov states for each treatment strategy. The models used specific transition probabilities and costs for the respective drug treatments. Using these models, the expected costs and effects were compared between the different treatment strategies
Outcome measures used in economic evaluations	QALYs were compared between the different treatment strategies to calculate cost per QALY and ICERs. EQ-5D was used to calculate utilities. Also considered was cost per patient-year in the three DAS28 states
Direction of result with appropriate quadrant location	NE quadrant, except for a small number of studies in the NW quadrant, relating to comparisons between interventions 4 and 5. Etanercept alone was dominated by leflunomide/etanercept combinations. Versus usual treatment the ICERs were €163,556 per QALY for LEF–Etan and €297,151 per QALY for Etan–LEF. Versus leflunomide the ICERs were €317,627 per QALY for LEF–Etan and €517,061 per QALY for Etan–LEF
Statistical analysis for patient-level stochastic data	Not undertaken
Appropriateness of statistical analysis	NA
Uncertainty around cost-effectiveness expressed	Yes. Model uncertainty was explored using PSA. Distributions were specified for the transition probabilities, the costs and the utility values of the Markov states and for the response of etanercept (EULAR good/moderate) and leflunomide treatment (ACR20) after 3 months. 2.5–97.5 percentiles were reported from PSA for costs and QALYs, but no ICERs were given
Appropriateness of method dealing with uncertainty around cost effectiveness	Yes
Sensitivity analysis	Yes. One-way sensitivity analysis was applied to determine the relative importance of different parameters for the primary outcome. Correlations between the parameters and outcomes were calculated. Important model parameter values as defined by the correlation were also varied in a one-way sensitivity analysis
Modelling inputs and techniques appropriate	Yes
Authors' conclusions	Treatment strategies that include TNF inhibitors are probably the most effective for patients in whom two DMARDs have previously failed, of which one is MTX. From these strategies, treatment starting with leflunomide, and in the case of non-response switching to a TNF inhibitor, probably results in the most favourable ratio between the extra costs and effects

PSA, probabilistic sensitivity analysis.

TABLE 82 *Brennan* et al.*, 2004*[160]

Authors	Brennan, Bansback, Reynolds, Conway
Date	2004
Type of economic evaluation	Cost–utility analysis
Country of origin	UK
Currency used	Pounds sterling
Year to which costs apply	2000
Perspective	NHS in the UK
Study population	Patients with RA who failed to respond previously to at least two DMARDs (MTX as first line and sulfasalazine as second line)
Intervention 1	Treatment pathway I: third option: etanercept monotherapy; fourth: intramuscular gold; and fifth: ciclosporin and MTX
Intervention 2	Treatment pathway II: third option: intramuscular gold; fourth: ciclosporin and MTX; and fifth: leflunomide
Source of effectiveness data	DAS28 scores were used. Comparative data on the DAS28 for etanercept was unavailable, therefore data from a Phase III study of etanercept vs placebo were used, alongside published data for other DMARDs. Patient characteristics of published data were compared with those of the Phase III study to identify studies that enrolled similar patients. Where comparable studies were unavailable, ACR20 response was assumed to be 35%, using published meta-analysis of patient with >10 years, disease duration. These sources were used to inform model parameter values relating to initial response to therapy and initial HAQ response Long-term HAQ response was estimated from published sources and data from a long-term, open-label study of etanercept. ERAS was used as a source of data for HAQ improvements during periods of non-response. Long-term withdrawal was estimated using data from a study based on clinical practice in Sweden, showing an annual withdrawal of 8.3% Evidence presented in four separate studies was used as a basis for the relationship between HAQ and utility to inform quality of life data. Variation in the results was small and the median relationship was used in the primary analysis. Trial data were used to inform response rates of treatment and HAQ improvements
Cost data handled appropriately	Yes. Drug and monitoring costs and other direct costs were examined for each treatment. Drug costs derived from current list prices and monitoring costs were estimated using BSR guidelines. Evidence from studies in the USA and Sweden suggests a strong correlation between HAQ score and direct costs. Costs reported in these studies were used to inform parameter values (converted to 2000 UK currency using the purchaser parity index and inflation). Both gave an almost identical linear relationship of £860 p.a. increase in direct costs. In the model the difference in the two comparators HAQ score trends is converted into a difference in direct healthcare costs, i.e. worse HAQ scores generate higher direct costs, pro rata Sensitivity analyses were used: first, to examine the impact of the additional costs associated with home help, residential and nursing home care and, secondly, to examine the impact of economic productivity to society through maintained employment. Data from a Swedish study were used to inform the latter
Modelling summary	A decision-analytic model was developed in Excel. Patients following each treatment pathway (etanercept vs DMARD sequence) were simulated. A cycle length of 6 months was used. A patient population of 10,000 was simulated over the lifetime and a Monte Carlo approach taken. Discounting was applied to costs (6% p.a.) and benefits (1.5% p.a.) in line with guidance from NICE
Outcome measures used in economic evaluations	QALYs through the use of etanercept compared with current UK clinical practice. HAQ and EQ-5D data were used to calculate QALYs through regression
Direction of result with appropriate quadrant location	NE quadrant. £16,330 per QALY
Statistical analysis for patient-level stochastic data	Yes: patient-level data were used taken from the model simulation
Appropriateness of statistical analysis	Yes

continued

TABLE 82 *Brennan* et al., *2004*[160] *(cont'd)*

Uncertainty around cost-effectiveness expressed	Uncertainty in the results was expressed in terms of conducting scenario-based one-way sensitivity analyses to investigate the impact of alternative scenarios for the key model parameter values
Appropriateness of method dealing with uncertainty around cost effectiveness	Yes
Sensitivity analysis	One-way sensitivity analysis (scenario-based) was undertaken: analysis as described above was performed, in addition to analyses of changes to the response rate of etanercept, changes to HAQ scores and changes to mortality estimates
Modelling inputs and techniques appropriate	Yes
Authors' conclusions	Etanercept is cost-effective compared with non-biological agents. NICE recognised it as cost-effective and recommended its availability for use in patients who have failed at least two DMARDs previously. This model was used to inform the decision taken by NICE

TABLE 83 *Kobelt* et al., *2004*[163]

Authors	Kobelt, Eberhardt, Geborek
Date	2004
Type of economic evaluation	Cost–utility analyses
Country of origin	Sweden, France
Currency used	Euros
Year to which costs apply	2002
Perspective	Societal
Study population	Patients with RA who failed to respond to at least two DMARDs, including MTX, in Sweden
Intervention 1	Etanercept or infliximab
Intervention 2	Baseline level (failed at least two DMARDs, including MTX)
Source of effectiveness data	Follow-up of patients from a cohort treated with etanercept or infliximab
Clinical outcomes measured and methods of valuation used	The Swedish version of the HAQ, DAS28 and the EQ-5D were used during the first year of follow-up
Cost data handled appropriately	Yes. Direct costs were based on unit cost data from Lund (the largest centre used in the trial), and a Swedish pharmaceutical lexicon. Indirect costs were estimated by the human capital method using the average annual gross salary. Short-term sick leave was based on the number of days of absence and the loss of productivity was based on the proportion of full-time work of patients aged >65 years
Modelling summary	Not undertaken
Outcome measures used in economic evaluations	Mean utilities per year and QALY gained with 1 year of treatment, based on EQ-5D data
Direction of result with appropriate quadrant location	NE quadrant. After 3 months of treatment: €43,500 per QALY; after 6 weeks treatment: €36,900 per QALY
Statistical analysis for patient-level stochastic data	Yes
Appropriateness of statistical analysis	Yes: means and standard deviations reported. No bootstrapping was undertaken, and this may have been appropriate given the small data set
Uncertainty around cost-effectiveness expressed	Not undertaken
Appropriateness of method dealing with uncertainty around cost effectiveness	NA

continued

TABLE 83 *Kobelt* et al., *2004*[163] *(cont'd)*

Sensitivity analysis	Sensitivity analysis was undertaken on all 160 patients: all patients who began one of the treatments. The main economic evaluation was based on those patients who continued to receive TNF inhibitor treatment for at least 12 months and had complete data (116 patients)
Modelling inputs and techniques appropriate	NA
Authors' conclusions	Cost-effectiveness ratios are within the generally accepted threshold of €50,000, but need to be confirmed with larger samples. Assuming that the improvements occurred within 3 months after treatment, the cost per QALY is €36,900. Sensitivity analysis, including all 160 patients, gave an estimated cost per QALY of €53,600. The cost per QALY increases for patient groups with less severe disease

TABLE 84 *Chiou* et al., *2004*[170]

Authors	Chiou, Choi, Reyes
Date	2004
Type of economic evaluation	Cost–utility analysis
Country of origin	USA
Currency used	US dollars
Year to which costs apply	2003
Perspective	Healthcare (payers)
Study population	Patients with moderate to severe RA who were deemed candidates for the following biological monotherapies and combination therapies
Intervention 1	Adalimumab
Intervention 2	Anakinra (reference case for monotherapy)
Intervention 3	Etanercept
Intervention 4	Adalimumab + MTX
Intervention 5	Anakinra + MTX
Intervention 6	Etanercept + MTX
Intervention 7	Infliximab + MTX
Source of effectiveness data	Effectiveness data were sourced from a review of previously published RCTs. The results of the review were presented to an expert panel of rheumatologists who selected the relevant clinical trials based on similar patient inclusion criteria and baseline characteristics. ACR response criteria: ACR20, ACR50 and ACR70 were used in the model. Probabilities for achieving ACR20, ACR50 and ACR70 for each treatment strategy were sourced from published literature. The absolute response rates from the clinical trial data with the most comparable patient population characteristics and study design were used as input data for the model. SAE rates were also sourced from clinical trial data. The same expert panel classified the adverse events, associated with each treatment strategy, into severity levels and estimated the corresponding medical resource use associated with each. SAEs were categorised as mild, moderate or severe. The highest frequency reported in a study was used to assign the probability within each severity classification. Probabilities for being in each health state were determined by the product of the probability of achieving each ACR response criterion and for developing different levels of SAEs, assuming that the probabilities for achieving each were independent
Cost data handled appropriately	Yes. Drug costs were based on US average wholesale prices. Healthcare resource costs for medication, injection and infusion, monitoring and management of SAEs were obtained from the 2003 American Medical Association Current Procedural Terminology (CPT codes) codebook, the 2003 Medicare Reimbursement Fee Schedule and the Medstat Diagnosis Related Group (DRG) Guide. The costs of complications were estimated as follows: a mild complication included the cost of one visit every 6 months and associated laboratory tests, the cost of a moderate complication included that of a mild complication plus the cost of antibiotics, and the cost of a severe complication included the cost of hospitalisation for pneumonia or sepsis

continued

TABLE 84 *Chiou* et al., *2004*[170] *(cont'd)*

Modelling summary	A decision tree was developed in Data 4.0 (TreeAge software) to compare the costs and outcomes of a hypothetical cohort of patients. The time-horizon was 1 year, and effectiveness was measured at 6 and 12 months. The structure of the model is flexible, allowing for data that may be available over a longer follow-up period. If effectiveness data were not available at 12 months, 6- and 12-month effectiveness data were assumed to be equivalent. Within the model 16 health states were used: these were the product of the severity of SAE and the ACR response criteria, e.g. a patient could have no ACR, ACR20, ACR50 or ACR70 and could be experiencing no SAE, mild SAEs, moderate SAEs or severe SAEs
Outcome measures used in economic evaluations	Effectiveness was measured in QALYs. It was assumed that patients would live with one of the 16 health states at any given time. Preference weights for each health state, used to calculate the QALYs, were measured using a VAS (HAQ) obtained from a survey of 748 patients with RA
Direction of result with appropriate quadrant location	NE quadrant. Monotherapies: etanercept NE quadrant, US$13,387 per QALY. Adalimumab dominated. Combination therapies: etanercept + MTX NE quadrant, US$7925. Adalimumab + MTX and infliximab + MTX dominated
Statistical analysis for patient-level stochastic data	Not undertaken
Appropriateness of statistical analysis	NA
Uncertainty around cost-effectiveness expressed	Not undertaken
Appropriateness of method dealing with uncertainty around cost effectiveness	NA
Sensitivity analysis	Yes: one-way sensitivity analyses were performed on all input variables. Cost variables were varied from 50 to 200% of baseline and probability values increased and decreased by 50% of baseline. Cost of treatment and the probability of achieving ACR response criteria were the main drivers of ICERs. Costs of SAEs, probabilities of developing SAEs, healthcare resource costs and the cost of MTX did not affect the ICERs
Modelling inputs and techniques appropriate	Yes
Authors' conclusions	Anakinra was the least expensive option and etanercept dominated other treatments. Cost of drugs and probability for achieving response were the main drivers of ICERs

TABLE 85 *Bansback* et al., *2005*[166]

Authors	Bansback, Brennan, Ghatnekar
Date	2005
Type of economic evaluation	Cost–utility analysis
Country of origin	UK, Sweden
Currency used	Euros
Year to which costs apply	2001
Perspective	Healthcare
Study population	Patients with moderate to severe RA for whom at least two traditional DMARDs had failed (simulation of 10,000 patients)
Intervention 1	Adalimumab monotherapy
Intervention 2	Adalimumab + MTX (study nos DE009 and DE019)
Intervention 3	Adalimumab + MTX (study no. DE009)
Intervention 4	Etanercept monotherapy
Intervention 5	Etanercept + MTX
Intervention 6	Infliximab + MTX

continued

TABLE 85 *Bansback* et al.*, 2005*[166] *(cont'd)*

Intervention 7	Traditional drug treatment (DMARDs)
Source of effectiveness data	Treatment response data from a published review and conference abstracts. Two combination RCTs were available for adalimumab. The first, ARMADA, was similar to the etanercept and infliximab trials in design and patient numbers. The second, a larger, more comprehensive study, also included radiographic evaluations. In Sweden, decisions to continue treatment are made using the DAS response criteria. This study presents results for two definitions of classifying successful response: ACR20 and ACR50. Comparison of trials suggests similarities between the results of ACR and DAS responses. This model assumes that ACR20 corresponds to a moderate DAS28 score and ACR50 corresponds to a good DAS score. In addition, HAQ was mapped to a health utility measure (HUI 3). Analysis of patient-level adalimumab data was used to calculate HAQ improvement in ACR20 and ACR50 responders. The model assumed that HAQ worsened after withdrawal from treatment, immediately at the point of withdrawal and equalled the initial HAQ improvement for all treatments
Cost data handled appropriately	Yes
Modelling summary	A decision-analytic model building on two previously described models. Patient-based transition state model, simulating a population of 10,000 patients. A cycle length of 6 months was used, within which the risks of withdrawal, adverse events and mortality were determined, based on experiences of an average patient. Patients were simulated for their lifetime. Model parameter values were derived from patient-level data analysis of adalimumab RCTs or published sources
Outcome measures used in economic evaluations	At each 6-month cycle in the model the patients' health-related quality of life scores were evaluated by simple linear transformation from the HAQ-DI score. From this a cost–utility analysis was possible
Direction of result with appropriate quadrant location	NE quadrant For the group ACR50/DAS28 good: €34,167 per QALY (adalimumab + MTX) €34,922 per QALY (adalimumab + MTX)[a] €35,760 per QALY (etanercept + MTX) €48,333 per QALY (infliximab + MTX) €41,561 per QALY (adalimumab) €36,927 per QALY (etanercept) For the group ACR20/DAS28 moderate: €40,875 per QALY (adalimumab + MTX) €44,018 per QALY (adalimumab + MTX)[a] €51,976 per QALY (etanercept + MTX) €64,935 per QALY (infliximab + MTX) €65,499 per QALY (adalimumab) €42,480 per QALY (etanercept)
Statistical analysis for patient-level stochastic data	Patient-level data were used to calculate HAQ improvement in patients who were ACR20 and ACR50 responders
Appropriateness of statistical analysis	Yes
Uncertainty around cost-effectiveness expressed	Yes. Cost-effectiveness acceptability curve and cost-effectiveness plane
Appropriateness of method dealing with uncertainty around cost effectiveness	Yes. Appropriate methods were used: both central values and probability density functions were used to describe the distribution of uncertainty
Sensitivity analysis	Yes. Univariate sensitivity analysis and multivariate sensitivity analysis were used. Uncertainty in assumptions around model structure was also explored
Modelling inputs and techniques appropriate	Yes
Authors' conclusions	Adalimumab appears to be cost-effective for the treatment of moderate to severe RA. Results suggest that adalimumab is at least as cost-effective as other TNF inhibitors, with the exception of infliximab; the cost results were between €35,000 and €42,000 per QALY, a range normally considered cost-effective in European countries

[a] Including additional information from a larger adalimumab trial in a pooled analysis.

TABLE 86 *Kobelt* et al.*, 2005*[167]

Authors	Kobelt, Lindgren, Singh, Klareskog
Date	2005
Type of economic evaluation	Cost–utility analysis
Country of origin	Sweden, France, USA
Currency used	Euros
Year to which costs apply	2004
Perspective	Societal
Study population	Patients with active RA who failed to respond to at least two DMARDs, other than MTX. Patients who had been previously exposed to MTX were included provided they were deemed to be appropriate candidates for MTX treatment at the time of enrolment to the study
Intervention 1	Etanercept
Intervention 2	MTX
Intervention 3	Etanercept and MTX
Source of effectiveness data	A double-blind randomised clinical trial of 682 patients (TEMPO). Disease progression is based on observed transitions in the clinical trial for patients with an HAQ measurement used at both the start and the end of each year for the first 2 years. Transition probabilities for the model beyond the trial data are based on the average reported annual progression of HAQ (0.03). Disease activity and severity was measured in TEMPO by correlating the patient global VAS with the DAS28. As a result, it was found that a DAS28 of 3.2 corresponds to a score of 41 on the global VAS
Cost data handled appropriately	Yes: direct resource use included all healthcare and community services, as well as investments, devices, transportation and informal help. Indirect costs included early retirement due to RA, long- and short-term sick leave, and loss of leisure time. Costs and benefits were discounted at 3%. Cost data came from a survey of 616 Swedish patients, related to function and disease activity, plus 1810 patients' early retirement data
Modelling summary	A Markov model was developed, with five main functional states and cut-off points at HAQ 0.6, 1.1, 1.6 and 2.1. Each state is further separated into two substrates representing high and low disease activity. All resulting ten states are further subdivided according to those receiving study treatments or not. Changes in disease status are modelled as transitions between the states at intervals of 1 year (cycles). Costs and utility are assigned to each of the 20 states, and the model estimates expected costs and QALYs for defined cohorts of patients over given periods. A Monte Carlo simulation was run and bootstrapping was used to estimate uncertainty around input values. The model was run for 10 years of treatment, or for treatment in trial only for 2 years and extrapolation to 10 years
Outcome measures used in economic evaluations	Data related to function and disease activity (EQ-5D) obtained from a survey of 1016 patients with confirmed RA, carried out in 1997, and a more recent follow-up survey, conducted in 2002, of 616 patients. EQ-5D was related to HAQ scores and disease activity using multiple regression
Direction of result with appropriate quadrant location	NE quadrant. Treatment for 2 years, extrapolation to 10 years: etanercept alone dominated. Etanercept/MTX vs MTX €37,331 per QALY Treatment for 2 years, extrapolation to 5 years: etanercept alone dominated. Etanercept/MTX vs MTX €54,548 per QALY Treatment for 10 years: etanercept/MTX vs MTX €46,494 per QALY Treatment for 5 years, extrapolation to 10 years: etanercept/MTX vs MTX €47,316 per QALY
Statistical analysis for patient-level stochastic data	Not undertaken
Appropriateness of statistical analysis	NA
Uncertainty around cost-effectiveness expressed	Yes
Appropriateness of method dealing with uncertainty around cost effectiveness	Yes: the methods used were appropriate. A Monte Carlo simulation was run and bootstrapping was used to estimate the uncertainty around the model parameter values. Cost effectiveness acceptability curves were also used

continued

TABLE 86 *Kobelt* et al.*, 2005*[167] *(cont'd)*

Sensitivity analysis	Yes: sensitivity analysis was conducted and the results were found to be most sensitive to assumptions about the costs of treatment and the difference in utility between the treatment groups
Modelling inputs and techniques appropriate	Yes
Authors' conclusions	Incorporating the influence of disease activity allows better assessment of the effects of anti-TNF treatment on patients' general well-being. The cost per QALY gained with combination treatment with etanercept with MTX compared with MTX alone falls within the acceptable range and the probability that the cost-effectiveness ratio is below a threshold of €50,000 is 88%

Appendix 9

Details of strategy sets used in BRAM

TABLE 87 *Strategy set with etanercept followed by another TNF inhibitor*

			Moves dependent on toxicity	
Treatment	**Always move to**	**Relevant toxicity**	**If toxic, move to**	**Otherwise, move to**
MTX		MTX	SSZ	MTX+SSZ
SSZ	Etan			
MTX+SSZ	Etan			
Etan	Divergence point			
Option 1	Adal			
Adal	LEF			
Option 2	Infl+MTX			
Infl+MTX	LEF			
Option 3	LEF			
LEF	GST			
GST	AZA			
AZA	CyA			
CyA		CyA or MTX	DPen	CyA+MTX
CyA+MTX	DPen			
DPen	Pall			

TABLE 88 *Strategy set with infliximab followed by another TNF inhibitor*

			Moves dependent on toxicity	
Treatment	**Always move to**	**Relevant toxicity**	**If toxic, move to**	**Otherwise, move to**
MTX		MTX	SSZ	MTX+SSZ
SSZ	Infl+MTX			
MTX+SSZ	Infl+MTX			
Infl+MTX	Divergence point			
Option 1	Adal			
Adal	LEF			
Option 2	Etan			
Etan	LEF			
Option 3	LEF			
LEF	GST			
GST	AZA			
AZA	CyA			
CyA		CyA or MTX	DPen	CyA+MTX
CyA+MTX	DPen			
DPen	Pall			

TABLE 89 *Strategy set: adalimumab and infliximab possibly followed by etanercept*

			Moves dependent on toxicity	
Treatment	**Always move to**	**Relevant toxicity**	**If toxic, move to**	**Otherwise, move to**
MTX		MTX	SSZ	MTX+SSZ
SSZ	Adal			
MTX+SSZ	Adal			
Adal	Infl+MTX			
Infl+MTX	Divergence point			
Option 1	Etan			
Etan	LEF			
Option 2	LEF			
LEF	GST			
GST	AZA			
AZA	CyA			
CyA		CyA or MTX	DPen	CyA+MTX
CyA+MTX	DPen			
DPen	Pall			

TABLE 90 *Strategy set: etanercept and adalimumab possibly followed by infliximab*

			Moves dependent on toxicity	
Treatment	**Always move to**	**Relevant toxicity**	**If toxic, move to**	**Otherwise, move to**
MTX		MTX	SSZ	MTX+SSZ
SSZ	Etan			
MTX+SSZ	Etan			
Etan	Adal			
Adal	Divergence point			
Option 1	Infl+MTX			
Infl+MTX	LEF			
Option 2	LEF			
LEF	GST			
GST	AZA			
AZA	CyA			
CyA		CyA or MTX	DPen	CyA+MTX
CyA+MTX	DPen			
DPen	Pall			

TABLE 91 *Strategy set: etanercept and infliximab possibly followed by adalimumab*

			Moves dependent on toxicity	
Treatment	**Always move to**	**Relevant toxicity**	**If toxic, move to**	**Otherwise, move to**
MTX		MTX	SSZ	MTX+SSZ
SSZ	Etan			
MTX+SSZ	Etan			
Etan	Infl+MTX			
Infl+MTX	Divergence point			
Option 1	Adal			
Adal	LEF			
Option 2	LEF			
LEF	GST			
GST	AZA			
AZA	CyA			
CyA		CyA or MTX	DPen	CyA+MTX
CyA+MTX	DPen			
DPen	Pall			

TABLE 92 *Strategy set: infliximab and adalimumab possibly followed by etanercept*

			Moves dependent on toxicity	
Treatment	**Always move to**	**Relevant toxicity**	**If toxic, move to**	**Otherwise, move to**
MTX		MTX	SSZ	MTX+SSZ
SSZ	Infl+MTX			
MTX+SSZ	Infl+MTX			
Infl+MTX	Adal			
Adal	Divergence point			
Option 1	Etan			
Etan	LEF			
Option 2	LEF			
LEF	GST			
GST	AZA			
AZA	CyA			
CyA		CyA or MTX	DPen	CyA+MTX
CyA+MTX	DPen			
DPen	Pall			

TABLE 93 *Strategy set: infliximab and etanercept possibly followed by adalimumab*

			Moves dependent on toxicity	
Treatment	**Always move to**	**Relevant toxicity**	**If toxic, move to**	**Otherwise, move to**
MTX		MTX	SSZ	MTX+SSZ
SSZ	Infl+MTX			
MTX+SSZ	Infl+MTX			
Infl+MTX	Etan			
Etan	Divergence point			
Option 1	Adal			
Adal	LEF			
Option 2	LEF			
LEF	GST			
GST	AZA			
AZA	CyA			
CyA		CyA or MTX	DPen	CyA+MTX
CyA+MTX	DPen			
DPen	Pall			

Appendix 10
Sensitivity analysis

Extensive sensitivity analysis was carried out for all strategy sets involving the use of a single TNF inhibitor. As in the base case, for the HAQ improvement on starting a TNF inhibitor, the early RA values were used for the strategy set involving TNF inhibitors at the start, the late RA values were used for TNF inhibitors last, and both sets of values were used for TNF inhibitors in third place.

There is a total of 18 variations on the original parameter set. These are described in detail at the start of each set of results. In each case, all parameters not mentioned in the description of the variation were assumed to take their base-case values.

Variation 1

For this variation, it was assumed that there was no progression in HAQ score while on TNF inhibitors, and progression was as for the base case on other treatments.

TABLE 94 *Variation 1: TNF inhibitors first (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	49,558	103	9.5740	0.0182
Etan	64,270	125	10.3899	0.0201
Adal+MTX	49,912	104	9.2247	0.0177
Etan+MTX	64,499	126	10.0596	0.0200
Infl+MTX	49,188	99	9.0404	0.0177
Base	15,322	21	8.3056	0.0158
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	34,236	101	1.2685	0.0177
Etan – Base	48,948	122	2.0844	0.0191
Ad+M – Base	34,590	103	0.9191	0.0177
Et+M – Base	49,177	124	1.7541	0.0192
In+M – Base	33,866	97	0.7348	0.0175
Ad+M – Adal	354	141	–0.3493	0.0187
Et+M – Etan	229	167	–0.3303	0.0210
Etan – Adal	14,712	154	0.8159	0.0198
Et+M – Ad+M	14,587	156	0.8349	0.0200
Ad+M – In+M	724	138	0.1844	0.0185
Et+M – In+M	15,311	153	1.0193	0.0199
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	27,000		26,200 to 27,800	
Etan – Base	23,500		23,000 to 23,900	
Ad+M – Base	37,600		36,200 to 39,200	
Et+M – Base	28,000		27,400 to 28,700	
In+M – Base	46,100		44,000 to 48,400	
Ad+M – Adal	Adal alone dominates Adal+MTX			
Et+M – Etan	Etan alone more effective than Etan+MTX; diff. cost not significant			
Etan – Adal	18,000		17,100 to 19,000	
Et+M – Ad+M	17,500		16,600 to 18,400	
Ad+M – In+M	3,930		2,230 to 5,620	
Et+M – In+M	15,000		14,400 to 15,700	

TABLE 95 *Variation 1: TNF inhibitors third (early RA values) (20,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	48,371	221	6.8542	0.0366
Etan	61,650	271	7.7651	0.0413
Adal+MTX	48,830	224	7.0461	0.0368
Etan+MTX	61,349	270	7.8660	0.0416
Infl+MTX	48,298	212	6.9820	0.0365
Base	16,444	51	5.3484	0.0306
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	31,926	217	1.5058	0.0352
Etan – Base	45,206	263	2.4167	0.0390
Ad+M – Base	32,386	220	1.6977	0.0353
Et+M – Base	44,905	262	2.5176	0.0397
In+M – Base	31,854	208	1.6336	0.0352
Ad+M – Adal	459	295	0.1919	0.0380
Etan – Et+M	301	351	–0.1009	0.0440
Etan – Adal	13,280	326	0.9109	0.0411
Et+M – Ad+M	12,519	327	0.8199	0.0418
In+M – Ad+M	532	289	0.0641	0.0383
Et+M – In+M	13,051	321	0.8840	0.0415
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	21,200		20,200 to 22,300	
Etan – Base	18,700		18,100 to 19,400	
Ad+M – Base	19,100		18,300 to 19,900	
Et+M – Base	17,800		17,300 to 18,500	
In+M – Base	19,500		18,700 to 20,400	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Etan – Et+M	Etan+MTX more effective than Etan alone; diff. cost not significant			
Etan – Adal	14,600		13,200 to 16,200	
Et+M – Ad+M	15,300		13,700 to 17,200	
In+M – Ad+M	Comparison is inconclusive			
Et+M – In+M	14,800		13,300 to 16,500	

TABLE 96 *Variation 1: TNF inhibitors third (late RA values) (40,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	47,664	156	6.1760	0.0254
Etan	60,598	191	7.2320	0.0286
Adal+MTX	48,194	157	6.4741	0.0253
Etan+MTX	60,894	191	7.2297	0.0289
Infl+MTX	47,561	149	6.2132	0.0254
Base	16,490	36	5.4254	0.0218
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	31,174	152	0.7506	0.0234
Etan – Base	44,107	185	1.8066	0.0264
Ad+M – Base	31,704	153	1.0487	0.0238
Et+M – Base	44,404	186	1.8043	0.0268
In+M – Base	31,071	145	0.7878	0.0237
Ad+M – Adal	530	206	0.2981	0.0245
Et+M – Etan	296	247	0.0023	0.0293
Etan – Adal	12,934	228	1.0560	0.0269
Et+M – Ad+M	12,700	230	0.7556	0.0276
Ad+M – In+M	633	202	0.2609	0.0248
Et+M – In+M	13,333	224	1.0165	0.0273

continued

TABLE 96 *Variation 1: TNF inhibitors third (late RA values) (40,000 patients) (cont'd)*

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	41,500	39,100 to 44,300
Etan – Base	24,400	23,700 to 25,200
Ad+M – Base	30,200	28,900 to 31,700
Et+M – Base	24,600	23,900 to 25,400
In+M – Base	39,400	37,200 to 42,000
Ad+M – Adal	1,780	362 to 3,190
Et+M – Etan	Comparison is inconclusive	
Etan – Adal	12,200	11,500 to 13,100
Et+M – Ad+M	16,800	15,500 to 18,300
Ad+M – In+M	2,420	811 to 4,040
Et+M – In+M	13,100	12,300 to 14,000

TABLE 97 *Variation 1: TNF inhibitors last (20,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	36,801	219	2.3062	0.0253
Etan	49,842	267	3.6405	0.0320
Adal+MTX	37,043	221	2.5987	0.0259
Etan+MTX	49,381	267	3.6409	0.0323
Infl+MTX	36,517	211	2.3587	0.0258
Base	2,848	11	1.0512	0.0185
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	33,954	217	1.2550	0.0188
Etan – Base	46,994	264	2.5893	0.0276
Ad+M – Base	34,195	219	1.5475	0.0202
Et+M – Base	46,533	264	2.5897	0.0282
In+M – Base	33,670	209	1.3076	0.0198
Ad+M – Adal	242	301	0.2925	0.0246
Etan – Et+M	461	353	–0.0004	0.0361
Etan – Adal	13,041	330	1.3343	0.0305
Et+M – Ad+M	12,338	331	1.0422	0.0321
Ad+M – In+M	526	294	0.2400	0.0253
Et+M – In+M	12,863	323	1.2821	0.0315
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	27,100		26,200 to 28,000	
Etan – Base	18,100		17,700 to 18,600	
Ad+M – Base	22,100		21,500 to 22,800	
Et+M – Base	18,000		17,500 to 18,400	
In+M – Base	25,700		24,900 to 26,600	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Et+M – Etan	Comparison is inconclusive			
Etan – Adal	9,770		9,110 to 10,400	
Et+M – Ad+M	11,800		10,900 to 12,900	
Ad+M – In+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant			
Et+M – In+M	10,000		9,330 to 10,700	

Variation 2

For this variation, it was assumed that HAQ progression on all active treatments was at 0.03 per year.

TABLE 98 *Variation 2: TNF inhibitors first (200,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	49,443	72	9.5963	0.0130
Etan	63,882	87	9.8239	0.0132
Adal+MTX	49,787	73	9.0930	0.0122
Etan+MTX	64,093	88	9.3620	0.0122
Infl+MTX	49,186	70	8.9392	0.0122
Base	15,420	15	9.2826	0.0125
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	34,023	71	0.3137	0.0128
Etan – Base	48,462	85	0.5413	0.0130
Ad+M – Base	34,367	72	–0.1896	0.0125
Et+M – Base	48,673	86	0.0794	0.0128
In+M – Base	33,766	68	–0.3433	0.0125
Ad+M – Adal	345	98	–0.5033	0.0127
Et+M – Etan	211	116	–0.4619	0.0131
Etan – Adal	14,440	107	0.2276	0.0131
Et+M – Ad+M	14,306	109	0.2690	0.0126
Ad+M – In+M	601	97	0.1537	0.0123
Et+M – In+M	14,907	107	0.4228	0.0126

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	108,000	100,000 to 118,000
Etan – Base	89,500	85,400 to 94,100
Ad+M – Base	Base dominates Adal+MTX	
Et+M – Base	613,000	463,000 to 906,000
In+M – Base	Base dominates Infl+MTX	
Ad+M – Adal	Adal alone dominates Adal+MTX	
Et+M – Etan	Etan alone more effective than Etan+MTX; diff. cost not significant	
Etan – Adal	63,500	56,900 to 71,800
Et+M – Ad+M	53,200	48,600 to 58,700
Ad+M – In+M	3,910	2,510 to 5,310
Et+M – In+M	35,300	33,200 to 37,600

TABLE 99 *Variation 2: TNF inhibitors third (early RA values) (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	48,569	98	6.9994	0.0159
Etan	61,074	119	7.4020	0.0166
Adal+MTX	48,640	98	7.1398	0.0159
Etan+MTX	61,329	119	7.4999	0.0166
Infl+MTX	48,158	94	7.0644	0.0158
Base	16,590	23	6.2559	0.0151
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	31,979	96	0.7435	0.0155
Etan – Base	44,484	116	1.1462	0.0161
Ad+M – Base	32,049	96	0.8840	0.0156
Et+M – Base	44,738	116	1.2441	0.0162
In+M – Base	31,567	92	0.8086	0.0155
Ad+M – Adal	70	131	0.1405	0.0160
Et+M – Etan	255	154	0.0979	0.0171
Etan – Adal	12,505	144	0.4027	0.0165

continued

TABLE 99 *Variation 2: TNF inhibitors third (early RA values) (100,000 patients) (cont'd)*

Et+M – Ad+M	12,689	144	0.3601	0.0166
Ad+M – In+M	482	128	0.0754	0.0160
Et+M – In+M	13,171	141	0.4355	0.0165

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	43,000	41,300 to 44,900
Etan – Base	38,800	37,700 to 40,000
Ad+M – Base	36,300	35,000 to 37,600
Et+M – Base	36,000	35,000 to 36,900
In+M – Base	39,000	37,600 to 40,600
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Et+M – Etan	Etan+MTX more effective than Etan alone; diff. cost not significant	
Etan – Adal	31,100	28,600 to 33,900
Et+M – Ad+M	35,200	32,200 to 38,900
Ad+M – In+M	6,390	2,050 to 10,700
Et+M – In+M	30,200	28,000 to 32,800

TABLE 100 *Variation 2: TNF inhibitors third (late RA values) (400,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	47,823	49	6.3067	0.0079
Etan	60,550	59	6.8904	0.0082
Adal+MTX	48,056	49	6.5602	0.0079
Etan+MTX	60,660	59	6.8825	0.0082
Infl+MTX	47,505	47	6.3152	0.0079
Base	16,546	11	6.2482	0.0075

Comparison	Diff. cost (£)	QSE	Diff. QALY	QSE
Adal – Base	31,277	48	0.0584	0.0075
Etan – Base	44,004	58	0.6421	0.0079
Ad+M – Base	31,510	48	0.3119	0.0076
Et+M – Base	44,114	58	0.6343	0.0079
In+M – Base	30,959	46	0.0669	0.0076
Ad+M – Adal	233	65	0.2535	0.0075
Et+M – Etan	111	77	–0.0079	0.0082
Etan – Adal	12,727	71	0.5837	0.0078
Et+M – Ad+M	12,605	71	0.3223	0.0079
Ad+M – In+M	551	63	0.2450	0.0076
Et+M – In+M	13,155	70	0.5673	0.0079

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	535,000	426,000 to 721,000
Etan – Base	68,500	66,900 to 70,300
Ad+M – Base	101,000	96,300 to 106,000
Et+M – Base	69,600	67,800 to 71,300
In+M – Base	462,000	377,000 to 597,000
Ad+M – Adal	920	407 to 1,430
Et+M – Etan	Comparison is inconclusive	
Etan – Adal	21,800	21,200 to 22,500
Et+M – Ad+M	39,100	37,200 to 41,200
Ad+M – In+M	2,250	1,710 to 2,780
Et+M – In+M	23,200	22,500 to 23,900

TABLE 101 *Variation 2: TNF inhibitors last (40,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	36,137	151	2.5122	0.0164
Etan	49,203	186	3.5657	0.0193
Adal+MTX	36,712	154	2.7769	0.0166
Etan+MTX	49,570	187	3.5483	0.0196
Infl+MTX	36,295	147	2.5568	0.0167
Base	2,866	8	1.6689	0.0141
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	33,271	150	0.8433	0.0120
Etan – Base	46,337	184	1.8969	0.0163
Ad+M – Base	33,846	152	1.1080	0.0128
Et+M – Base	46,704	185	1.8794	0.0166
In+M – Base	33,429	145	0.8879	0.0125
Ad+M – Adal	575	208	0.2647	0.0148
Et+M – Etan	366	247	–0.0175	0.0209
Etan – Adal	13,066	228	1.0535	0.0179
Et+M – Ad+M	12,857	229	0.7714	0.0185
Ad+M – In+M	417	205	0.2201	0.0153
Et+M – In+M	13,275	226	0.9915	0.0185
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	39,500		38,300 to 40,700	
Etan – Base	24,400		24,000 to 24,900	
Ad+M – Base	30,500		29,800 to 31,300	
Et+M – Base	24,900		24,400 to 25,300	
In+M – Base	37,600		36,600 to 38,800	
Ad+M – Adal	2,170		583 to 3,760	
Et+M – Etan		Comparison is inconclusive		
Etan – Adal	12,400		11,800 to 13,000	
Et+M – Ad+M	16,700		15,700 to 17,700	
Ad+M – In+M	1,900		11 to 3,780	
Et+M – In+M	13,400		12,700 to 14,100	

Variation 3

For this variation, it was assumed that HAQ progression on all treatments (including palliation) was at 0.03 per year.

TABLE 102 *Variation 3: TNF inhibitors first (200,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	49,569	72	9.7112	0.0131
Etan	63,858	87	9.8759	0.0133
Adal+MTX	49,774	73	9.2703	0.0124
Etan+MTX	64,028	88	9.5070	0.0128
Infl+MTX	49,024	69	9.1106	0.0125
Base	15,432	15	9.4317	0.0127
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	34,137	71	0.2796	0.0127
Etan – Base	48,426	85	0.4442	0.0129
Ad+M – Base	34,342	72	–0.1614	0.0124
Et+M – Base	48,596	86	0.0754	0.0127
In+M – Base	33,592	68	–0.3210	0.0124
Ad+M – Adal	205	98	–0.4410	0.0125

continued

TABLE 102 *Variation 3: TNF inhibitors first (200,000 patients) (cont'd)*

Et+M – Etan	170	116	–0.3689	0.0130
Etan – Adal	14,288	107	0.1647	0.0130
Et+M – Ad+M	14,254	109	0.2368	0.0124
Ad+M – In+M	750	97	0.1596	0.0121
Et+M – In+M	15,004	107	0.3964	0.0124

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	122,000	112,000 to 134,000
Etan – Base	109,000	103,000 to 116,000
Ad+M – Base	Base dominates Adal+MTX	
Et+M – Base	645,000	483,000 to 971,000
In+M – Base	Base dominates Infl+MTX	
Ad+M – Adal	Adal alone dominates Adal+MTX	
Et+M – Etan	Etan alone more effective than Etan+MTX; diff. cost not significant	
Etan – Adal	86,800	74,900 to 103,000
Et+M – Ad+M	60,200	54,400 to 67,300
Ad+M – In+M	4,700	3,290 to 6,110
Et+M – In+M	37,900	35,600 to 40,500

TABLE 103 *Variation 3: TNF inhibitors third (early RA values) (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	48,353	98	7.1282	0.0162
Etan	61,090	119	7.5230	0.0169
Adal+MTX	48,521	98	7.2854	0.0163
Etan+MTX	61,314	119	7.6104	0.0169
Infl+MTX	48,159	94	7.2431	0.0162
Base	16,597	23	6.5465	0.0157

Comparison	Diff. cost (£)	QSE	Diff. QALY	QSE
Adal – Base	31,756	96	0.5816	0.0153
Etan – Base	44,493	115	0.9765	0.0160
Ad+M – Base	31,924	96	0.7389	0.0153
Et+M – Base	44,717	116	1.0639	0.0160
In+M – Base	31,562	92	0.6966	0.0153
Ad+M – Adal	169	131	0.1573	0.0157
Et+M – Etan	224	155	0.0874	0.0169
Etan – Adal	12,737	144	0.3948	0.0164
Et+M – Ad+M	12,792	144	0.3250	0.0163
Ad+M – In+M	363	128	0.0423	0.0157
Et+M – In+M	13,155	141	0.3673	0.0163

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	54,600	51,900 to 57,700
Etan – Base	45,600	44,100 to 47,100
Ad+M – Base	43,200	41,500 to 45,100
Et+M – Base	42,000	40,800 to 43,400
In+M – Base	45,300	43,400 to 47,400
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Et+M – Etan	Etan+MTX more effective than Etan alone; diff. cost not significant	
Etan – Adal	32,300	29,700 to 35,300
Et+M – Ad+M	39,400	35,700 to 43,900
Ad+M – In+M	8,570	Not determined
Et+M – In+M	35,800	32,800 to 39,400

TABLE 104 *Variation 3: TNF inhibitors third (late RA values) (200,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	47,618	69	6.4691	0.0115
Etan	60,491	84	7.0178	0.0117
Adal+MTX	48,013	69	6.7402	0.0114
Etan+MTX	60,620	84	7.0029	0.0119
Infl+MTX	47,539	66	6.5037	0.0115
Base	16,572	16	6.5310	0.0111
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	31,046	67	–0.0620	0.0105
Etan – Base	43,919	81	0.4868	0.0109
Ad+M – Base	31,441	68	0.2092	0.0106
Et+M – Base	44,048	82	0.4719	0.0111
In+M – Base	30,966	65	–0.0274	0.0105
Ad+M – Adal	394	91	0.2712	0.0106
Et+M – Etan	130	109	–0.0148	0.0115
Etan – Adal	12,872	100	0.5487	0.0110
Et+M – Ad+M	12,608	101	0.2627	0.0111
Ad+M – In+M	474	90	0.2366	0.0106
Et+M – In+M	13,082	99	0.4993	0.0112
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base		Base dominates Adal		
Etan – Base	90,200		86,300 to 94,500	
Ad+M – Base	150,000		137,000 to 167,000	
Et+M – Base	93,300		89,100 to 97,900	
In+M – Base		Base dominates Infl+MTX		
Ad+M – Adal	1,450		770 to 2,140	
Et+M – Etan		Comparison is inconclusive		
Etan – Adal	23,500		22,500 to 24,500	
Et+M – Ad+M	48,000		44,200 to 52,500	
Ad+M – In+M	2,000		1,230 to 2,780	
Et+M – In+M	26,200		25,000 to 27,500	

TABLE 105 *Variation 3: TNF inhibitors last (20,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	36,505	217	3.0616	0.0268
Etan	49,138	263	3.9234	0.0289
Adal+MTX	36,861	219	3.3262	0.0268
Etan+MTX	48,704	263	3.8854	0.0295
Infl+MTX	36,554	210	3.0937	0.0273
Base	2,913	12	2.5375	0.0256
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	33,591	214	0.5241	0.0188
Etan – Base	46,224	260	1.3859	0.0237
Ad+M – Base	33,947	217	0.7887	0.0196
Et+M – Base	45,790	260	1.3479	0.0238
In+M – Base	33,640	208	0.5562	0.0192
Ad+M – Adal	356	297	0.2646	0.0216
Etan – Et+M	434	348	0.0380	0.0290
Etan – Adal	12,633	323	0.8618	0.0255
Et+M – Ad+M	11,843	326	0.5592	0.0260
In+M – Ad+M	307	292	0.2325	0.0222
Et+M – In+M	12,150	319	0.7917	0.0260

continued

TABLE 105 *Variation 3: TNF inhibitors last (20,000 patients) (cont'd)*

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	64,100	59,700 to 69,100
Etan – Base	33,400	32,200 to 34,600
Ad+M – Base	43,000	40,900 to 45,400
Et+M – Base	34,000	32,800 to 35,300
In+M – Base	60,500	56,500 to 65,000
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Etan – Et+M	Comparison is inconclusive	
Etan – Adal	14,700	13,600 to 15,900
Et+M – Ad+M	21,200	19,100 to 23,700
In+M – Ad+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant	
Et+M – In+M	15,300	14,200 to 16,800

Variation 4

For this variation, it was assumed that HAQ progression on all treatments was at 0.06 per year.

TABLE 106 *Variation 4: TNF inhibitors first (1,000,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	49,224	32	7.7643	0.0046
Etan	63,281	39	7.8800	0.0047
Adal+MTX	49,404	32	7.3785	0.0044
Etan+MTX	63,465	39	7.5377	0.0045
Infl+MTX	48,751	31	7.2236	0.0044
Base	15,234	7	7.3969	0.0044
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	33,990	31	0.3674	0.0049
Etan – Base	48,047	38	0.4830	0.0050
Ad+M – Base	34,170	32	–0.0185	0.0048
Et+M – Base	48,231	38	0.1408	0.0049
In+M – Base	33,517	30	–0.1733	0.0048
Ad+M – Adal	180	44	–0.3858	0.0049
Et+M – Etan	184	51	–0.3423	0.0050
Etan – Adal	14,057	47	0.1157	0.0050
Et+M – Ad+M	14,061	48	0.1592	0.0048
In+M – Ad+M	653	43	0.1548	0.0047
Et+M – In+M	14,714	47	0.3141	0.0048
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	92,500		90,100 to 95,100	
Etan – Base	99,500		97,500 to 102,000	
Ad+M – Base	Base dominates Adal+MTX			
Et+M – Base	343,000		320,000 to 368,000	
In+M – Base	Base dominates Infl+MTX			
Ad+M – Adal	Adal alone dominates Adal+MTX			
Et+M – Etan	Etan alone dominates Etan+MTX			
Etan – Adal	122,000		112,000 to 133,000	
Et+M – Ad+M	88,300		83,200 to 94,000	
In+M – Ad+M	4,220		3,610 to 4,830	
Et+M – In+M	46,900		45,400 to 48,400	

TABLE 107 *Variation 4: TNF inhibitors third (early RA values) (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	48,100	97	5.2549	0.0131
Etan	60,598	117	5.5899	0.0135
Adal+MTX	48,344	98	5.4002	0.0129
Etan+MTX	60,707	118	5.6922	0.0135
Infl+MTX	47,877	93	5.3595	0.0130
Base	16,461	23	4.6139	0.0125
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	31,639	95	0.6409	0.0136
Etan – Base	44,137	114	0.9759	0.0141
Ad+M – Base	31,883	96	0.7863	0.0136
Et+M – Base	44,246	115	1.0782	0.0142
In+M – Base	31,415	91	0.7455	0.0135
Ad+M – Adal	244	130	0.1454	0.0141
Et+M – Etan	109	153	0.1023	0.0150
Etan – Adal	12,498	142	0.3350	0.0145
Et+M – Ad+M	12,363	142	0.2919	0.0145
Ad+M – In+M	467	127	0.0408	0.0140
Et+M – In+M	12,831	141	0.3327	0.0145
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	49,400		47,300 to 51,600	
Etan – Base	45,200		43,900 to 46,600	
Ad+M – Base	40,500		39,200 to 42,000	
Et+M – Base	41,000		40,000 to 42,200	
In+M – Base	42,100		40,600 to 43,700	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Et+M – Etan	Etan+MTX more effective than Etan alone; diff. cost not significant			
Etan – Adal	37,300		34,200 to 41,000	
Et+M – Ad+M	42,400		38,400 to 47,200	
Ad+M – In+M	11,500		6,110 to 92,700	
Et+M – In+M	38,600		35,400 to 42,400	

TABLE 108 *Variation 4: TNF inhibitors third (late RA values) (200,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	47,417	68	4.5550	0.0092
Etan	59,961	83	5.0714	0.0094
Adal+MTX	47,781	69	4.8287	0.0091
Etan+MTX	60,035	83	5.0689	0.0095
Infl+MTX	47,068	66	4.5821	0.0092
Base	16,382	16	4.6147	0.0088
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	31,034	67	–0.0596	0.0093
Etan – Base	43,579	80	0.4568	0.0097
Ad+M – Base	31,399	67	0.2141	0.0093
Et+M – Base	43,652	81	0.4542	0.0097
In+M – Base	30,686	64	–0.0325	0.0093
Ad+M – Adal	364	90	0.2737	0.0093
Et+M – Etan	73	107	–0.0025	0.0101
Etan – Adal	12,545	99	0.5164	0.0097
Et+M – Ad+M	12,254	100	0.2402	0.0098
In+M – Ad+M	713	89	0.2466	0.0094
Et+M – In+M	12,967	98	0.4867	0.0098

continued

TABLE 108 *Variation 4: TNF inhibitors third (late RA values) (200,000 patients) (cont'd)*

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	Base dominates Adal	
Etan – Base	95,400	91,500 to 99,600
Ad+M – Base	147,000	135,000 to 161,000
Et+M – Base	96,100	92,100 to 100,000
In+M – Base	Base dominates Infl+MTX	
Ad+M – Adal	1,330	665 to 2,000
Et+M – Etan	Comparison is inconclusive	
Etan – Adal	24,300	23,300 to 25,300
Et+M – Ad+M	51,000	47,100 to 55,700
In+M – Ad+M	2,890	2,140 to 3,640
Et+M – In+M	26,600	25,500 to 27,800

TABLE 109 *Variation 4: TNF inhibitors last (20,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	35,868	213	1.0425	0.0190
Etan	48,695	259	1.9916	0.0222
Adal+MTX	36,319	215	1.3258	0.0191
Etan+MTX	48,859	259	2.0122	0.0229
Infl+MTX	35,780	206	1.0933	0.0194
Base	2,833	11	0.4757	0.0166
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	33,035	211	0.5668	0.0142
Etan – Base	45,863	256	1.5159	0.0195
Ad+M – Base	33,486	213	0.8501	0.0149
Et+M – Base	46,027	256	1.5365	0.0203
In+M – Base	32,947	204	0.6176	0.0149
Ad+M – Adal	451	291	0.2834	0.0179
Et+M – Etan	164	339	0.0206	0.0258
Etan – Adal	12,827	321	0.9492	0.0217
Et+M – Ad+M	12,541	320	0.6864	0.0231
Ad+M – In+M	539	287	0.2325	0.0186
Et+M – In+M	13,080	316	0.9189	0.0231
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	58,300		55,400 to 61,500	
Etan – Base	30,300		29,400 to 31,100	
Ad+M – Base	39,400		38,000 to 40,900	
Et+M – Base	30,000		29,100 to 30,800	
In+M – Base	53,300		50,800 to 56,100	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Et+M – Etan	Comparison is inconclusive			
Etan – Adal	13,500		12,600 to 14,400	
Et+M – Ad+M	18,300		16,800 to 20,000	
Ad+M – In+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant			
Et+M – In+M	14,200		13,300 to 15,300	

Variation 5

For this variation, no effect of HAQ on mortality was assumed.

TABLE 110 *Variation 5: TNF inhibitors first (2,000,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	51,012	23	9.3150	0.0038
Etan	65,955	28	9.6947	0.0040
Adal+MTX	50,983	23	8.7897	0.0036
Etan+MTX	66,074	28	9.2429	0.0039
Infl+MTX	50,480	22	8.6424	0.0036
Base	16,139	5	8.6245	0.0036
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	34,873	23	0.6905	0.0039
Etan – Base	49,817	28	1.0702	0.0040
Ad+M – Base	34,844	23	0.1652	0.0038
Et+M – Base	49,935	28	0.6185	0.0040
In+M – Base	34,341	22	0.0179	0.0038
Adal – Ad+M	29	32	0.5253	0.0039
Et+M – Etan	118	38	–0.4518	0.0041
Etan – Adal	14,943	35	0.3797	0.0041
Et+M – Ad+M	15,091	35	0.4533	0.0040
Ad+M – In+M	503	31	0.1473	0.0038
Et+M – In+M	15,594	35	0.6005	0.0040
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	50,500		49,900 to 51,100	
Etan – Base	46,500		46,200 to 46,900	
Ad+M – Base	211,000		202,000 to 221,000	
Et+M – Base	80,700		79,700 to 81,800	
In+M – Base	1,910,000		1,340,000 to 3,340,000	
Adal – Ad+M	Adal alone more effective than Adal+MTX; diff. cost not significant			
Et+M – Etan	Etan alone dominates Etan+MTX			
Etan – Adal	39,400		38,500 to 40,200	
Et+M – Ad+M	33,300		32,700 to 33,900	
Ad+M – In+M	3,410		2,950 to 3,870	
Et+M – In+M	26,000		25,600 to 26,300	

TABLE 111 *Variation 5: TNF inhibitors third (early RA values) (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	49,798	100	6.3972	0.0153
Etan	63,034	121	6.9544	0.0163
Adal+MTX	49,814	100	6.5335	0.0153
Etan+MTX	62,915	121	7.0522	0.0163
Infl+MTX	49,551	96	6.4934	0.0153
Base	17,285	23	5.3888	0.0142
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	32,513	98	1.0083	0.0152
Etan – Base	45,749	118	1.5656	0.0161
Ad+M – Base	32,529	98	1.1447	0.0152
Et+M – Base	45,630	118	1.6634	0.0162
In+M – Base	32,266	94	1.1046	0.0152
Ad+M – Adal	16	134	0.1364	0.0158
Etan – Et+M	119	158	–0.0978	0.0173
Etan – Adal	13,236	147	0.5573	0.0166

continued

TABLE 111 *Variation 5: TNF inhibitors third (early RA values) (100,000 patients) (cont'd)*

Et+M – Ad+M	13,101	148	0.5187	0.0166
Ad+M – In+M	263	131	0.0401	0.0158
Et+M – In+M	13,364	145	0.5588	0.0166

Comparison	**ICER (£ per QALY)**	**Quasi-CI**
Adal – Base	32,200	31,300 to 33,300
Etan – Base	29,200	28,600 to 29,900
Ad+M – Base	28,400	27,700 to 29,200
Et+M – Base	27,400	26,900 to 28,000
In+M – Base	29,200	28,400 to 30,100
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Et+M – Etan	Etan+MTX more effective than Etan alone; diff. cost not significant	
Etan – Adal	23,800	22,300 to 25,400
Et+M – Ad+M	25,300	23,700 to 27,100
Ad+M – In+M	6,560	Dominates to 14,900
Et+M – In+M	23,900	22,500 to 25,500

TABLE 112 *Variation 5: TNF inhibitors third (late RA values) (100,000 patients)*

Option	**Cost (£)**	**QSE**	**QALYs**	**QSE**
Adal	49,757	99	5.7131	0.0151
Etan	62,853	121	6.4337	0.0159
Adal+MTX	49,833	100	5.9854	0.0151
Etan+MTX	62,864	121	6.4188	0.0162
Infl+MTX	49,590	96	5.7287	0.0152
Base	17,271	23	5.3807	0.0142

Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	32,487	98	0.3324	0.0145
Etan – Base	45,582	118	1.0530	0.0154
Ad+M – Base	32,562	98	0.6047	0.0146
Et+M – Base	45,594	118	1.0381	0.0157
In+M – Base	32,319	94	0.3481	0.0146
Ad+M – Adal	75	134	0.2723	0.0147
Et+M – Etan	11	158	–0.0149	0.0164
Etan – Adal	13,096	147	0.7206	0.0154
Et+M – Ad+M	13,032	148	0.4334	0.0158
Ad+M – In+M	243	131	0.2566	0.0148
Et+M – In+M	13,274	145	0.6900	0.0158

Comparison	**ICER (£ per QALY)**	**Quasi-CI**
Adal – Base	97,700	89,900 to 107,000
Etan – Base	43,300	42,000 to 44,600
Ad+M – Base	53,800	51,400 to 56,600
Et+M – Base	43,900	42,600 to 45,300
In+M – Base	92,900	85,600 to 101,000
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Et+M – Etan	Comparison is inconclusive	
Etan – Adal	18,200	17,300 to 19,100
Et+M – Ad+M	30,100	27,900 to 32,600
Ad+M – In+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant	
Et+M – In+M	19,200	18,300 to 20,300

TABLE 113 *Variation 5: TNF inhibitors last (20,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	38,154	224	1.6229	0.0230
Etan	51,491	271	2.8279	0.0280
Adal+MTX	37,604	223	1.9000	0.0234
Etan+MTX	51,024	270	2.7969	0.0282
Infl+MTX	37,743	213	1.6469	0.0235
Base	3,258	12	0.7532	0.0194
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	34,896	223	0.8697	0.0163
Etan – Base	48,233	269	2.0746	0.0237
Ad+M – Base	34,346	221	1.1468	0.0174
Et+M – Base	47,766	267	2.0437	0.0243
In+M – Base	34,485	212	0.8937	0.0172
Adal – Ad+M	550	305	–0.2771	0.0207
Etan – Et+M	467	360	0.0309	0.0311
Etan – Adal	13,338	335	1.2049	0.0258
Et+M – Ad+M	13,420	334	0.8970	0.0272
In+M – Ad+M	139	298	–0.2530	0.0214
Et+M – In+M	13,281	329	1.1500	0.0269
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	40,100		38,600 to 41,800	
Etan – Base	23,200		22,700 to 23,900	
Ad+M – Base	30,000		29,000 to 31,000	
Et+M – Base	23,400		22,800 to 24,000	
In+M – Base	38,600		37,100 to 40,200	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Et+M – Etan	Comparison is inconclusive			
Etan – Adal	11,100		10,300 to 11,800	
Et+M – Ad+M	15,000		13,900 to 16,200	
In+M – Ad+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant			
Et+M – In+M	11,500		10,800 to 12,300	

Variation 6

In this variation, a mortality ratio of 2.73^{HAQ} was assumed, as reported by Sokka and colleagues.[199]

TABLE 114 *Variation 6: TNF inhibitors first (200,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	45,580	69	7.9578	0.0116
Etan	58,199	84	8.2524	0.0121
Adal+MTX	46,298	71	7.7037	0.0110
Etan+MTX	58,780	85	8.0276	0.0116
Infl+MTX	45,229	67	7.5142	0.0110
Base	13,334	15	7.4406	0.0107
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	32,246	68	0.5172	0.0113
Etan – Base	44,866	81	0.8118	0.0116
Ad+M – Base	32,965	69	0.2631	0.0110
Et+M – Base	45,447	82	0.5870	0.0114
In+M – Base	31,896	65	0.0737	0.0109
Ad+M – Adal	718	93	–0.2541	0.0113
Et+M – Etan	581	109	–0.2248	0.0121

continued

TABLE 114 *Variation 6: TNF inhibitors first (200,000 patients) (cont'd)*

Etan – Adal	12,620	101	0.2947	0.0119
Et+M – Ad+M	12,482	103	0.3239	0.0115
Ad+M – In+M	1,069	92	0.1895	0.0110
Et+M – In+M	13,551	101	0.5134	0.0115

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	62,300	59,700 to 65,200
Etan – Base	55,300	53,700 to 56,900
Ad+M – Base	125,000	116,000 to 137,000
Et+M – Base	77,400	74,500 to 80,600
In+M – Base	433,000	334,000 to 615,000
Ad+M – Adal	Adal alone dominates Adal+MTX	
Et+M – Etan	Etan alone dominates Etan+MTX	
Etan – Adal	42,800	39,600 to 46,700
Et+M – Ad+M	38,500	35,900 to 41,600
Ad+M – In+M	5,640	4,470 to 6,810
Et+M – In+M	26,400	25,200 to 27,700

TABLE 115 *Variation 6: TNF inhibitors third (early RA values) (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	44,583	95	5.9748	0.0143
Etan	56,078	114	6.4647	0.0153
Adal+MTX	45,074	95	6.1281	0.0143
Etan+MTX	56,534	115	6.5723	0.0153
Infl+MTX	44,746	91	6.1093	0.0142
Base	14,431	22	5.1390	0.0129

Comparison	Diff. cost (£)	QSE	Diff. QALY	QSE
Adal – Base	30,152	92	0.8358	0.0140
Etan – Base	41,647	110	1.3256	0.0149
Ad+M – Base	30,643	93	0.9890	0.0140
Et+M – Base	42,103	111	1.4333	0.0150
In+M – Base	30,315	89	0.9703	0.0140
Ad+M – Adal	492	125	0.1533	0.0148
Et+M – Etan	456	147	0.1076	0.0163
Etan – Adal	11,495	136	0.4899	0.0154
Et+M – Ad+M	11,460	138	0.4442	0.0155
Ad+M – In+M	328	123	0.0188	0.0148
Et+M – In+M	11,788	135	0.4630	0.0155

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	36,100	34,900 to 37,300
Etan – Base	31,400	30,700 to 32,200
Ad+M – Base	31,000	30,100 to 31,900
Et+M – Base	29,400	28,800 to 30,000
In+M – Base	31,200	30,300 to 32,200
Ad+M – Adal	3,210	1,460 to 4,950
Et+M – Etan	4,240	1,220 to 7,260
Etan – Adal	23,500	22,000 to 25,200
Et+M – Ad+M	25,800	24,000 to 27,900
Ad+M – In+M	Adal+MTX more costly than Infl+MTX; diff. QALY not significant	
Et+M – In+M	25,500	23,800 to 27,400

TABLE 116 *Variation 6: TNF inhibitors third (late RA values) (1,000,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	41,814	29	5.1891	0.0045
Etan	54,024	36	5.8965	0.0047
Adal+MTX	43,010	29	5.4874	0.0044
Etan+MTX	53,985	36	5.8899	0.0048
Infl+MTX	41,754	28	5.2320	0.0045
Base	14,422	7	5.1488	0.0041
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	27,392	28	0.0403	0.0042
Etan – Base	39,602	34	0.7477	0.0045
Ad+M – Base	28,588	28	0.3386	0.0043
Et+M – Base	39,563	34	0.7410	0.0046
In+M – Base	27,333	27	0.0832	0.0043
Ad+M – Adal	1,196	38	0.2983	0.0043
Etan – Et+M	39	45	0.0066	0.0049
Etan – Adal	12,210	41	0.7074	0.0046
Et+M – Ad+M	10,976	42	0.4025	0.0047
Ad+M – In+M	1,255	37	0.2554	0.0044
Et+M – In+M	12,231	41	0.6579	0.0047
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	680,000		562,000 to 861,000	
Etan – Base	53,000		52,300 to 53,600	
Ad+M – Base	84,400		82,400 to 86,600	
Et+M – Base	53,400		52,700 to 54,100	
In+M – Base	329,000		298,000 to 366,000	
Ad+M – Adal	4,010		3,730 to 4,290	
Et+M – Etan		Comparison is inconclusive		
Etan – Adal	17,300		17,000 to 17,500	
Et+M – Ad+M	27,300		26,600 to 28,000	
Ad+M – In+M	4,910		4,580 to 5,250	
Et+M – In+M	18,600		18,300 to 18,900	

TABLE 117 *Variation 6: TNF inhibitors last (40,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	31,938	141	2.3301	0.0146
Etan	45,099	177	3.4063	0.0183
Adal+MTX	33,386	144	2.5975	0.0149
Etan+MTX	44,820	177	3.3885	0.0185
Infl+MTX	32,290	137	2.4002	0.0151
Base	2,037	7	1.5331	0.0116
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	29,901	140	0.7970	0.0111
Etan – Base	43,061	175	1.8731	0.0158
Ad+M – Base	31,349	143	1.0643	0.0117
Et+M – Base	42,783	175	1.8553	0.0161
In+M – Base	30,253	135	0.8671	0.0117
Ad+M – Adal	1,448	192	0.2674	0.0142
Etan – Et+M	278	233	0.0178	0.0210
Etan – Adal	13,161	213	1.0762	0.0176
Et+M – Ad+M	11,434	216	0.7910	0.0182
Ad+M – In+M	1,096	189	0.1973	0.0147
Et+M – In+M	12,530	210	0.9883	0.0183

continued

TABLE 117 *Variation 6: TNF inhibitors last (40,000 patients) (cont'd)*

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	37,500	36,500 to 38,600
Etan – Base	23,000	22,600 to 23,400
Ad+M – Base	29,500	28,800 to 30,200
Et+M – Base	23,100	22,600 to 23,500
In+M – Base	34,900	33,900 to 35,900
Ad+M – Adal	5,420	3,870 to 6,970
Et+M – Etan	Comparison is inconclusive	
Etan – Adal	12,200	11,700 to 12,800
Et+M – Ad+M	14,500	13,600 to 15,400
Ad+M – In+M	5,560	3,470 to 7,640
Et+M – In+M	12,700	12,100 to 13,300

Variation 7

In this variation, the effectiveness of conventional DMARDs was reduced by 50%. This was done by reducing the a parameter for HAQ multiplier by 50%, keeping the value of $a + b$ fixed. For example, for leflunomide $a = 0.57$ and $b = 0.65$. This was changed to $a = 0.285$ and $b = 0.935$.

TABLE 118 *Variation 7: TNF inhibitors first (40,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	49,297	161	7.5581	0.0248
Etan	63,619	196	8.1659	0.0264
Adal+MTX	49,206	162	7.4410	0.0242
Etan+MTX	64,015	198	8.0980	0.0259
Infl+MTX	49,286	156	7.3395	0.0242
Base	15,139	34	6.5733	0.0234
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	34,158	158	0.9848	0.0234
Etan – Base	48,480	192	1.5926	0.0248
Ad+M – Base	34,067	160	0.8677	0.0230
Et+M – Base	48,875	193	1.5247	0.0248
In+M – Base	34,147	154	0.7662	0.0229
Adal – Ad+M	92	220	0.1171	0.0242
Et+M – Etan	395	261	–0.0679	0.0269
Etan – Adal	14,322	241	0.6078	0.0257
Et+M – Ad+M	14,809	244	0.6570	0.0255
In+M – Ad+M	80	216	–0.1015	0.0240
Et+M – In+M	14,729	241	0.7585	0.0255
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	34,700		33,100 to 36,400	
Etan – Base	30,400		29,500 to 31,500	
Ad+M – Base	39,300		37,300 to 41,500	
Et+M – Base	32,100		31,000 to 33,200	
In+M – Base	44,600		42,000 to 47,400	
Adal – Ad+M	Adal alone more effective than Adal+MTX; diff. cost not significant			
Et+M – Etan	Etan alone more effective than Etan +MTX; diff. cost not significant			
Etan – Adal	23,600		21,600 to 25,900	
Et+M – Ad+M	22,500		20,800 to 24,600	
In+M – Ad+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant			
Et+M – In+M	19,400		18,100 to 21,000	

TABLE 119 *Variation 7: TNF inhibitors third (early RA values) (20,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	48,650	222	5.4799	0.0317
Etan	61,379	267	6.2553	0.0344
Adal+MTX	48,423	221	5.6541	0.0319
Etan+MTX	61,220	267	6.2992	0.0345
Infl+MTX	48,015	212	5.5708	0.0316
Base	16,317	52	4.2654	0.0289
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	32,334	216	1.2145	0.0287
Etan – Base	45,063	260	1.9899	0.0320
Ad+M – Base	32,107	216	1.3887	0.0289
Et+M – Base	44,904	259	2.0338	0.0320
In+M – Base	31,699	207	1.3054	0.0288
Adal – Ad+M	227	294	–0.1742	0.0316
Etan – Et+M	159	350	–0.0438	0.0365
Etan – Adal	12,729	323	0.7754	0.0341
Et+M – Ad+M	12,797	325	0.6451	0.0343
Ad+M – In+M	408	289	0.0833	0.0316
Et+M – In+M	13,205	319	0.7284	0.0342
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	26,600		25,400 to 28,000	
Etan – Base	22,600		21,900 to 23,400	
Ad+M – Base	23,100		22,200 to 24,200	
Et+M – Base	22,100		21,400 to 22,800	
In+M – Base	24,300		23,200 to 25,500	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Et+M – Etan	Comparison is inconclusive			
Etan – Adal	16,400		14,900 to 18,300	
Et+M – Ad+M	19,800		17,700 to 22,500	
Ad+M – In+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant			
Et+M – In+M	18,100		16,400 to 20,300	

TABLE 120 *Variation 7: TNF inhibitors third (late RA values) (40,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	47,660	155	4.8371	0.0221
Etan	60,622	189	5.7193	0.0239
Adal+MTX	48,035	155	5.0840	0.0221
Etan+MTX	60,555	189	5.6993	0.0241
Infl+MTX	47,352	149	4.8462	0.0223
Base	16,295	36	4.3003	0.0206
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	31,365	151	0.5367	0.0188
Etan – Base	44,327	183	1.4190	0.0213
Ad+M – Base	31,740	152	0.7837	0.0193
Et+M – Base	44,260	183	1.3990	0.0216
In+M – Base	31,058	145	0.5459	0.0190
Ad+M – Adal	375	205	0.2470	0.0198
Etan – Et+M	67	244	0.0200	0.0239
Etan – Adal	12,962	227	0.8823	0.0218
Et+M – Ad+M	12,520	227	0.6153	0.0223
Ad+M – In+M	682	202	0.2378	0.0202
Et+M – In+M	13,203	223	0.8531	0.0222

continued

TABLE 120 *Variation 7: TNF inhibitors third (late RA values) (40,000 patients) (cont'd)*

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	58,400	54,600 to 62,900
Etan – Base	31,200	30,300 to 32,200
Ad+M – Base	40,500	38,600 to 42,600
Et+M – Base	31,600	30,700 to 32,700
In+M – Base	56,900	53,200 to 61,200
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Et+M – Etan	Comparison is inconclusive	
Etan – Adal	14,700	13,900 to 15,600
Et+M – Ad+M	20,300	18,800 to 22,100
Ad+M – In+M	2,870	1,100 to 4,640
Et+M – In+M	15,500	14,600 to 16,500

TABLE 121 *Variation 7: TNF inhibitors last (20,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	36,804	218	1.9159	0.0224
Etan	49,802	263	3.0181	0.0269
Adal+MTX	37,244	220	2.2088	0.0229
Etan+MTX	49,641	264	3.0262	0.0274
Infl+MTX	36,534	208	1.9573	0.0229
Base	2,900	11	1.0582	0.0184
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	33,904	216	0.8577	0.0162
Etan – Base	46,902	260	1.9599	0.0227
Ad+M – Base	34,344	218	1.1506	0.0175
Et+M – Base	46,741	261	1.9680	0.0236
In+M – Base	33,634	206	0.8990	0.0171
Ad+M – Adal	440	299	0.2929	0.0209
Etan – Et+M	161	348	–0.0081	0.0301
Etan – Adal	12,998	324	1.1022	0.0251
Et+M – Ad+M	12,397	328	0.8174	0.0267
Ad+M – In+M	710	293	0.2515	0.0215
Et+M – In+M	13,107	320	1.0689	0.0266
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	39,500		38,000 to 41,200	
Etan – Base	23,900		23,300 to 24,600	
Ad+M – Base	29,800		28,900 to 30,900	
Et+M – Base	23,800		23,100 to 24,400	
In+M – Base	37,400		36,000 to 39,000	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Etan – Et+M	Comparison is inconclusive			
Etan – Adal	11,800		11,000 to 12,600	
Et+M – Ad+M	15,200		14,000 to 16,600	
Ad+M – In+M	2,820		442 to 5,200	
Et+M – In+M	12,300		11,500 to 13,200	

Variation 8

For this variation, the effectiveness of conventional DMARDs was increased by 50% compared to the base case.

TABLE 122 *Variation 8: TNF inhibitors first (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	49,674	102	10.2372	0.0182
Etan	63,645	123	10.3454	0.0188
Adal+MTX	49,702	103	9.4737	0.0170
Etan+MTX	64,356	125	9.7486	0.0178
Infl+MTX	49,177	98	9.3253	0.0171
Base	15,515	21	9.9405	0.0170
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	34,160	100	0.2967	0.0188
Etan – Base	48,130	120	0.4048	0.0191
Ad+M – Base	34,187	101	–0.4668	0.0184
Et+M – Base	48,841	122	–0.1920	0.0187
In+M – Base	33,662	97	–0.6152	0.0184
Ad+M – Adal	27	139	–0.7635	0.0187
Et+M – Etan	711	165	–0.5968	0.0193
Etan – Adal	13,970	152	0.1082	0.0192
Et+M – Ad+M	14,654	154	0.2748	0.0186
Ad+M – In+M	525	136	0.1484	0.0181
Et+M – In+M	15,179	151	0.4232	0.0185
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	115,000		102,000 to 132,000	
Etan – Base	119,000		109,000 to 131,000	
Ad+M – Base	Base dominates Adal+MTX			
Et+M – Base	Base dominates Etan+MTX			
In+M – Base	Base dominates Infl+MTX			
Ad+M – Adal	Adal alone more effective than Adal+MTX; diff. cost not significant			
Et+M – Etan	Etan alone dominates Etan+MTX			
Etan – Adal	129,000		95,300 to 200,000	
Et+M – Ad+M	53,300		46,900 to 61,800	
Ad+M – In+M	3,530		1,500 to 5,560	
Et+M – In+M	35,900		32,900 to 39,400	

TABLE 123 *Variation 8: TNF inhibitors third (early RA values) (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	48,434	99	7.0553	0.0158
Etan	60,764	119	7.4295	0.0166
Adal+MTX	48,453	98	7.2055	0.0157
Etan+MTX	61,044	119	7.5540	0.0167
Infl+MTX	48,044	94	7.1746	0.0157
Base	16,612	23	6.4132	0.0145
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	31,823	96	0.6420	0.0165
Etan – Base	44,152	115	1.0163	0.0170
Ad+M – Base	31,842	96	0.7922	0.0164
Et+M – Base	44,433	116	1.1407	0.0170
In+M – Base	31,432	92	0.7614	0.0164
Ad+M – Adal	19	131	0.1502	0.0168
Et+M – Etan	281	154	0.1245	0.0177

continued

TABLE 123 *Variation 8: TNF inhibitors third (early RA values) (100,000 patients) (cont'd)*

Etan – Adal	12,329	143	0.3743	0.0173
Et+M – Ad+M	12,591	144	0.3485	0.0173
Ad+M – In+M	410	128	0.0309	0.0167
Et+M – In+M	13,001	141	0.3794	0.0173

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	49,600	47,100 to 52,300
Etan – Base	43,400	42,000 to 45,000
Ad+M – Base	40,200	38,600 to 42,000
Et+M – Base	39,000	37,800 to 40,200
In+M – Base	41,300	39,600 to 43,200
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Et+M – Etan	Etan+MTX more effective than Etan alone; diff. cost not significant	
Etan – Adal	32,900	30,100 to 36,400
Et+M – Ad+M	36,100	32,800 to 40,200
Ad+M – In+M	Adal+MTX more costly than Infl+MTX; diff QALY not significant	
Et+M – In+M	34,300	31,300 to 37,800

TABLE 124 *Variation 8: TNF inhibitors third (late RA values) (200,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	47,668	69	6.3544	0.0111
Etan	60,199	84	6.9127	0.0116
Adal+MTX	47,941	69	6.6445	0.0110
Etan+MTX	60,509	84	6.8989	0.0117
Infl+MTX	47,363	66	6.3784	0.0111
Base	16,657	16	6.4152	0.0103

Comparison	Diff. cost (£)	QSE	Diff. QALY	QSE
Adal – Base	31,011	67	–0.0608	0.0113
Etan – Base	43,542	81	0.4975	0.0117
Ad+M – Base	31,284	67	0.2293	0.0114
Et+M – Base	43,852	82	0.4837	0.0119
In+M – Base	30,706	65	–0.0369	0.0114
Ad+M – Adal	273	91	0.2901	0.0113
Et+M – Etan	310	108	–0.0138	0.0121
Etan – Adal	12,531	100	0.5583	0.0117
Et+M – Ad+M	12,568	101	0.2544	0.0118
Ad+M – In+M	577	89	0.2661	0.0114
Et+M – In+M	13,145	98	0.5206	0.0118

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	Base dominates Adal	
Etan – Base	87,500	83,600 to 91,900
Ad+M – Base	136,000	124,000 to 151,000
Et+M – Base	90,700	86,400 to 95,300
In+M – Base	Base dominates Infl+MTX	
Ad+M – Adal	941	310 to 1,570
Et+M – Etan	Etan+MTX more costly than Etan; diff QALY not significant	
Etan – Adal	22,400	21,500 to 23,500
Et+M – Ad+M	49,400	45,200 to 54,500
Ad+M – In+M	2,170	1,470 to 2,870
Et+M – In+M	25,300	24,100 to 26,500

TABLE 125 *Variation 8: TNF inhibitors last (20,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	36,186	215	1.8335	0.0220
Etan	49,049	262	2.9338	0.0268
Adal+MTX	36,117	215	2.1086	0.0223
Etan+MTX	49,070	263	2.9087	0.0271
Infl+MTX	35,434	205	1.8284	0.0221
Base	2,812	11	0.9754	0.0180
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	33,374	213	0.8581	0.0159
Etan – Base	46,237	259	1.9584	0.0227
Ad+M – Base	33,305	213	1.1332	0.0171
Et+M – Base	46,258	260	1.9333	0.0233
In+M – Base	32,622	203	0.8530	0.0164
Adal – Ad+M	69	292	–0.2751	0.0205
Et+M – Etan	21	343	–0.0251	0.0297
Etan – Adal	12,863	320	1.1003	0.0250
Et+M – Ad+M	12,953	323	0.8002	0.0264
Ad+M – In+M	683	286	0.2802	0.0210
Et+M – In+M	13,636	317	1.0804	0.0260
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	38,900		37,400 to 40,500	
Etan – Base	23,600		23,000 to 24,200	
Ad+M – Base	29,400		28,500 to 30,400	
Et+M – Base	23,900		23,300 to 24,600	
In+M – Base	38,200		36,800 to 39,900	
Adal – Ad+M	Adal+MTX more effective than Adal alone; diff. cost not significant			
Et+M – Etan	Comparison is inconclusive			
Etan – Adal	11,700		10,900 to 12,500	
Et+M – Ad+M	16,200		15,000 to 17,600	
Ad+M – In+M	2,440		364 to 4,510	
Et+M – In+M	12,600		11,800 to 13,500	

Variation 9

For this variation, survival times on conventional DMARDs were reduced by 50%.

TABLE 126 *Variation 9: TNF inhibitors first (40,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	49,448	160	8.3841	0.0254
Etan	63,898	194	8.8538	0.0267
Adal+MTX	49,982	163	7.8754	0.0241
Etan+MTX	63,770	197	8.4103	0.0259
Infl+MTX	48,828	154	7.6905	0.0240
Base	15,589	32	7.5443	0.0235
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	33,859	157	0.8398	0.0254
Etan – Base	48,309	190	1.3095	0.0266
Ad+M – Base	34,393	161	0.3311	0.0247
Et+M – Base	48,181	192	0.8660	0.0260
In+M – Base	33,239	152	0.1462	0.0246
Ad+M – Adal	533	219	–0.5087	0.0256
Etan – Et+M	127	261	0.4435	0.0276

continued

TABLE 126 *Variation 9: TNF inhibitors first (40,000 patients) (cont'd)*

Etan – Adal	14,449	241	0.4697	0.0270
Et+M – Ad+M	13,789	244	0.5349	0.0261
Ad+M – In+M	1,154	217	0.1849	0.0248
Et+M – In+M	14,943	237	0.7198	0.0262

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	40,300	38,000 to 42,900
Etan – Base	36,900	35,400 to 38,500
Ad+M – Base	104,000	90,400 to 122,000
Et+M – Base	55,600	52,500 to 59,200
In+M – Base	227,000	170,000 to 343,000
Ad+M – Adal	Adal alone dominates Adal+MTX	
Etan – Et+M	Etan+MTX more effective than Etan alone; diff. cost not significant	
Etan – Adal	30,800	27,500 to 34,900
Et+M – Ad+M	25,800	23,400 to 28,800
Ad+M – In+M	6,240	3,350 to 9,130
Et+M – In+M	20,800	19,200 to 22,600

TABLE 127 *Variation 9: TNF inhibitors third (early RA values) (40,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	48,652	157	5.9790	0.0225
Etan	61,597	190	6.6380	0.0245
Adal+MTX	48,533	157	6.1027	0.0225
Etan+MTX	61,625	191	6.7264	0.0245
Infl+MTX	48,384	150	6.0913	0.0225
Base	15,954	32	4.8044	0.0202

Comparison	Diff. cost (£)	QSE	Diff. QALY	QSE
Adal – Base	32,698	155	1.1746	0.0211
Etan – Base	45,643	185	1.8336	0.0231
Ad+M – Base	32,580	155	1.2983	0.0212
Et+M – Base	45,671	187	1.9220	0.0234
In+M – Base	32,430	148	1.2869	0.0212
Adal – Ad+M	118	211	–0.1237	0.0230
Et+M – Etan	27	249	0.0884	0.0263
Etan – Adal	12,945	232	0.6590	0.0246
Et+M – Ad+M	13,091	232	0.6238	0.0248
Ad+M – In+M	150	207	0.0114	0.0229
Et+M – In+M	13,241	229	0.6351	0.0248

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	27,800	26,800 to 28,900
Etan – Base	24,900	24,300 to 25,600
Ad+M – Base	25,100	24,300 to 26,000
Et+M – Base	23,800	23,200 to 24,400
In+M – Base	25,200	24,400 to 26,100
Adal – Ad+M	Adal+MTX more effective than Adal alone; diff. cost not significant	
Et+M – Etan	Etan+MTX more effective than Etan alone; diff. cost not significant	
Etan – Adal	19,600	18,100 to 21,400
Et+M – Ad+M	21,000	19,300 to 23,000
Ad+M – In+M	Comparison is inconclusive	
Et+M – In+M	20,800	19,200 to 22,800

TABLE 128 *Variation 9: TNF inhibitors third (late RA values) (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	47,766	98	5.2589	0.0139
Etan	60,801	119	6.0926	0.0150
Adal+MTX	48,120	99	5.5438	0.0139
Etan+MTX	60,803	120	6.0658	0.0152
Infl+MTX	47,372	94	5.2900	0.0141
Base	15,905	20	4.7814	0.0127
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	31,861	97	0.4775	0.0125
Etan – Base	44,895	117	1.3112	0.0139
Ad+M – Base	32,215	97	0.7624	0.0127
Et+M – Base	44,898	117	1.2844	0.0140
In+M – Base	31,466	92	0.5086	0.0126
Ad+M – Adal	354	132	0.2849	0.0131
Et+M – Etan	2	155	–0.0269	0.0154
Etan – Adal	13,035	145	0.8337	0.0142
Et+M – Ad+M	12,683	145	0.5220	0.0145
Ad+M – In+M	748	129	0.2538	0.0132
Et+M – In+M	13,431	142	0.7758	0.0145
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	66,700		63,400 to 70,400	
Etan – Base	34,200		33,500 to 35,000	
Ad+M – Base	42,300		40,900 to 43,700	
Et+M – Base	35,000		34,200 to 35,800	
In+M – Base	61,900		58,900 to 65,100	
Ad+M – Adal	1,240		311 to 2,170	
Et+M – Etan		Comparison is inconclusive		
Etan – Adal	15,600		15,000 to 16,300	
Et+M – Ad+M	24,300		22,900 to 25,900	
Ad+M – In+M	2,950		1,890 to 4,010	
Et+M – In+M	17,300		16,600 to 18,100	

TABLE 129 *Variation 9: TNF inhibitors last (20,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	37,473	220	2.2513	0.0234
Etan	51,062	267	3.3807	0.0277
Adal+MTX	37,834	222	2.5615	0.0238
Etan+MTX	50,984	269	3.3579	0.0284
Infl+MTX	36,998	211	2.2586	0.0236
Base	3,020	12	1.3562	0.0200
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	34,454	218	0.8951	0.0170
Etan – Base	48,042	265	2.0245	0.0235
Ad+M – Base	34,814	220	1.2053	0.0183
Et+M – Base	47,964	267	2.0018	0.0245
In+M – Base	33,979	209	0.9025	0.0174
Ad+M – Adal	361	302	0.3102	0.0216
Etan – Et+M	78	357	0.0228	0.0306
Etan – Adal	13,588	331	1.1294	0.0258
Et+M – Ad+M	13,150	334	0.7965	0.0274
Ad+M – In+M	836	297	0.3028	0.0219
Et+M – In+M	13,985	330	1.0993	0.0271

continued

TABLE 129 *Variation 9: TNF inhibitors last (20,000 patients) (cont'd)*

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	38,500	37,000 to 40,100
Etan – Base	23,700	23,100 to 24,400
Ad+M – Base	28,900	28,000 to 29,900
Et+M – Base	24,000	23,300 to 24,600
In+M – Base	37,700	36,200 to 39,200
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Etan – Et+M	Comparison is inconclusive	
Etan – Adal	12,000	11,200 to 12,800
Et+M – Ad+M	16,500	15,200 to 18,100
Ad+M – In+M	2,760	757 to 4,760
Et+M – In+M	12,700	11,900 to 13,700

Variation 10

In this variation, long-term survival times on conventional DMARDs were increased by 50% compared to the base case.

TABLE 130 *Variation 10: TNF inhibitors first (1,000,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	49,349	32	9.1995	0.0054
Etan	63,709	39	9.4888	0.0056
Adal+MTX	49,406	33	8.8607	0.0052
Etan+MTX	63,822	40	9.1948	0.0055
Infl+MTX	48,782	31	8.6889	0.0052
Base	15,056	7	8.6331	0.0051
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	34,293	32	0.5664	0.0055
Etan – Base	48,653	38	0.8556	0.0056
Ad+M – Base	34,351	32	0.2275	0.0054
Et+M – Base	48,766	39	0.5617	0.0056
In+M – Base	33,727	31	0.0558	0.0054
Ad+M – Adal	57	44	–0.3389	0.0055
Et+M – Etan	113	52	–0.2940	0.0057
Etan – Adal	14,360	48	0.2892	0.0057
Et+M – Ad+M	14,415	49	0.3341	0.0056
Ad+M – In+M	624	43	0.1717	0.0054
Et+M – In+M	15,039	48	0.5059	0.0056
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	60,500		59,400 to 61,700	
Etan – Base	56,900		56,100 to 57,600	
Ad+M – Base	151,000		144,000 to 158,000	
Et+M – Base	86,800		85,100 to 88,600	
In+M – Base	605,000		507,000 to 749,000	
Ad+M – Adal	Adal alone more effective than Adal+MTX; diff. cost not significant			
Et+M – Etan	Etan alone dominates Etan+MTX			
Etan – Adal	49,700		47,800 to 51,700	
Et+M – Ad+M	43,100		41,700 to 44,700	
Ad+M – In+M	3,630		3,080 to 4,190	
Et+M – In+M	29,700		29,100 to 30,400	

TABLE 131 *Variation 10: TNF inhibitors third (early RA values) (40,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	48,020	155	6.5747	0.0244
Etan	61,120	188	7.0687	0.0257
Adal+MTX	48,339	155	6.6981	0.0242
Etan+MTX	61,228	189	7.1102	0.0257
Infl+MTX	48,105	150	6.6926	0.0243
Base	16,523	37	5.7705	0.0227
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	31,497	152	0.8042	0.0249
Etan – Base	44,597	182	1.2982	0.0258
Ad+M – Base	31,816	152	0.9275	0.0246
Et+M – Base	44,705	183	1.3397	0.0258
In+M – Base	31,582	146	0.9220	0.0245
Ad+M – Adal	319	206	0.1233	0.0254
Et+M – Etan	108	244	0.0415	0.0273
Etan – Adal	13,100	227	0.4940	0.0263
Et+M – Ad+M	12,889	227	0.4122	0.0262
Ad+M – In+M	234	202	0.0055	0.0254
Et+M – In+M	13,123	224	0.4177	0.0264
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	39,200		36,900 to 41,800	
Etan – Base	34,400		33,000 to 35,800	
Ad+M – Base	34,300		32,500 to 36,300	
Et+M – Base	33,400		32,100 to 34,700	
In+M – Base	34,300		32,500 to 36,200	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Et+M – Etan	Comparison is inconclusive			
Etan – Adal	26,500		23,800 to 29,900	
Et+M – Ad+M	31,300		27,600 to 36,000	
Ad+M – In+M	Comparison is inconclusive			
Et+M – In+M	31,400		27,800 to 36,200	

TABLE 132 *Variation 10: TNF inhibitors third (late RA values) (200,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	47,421	69	5.8207	0.0108
Etan	60,281	84	6.4823	0.0113
Adal+MTX	47,890	69	6.0967	0.0107
Etan+MTX	60,167	84	6.4569	0.0114
Infl+MTX	47,275	66	5.8505	0.0108
Base	16,478	17	5.7252	0.0101
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	30,943	67	0.0955	0.0106
Etan – Base	43,803	81	0.7571	0.0112
Ad+M – Base	31,412	68	0.3714	0.0107
Et+M – Base	43,690	81	0.7317	0.0113
In+M – Base	30,797	64	0.1253	0.0107
Ad+M – Adal	469	91	0.2760	0.0107
Etan – Et+M	113	108	0.0253	0.0117
Etan – Adal	12,861	100	0.6616	0.0111
Et+M – Ad+M	12,277	100	0.3603	0.0113
Ad+M – In+M	615	89	0.2461	0.0107
Et+M – In+M	12,893	98	0.6064	0.0113

continued

TABLE 132 *Variation 10: TNF inhibitors third (late RA values) (200,000 patients) (cont'd)*

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	324,000	265,000 to 417,000
Etan – Base	57,900	56,200 to 59,600
Ad+M – Base	84,600	80,000 to 89,700
Et+M – Base	59,700	57,900 to 61,600
In+M – Base	246,000	210,000 to 296,000
Ad+M – Adal	1,700	1,030 to 2,370
Etan – Et+M	Comparison is inconclusive	
Etan – Adal	19,400	18,700 to 20,200
Et+M – Ad+M	34,100	32,000 to 36,400
Ad+M – In+M	2,500	1,740 to 3,260
Et+M – In+M	21,300	20,400 to 22,100

TABLE 133 *Variation 10: TNF inhibitors last (20,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	35,547	213	1.7509	0.0217
Etan	48,513	259	2.8543	0.0263
Adal+MTX	36,079	215	2.0217	0.0220
Etan+MTX	48,990	261	2.8815	0.0269
Infl+MTX	35,384	203	1.7622	0.0220
Base	2,789	11	0.9214	0.0179
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	32,758	211	0.8294	0.0161
Etan – Base	45,724	257	1.9328	0.0226
Ad+M – Base	33,290	213	1.1003	0.0166
Et+M – Base	46,201	259	1.9601	0.0231
In+M – Base	32,594	201	0.8407	0.0162
Ad+M – Adal	532	292	0.2709	0.0202
Et+M – Etan	476	344	0.0273	0.0297
Etan – Adal	12,966	318	1.1034	0.0251
Et+M – Ad+M	12,911	323	0.8598	0.0261
Ad+M – In+M	695	284	0.2596	0.0204
Et+M – In+M	13,606	314	1.1193	0.0258
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	39,500		37,900 to 41,200	
Etan – Base	23,700		23,100 to 24,300	
Ad+M – Base	30,300		29,300 to 31,300	
Et+M – Base	23,600		23,000 to 24,200	
In+M – Base	38,800		37,300 to 40,400	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Et+M – Etan	Comparison is inconclusive			
Etan – Adal	11,800		11,000 to 12,500	
Et+M – Ad+M	15,000		13,900 to 16,300	
Ad+M – In+M	2,680		449 to 4,910	
Et+M – In+M	12,200		11,400 to 12,900	

Variation 11

In this variation, the long-term survival times on TNF inhibitors were reduced by 50%.

TABLE 134 *Variation 11: TNF inhibitors first (200,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	38,822	54	8.7520	0.0115
Etan	51,459	73	9.0597	0.0119
Adal+MTX	38,771	54	8.1127	0.0110
Etan+MTX	51,404	74	8.5160	0.0115
Infl+MTX	38,772	52	8.0226	0.0110
Base	15,356	15	8.3124	0.0111
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	23,466	53	0.4396	0.0118
Etan – Base	36,103	72	0.7473	0.0121
Ad+M – Base	23,415	54	–0.1997	0.0115
Et+M – Base	36,048	72	0.2036	0.0118
In+M – Base	23,416	51	–0.2898	0.0115
Adal – Ad+M	50	73	0.6393	0.0116
Etan – Et+M	55	99	0.5437	0.0121
Etan – Adal	12,637	87	0.3077	0.0121
Et+M – Ad+M	12,632	88	0.4033	0.0116
In+M – Ad+M	1	72	–0.0901	0.0113
Et+M – In+M	12,632	87	0.4934	0.0116
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	53,400		50,700 to 56,400	
Etan – Base	48,300		46,800 to 49,900	
Ad+M – Base	Base dominates Adal+MTX			
Et+M – Base	177,000		159,000 to 200,000	
In+M – Base	Base dominates Infl+MTX			
Adal – Ad+M	Adal alone more effective than Adal+MTX; diff. cost not significant			
Et+M – Etan	Etan alone more effective than Etan+MTX; diff. cost not significant			
Etan – Adal	41,100		38,000 to 44,600	
Et+M – Ad+M	31,300		29,600 to 33,300	
In+M – Ad+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant			
Et+M – In+M	25,600		24,400 to 26,900	

TABLE 135 *Variation 11: TNF inhibitors third (early RA values) (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	38,639	74	5.9879	0.0143
Etan	50,057	100	6.4353	0.0150
Adal+MTX	38,722	74	6.0756	0.0143
Etan+MTX	50,158	100	6.5242	0.0151
Infl+MTX	38,801	71	6.0527	0.0143
Base	16,468	23	5.3842	0.0137
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	22,171	73	0.6037	0.0142
Etan – Base	33,589	97	1.0511	0.0149
Ad+M – Base	22,254	73	0.6914	0.0143
Et+M – Base	33,690	97	1.1400	0.0149
In+M – Base	22,332	70	0.6685	0.0142
Ad+M – Adal	83	99	0.0877	0.0146
Et+M – Etan	101	132	0.0889	0.0157
Etan – Adal	11,418	117	0.4474	0.0151

continued

TABLE 135 *Variation 11: TNF inhibitors third (early RA values) (100,000 patients) (cont'd)*

Et+M – Ad+M	11,436	117	0.4486	0.0152
In+M – Ad+M	78	96	–0.0229	0.0145
Et+M – In+M	11,357	116	0.4715	0.0152

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	36,700	35,100 to 38,600
Etan – Base	32,000	31,100 to 32,900
Ad+M – Base	32,200	30,900 to 33,600
Et+M – Base	29,600	28,800 to 30,400
In+M – Base	33,400	32,000 to 34,900
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Et+M – Etan	Etan+MTX more effective than Etan alone; diff. cost not significant	
Etan – Adal	25,500	23,800 to 27,500
Et+M – Ad+M	25,500	23,800 to 27,400
In+M – Ad+M	Comparison is inconclusive	
Et+M – In+M	24,100	22,600 to 25,800

TABLE 136 *Variation 11: TNF inhibitors third (late RA values) (200,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	38,431	52	5.5641	0.0101
Etan	49,697	70	6.0961	0.0106
Adal+MTX	38,502	52	5.7344	0.0101
Etan+MTX	49,806	70	6.0959	0.0106
Infl+MTX	38,541	50	5.5583	0.0101
Base	16,490	16	5.3809	0.0097

Comparison	Diff. cost (£)	QSE	Diff. QALY	QSE
Adal – Base	21,940	51	0.1832	0.0099
Etan – Base	33,207	69	0.7153	0.0103
Ad+M – Base	22,012	51	0.3536	0.0099
Et+M – Base	33,316	69	0.7150	0.0103
In+M – Base	22,050	49	0.1774	0.0099
Ad+M – Adal	72	69	0.1704	0.0099
Et+M – Etan	109	93	–0.0003	0.0107
Etan – Adal	11,266	82	0.5321	0.0102
Et+M – Ad+M	11,304	82	0.3614	0.0104
In+M – Ad+M	38	68	–0.1762	0.0099
Et+M – In+M	11,265	81	0.5376	0.0104

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	120,000	108,000 to 134,000
Etan – Base	46,400	45,100 to 47,800
Ad+M – Base	62,300	58,900 to 66,000
Et+M – Base	46,600	45,300 to 48,000
In+M – Base	124,000	112,000 to 140,000
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Et+M – Etan	Comparison is inconclusive	
Etan – Adal	21,200	20,300 to 22,100
Et+M – Ad+M	31,300	29,500 to 33,200
In+M – Ad+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant	
Et+M – In+M	21,000	20,100 to 21,900

TABLE 137 *Variation 11: TNF inhibitors last (20,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	26,797	159	1.5818	0.0202
Etan	38,999	222	2.4968	0.0240
Adal+MTX	26,804	163	1.7647	0.0206
Etan+MTX	38,450	220	2.4194	0.0240
Infl+MTX	26,971	155	1.5903	0.0205
Base	2,850	11	1.0352	0.0185
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	23,946	158	0.5466	0.0135
Etan – Base	36,149	220	1.4617	0.0190
Ad+M – Base	23,954	161	0.7295	0.0144
Et+M – Base	35,599	218	1.3842	0.0193
In+M – Base	24,121	154	0.5551	0.0138
Ad+M – Adal	7	222	0.1829	0.0163
Etan – Et+M	550	300	0.0775	0.0243
Etan – Adal	12,202	265	0.9151	0.0205
Et+M – Ad+M	11,645	265	0.6547	0.0213
In+M – Ad+M	167	220	–0.1744	0.0166
Et+M – In+M	11,479	261	0.8291	0.0209
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	43,800		41,700 to 46,200	
Etan – Base	24,700		24,000 to 25,500	
Ad+M – Base	32,800		31,500 to 34,300	
Et+M – Base	25,700		25,000 to 26,500	
In+M – Base	43,500		41,300 to 45,800	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Et+M – Etan	Etan alone more effective than Etan+MTX; diff. cost not significant			
Etan – Adal	13,300		12,600 to 14,200	
Et+M – Ad+M	17,800		16,500 to 19,300	
In+M – Ad+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant			
Et+M – In+M	13,800		13,000 to 14,900	

Variation 12

In this variation, survival times on TNF inhibitors were increased by 50% compared to the base case.

TABLE 138 *Variation 12: TNF inhibitors first (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	56,493	116	9.0677	0.0172
Etan	70,886	132	9.4132	0.0179
Adal+MTX	56,728	117	8.7667	0.0164
Etan+MTX	71,163	133	9.1543	0.0174
Infl+MTX	55,594	111	8.5600	0.0164
Base	15,320	21	8.3179	0.0158
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	41,173	113	0.7498	0.0172
Etan – Base	55,566	129	1.0953	0.0177
Ad+M – Base	41,408	115	0.4488	0.0168
Et+M – Base	55,843	129	0.8364	0.0175
In+M – Base	40,275	109	0.2421	0.0168
Ad+M – Adal	235	156	–0.3010	0.0174
Et+M – Etan	277	173	–0.2589	0.0184

continued

TABLE 138 *Variation 12: TNF inhibitors first (100,000 patients) (cont'd)*

Etan – Adal	14,393	164	0.3455	0.0180
Et+M – Ad+M	14,435	166	0.3876	0.0177
Ad+M – In+M	1,133	154	0.2067	0.0171
Et+M – In+M	15,569	163	0.5942	0.0177

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	54,900	52,500 to 57,600
Etan – Base	50,700	49,100 to 52,400
Ad+M – Base	92,300	85,800 to 99,800
Et+M – Base	66,800	64,100 to 69,700
In+M – Base	166,000	146,000 to 193,000
Ad+M – Adal	Adal alone more effective than Adal+MTX; diff. cost not significant	
Et+M – Etan	Etan alone more effective than Etan+MTX; diff. cost not significant	
Etan – Adal	41,700	37,600 to 46,600
Et+M – Ad+M	37,200	34,000 to 41,100
Ad+M – In+M	5,480	3,740 to 7,220
Et+M – In+M	26,200	24,600 to 28,000

TABLE 139 *Variation 12: TNF inhibitors third (early RA values) (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	54,611	111	6.5295	0.0154
Etan	67,263	127	7.0841	0.0165
Adal+MTX	54,797	112	6.7368	0.0154
Etan+MTX	67,427	128	7.2198	0.0165
Infl+MTX	54,229	107	6.6898	0.0154
Base	16,488	23	5.3802	0.0137

Comparison	Diff. cost (£)	QSE	Diff. QALY	QSE
Adal – Base	38,123	108	1.1492	0.0151
Etan – Base	50,775	123	1.7039	0.0161
Ad+M – Base	38,309	109	1.3566	0.0153
Et+M – Base	50,939	124	1.8396	0.0162
In+M – Base	37,741	104	1.3096	0.0152
Ad+M – Adal	186	147	0.2074	0.0162
Et+M – Etan	164	162	0.1357	0.0176
Etan – Adal	12,652	156	0.5547	0.0169
Et+M – Ad+M	12,630	156	0.4830	0.0169
Ad+M – In+M	568	144	0.0470	0.0162
Et+M – In+M	13,198	153	0.5300	0.0169

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	33,200	32,300 to 34,100
Etan – Base	29,800	29,200 to 30,400
Ad+M – Base	28,200	27,600 to 28,900
Et+M – Base	27,700	27,200 to 28,200
In+M – Base	28,800	28,100 to 29,500
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Et+M – Etan	Etan+MTX more effective than Etan alone; diff. cost not significant	
Etan – Adal	22,800	21,400 to 24,400
Et+M – Ad+M	26,100	24,300 to 28,200
Ad+M – In+M	12,100	6,510 to 83,000
Et+M – In+M	24,900	23,300 to 26,700

TABLE 140 *Variation 12: TNF inhibitors third (late RA values) (40,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	53,637	174	5.6256	0.0237
Etan	66,384	201	6.4225	0.0252
Adal+MTX	53,914	174	5.9687	0.0237
Etan+MTX	66,339	201	6.3959	0.0256
Infl+MTX	53,072	167	5.6571	0.0238
Base	16,470	36	5.3761	0.0217
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	37,167	169	0.2495	0.0227
Etan – Base	49,914	194	1.0464	0.0244
Ad+M – Base	37,443	170	0.5926	0.0230
Et+M – Base	49,868	195	1.0198	0.0249
In+M – Base	36,601	162	0.2811	0.0230
Ad+M – Adal	277	228	0.3431	0.0233
Etan – Et+M	45	254	0.0266	0.0262
Etan – Adal	12,747	242	0.7969	0.0245
Et+M – Ad+M	12,425	244	0.4272	0.0252
Ad+M – In+M	842	223	0.3116	0.0236
Et+M – In+M	13,267	237	0.7387	0.0251
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	149,000		126,000 to 182,000	
Etan – Base	47,700		45,500 to 50,100	
Ad+M – Base	63,200		58,600 to 68,500	
Et+M – Base	48,900		46,600 to 51,400	
In+M – Base	130,000		112,000 to 156,000	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Etan – Et+M	Comparison is inconclusive			
Etan – Adal	16,000		14,900 to 17,200	
Et+M – Ad+M	29,100		25,900 to 33,200	
Ad+M – In+M	2,700		1,210 to 4,190	
Et+M – In+M	18,000		16,700 to 19,500	

TABLE 141 *Variation 12: TNF inhibitors last (20,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	42,047	244	2.0899	0.0236
Etan	55,244	282	3.3320	0.0287
Adal+MTX	42,667	244	2.4122	0.0240
Etan+MTX	55,230	282	3.3098	0.0292
Infl+MTX	41,638	234	2.0948	0.0241
Base	2,865	11	1.0366	0.0184
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	39,182	241	1.0533	0.0178
Etan – Base	52,379	278	2.2954	0.0250
Ad+M – Base	39,802	242	1.3756	0.0189
Et+M – Base	52,365	279	2.2732	0.0257
In+M – Base	38,773	232	1.0582	0.0186
Ad+M – Adal	620	327	0.3223	0.0231
Etan – Et+M	13	365	0.0222	0.0329
Etan – Adal	13,197	349	1.2421	0.0282
Et+M – Ad+M	12,563	349	0.8976	0.0293
Ad+M – In+M	1,030	322	0.3174	0.0239
Et+M – In+M	13,593	343	1.2150	0.0292

continued

TABLE 141 *Variation 12: TNF inhibitors last (20,000 patients) (cont'd)*

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	37,200	35,900 to 38,600
Etan – Base	22,800	22,300 to 23,400
Ad+M – Base	28,900	28,100 to 29,800
Et+M – Base	23,000	22,500 to 23,600
In+M – Base	36,600	35,300 to 38,000
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Et+M – Etan	Comparison is inconclusive	
Etan – Adal	10,600	9,880 to 11,400
Et+M – Ad+M	14,000	12,900 to 15,300
Ad+M – In+M	3,240	1,160 to 5,330
Et+M – In+M	11,200	10,400 to 12,000

Variation 13

In this variation, the possibility was considered of reviewing the effectiveness of TNF inhibitors at 12 weeks rather than at 24 weeks. For the purpose of this analysis, the proportion of short-term quitters was left unchanged.

TABLE 142 *Variation 13: TNF inhibitors first (4,000,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	48,362	16	8.9326	0.0027
Etan	63,011	20	9.2897	0.0028
Adal+MTX	48,531	16	8.4856	0.0025
Etan+MTX	63,129	20	8.9015	0.0027
Infl+MTX	47,903	16	8.3299	0.0025
Base	15,338	3	8.3150	0.0025
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	33,024	16	0.6176	0.0027
Etan – Base	47,673	19	0.9747	0.0028
Ad+M – Base	33,194	16	0.1706	0.0026
Et+M – Base	47,791	19	0.5864	0.0027
In+M – Base	32,566	15	0.0149	0.0026
Ad+M – Adal	170	22	–0.4470	0.0027
Et+M – Etan	118	26	–0.3882	0.0028
Etan – Adal	14,649	24	0.3571	0.0028
Et+M – Ad+M	14,598	25	0.4158	0.0027
Ad+M – In+M	628	22	0.1557	0.0026
Et+M – In+M	15,226	24	0.5716	0.0027
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	53,500		53,000 to 53,900	
Etan – Base	48,900		48,600 to 49,200	
Ad+M – Base	195,000		189,000 to 201,000	
Et+M – Base	81,500		80,700 to 82,300	
In+M – Base	2,190,000		1,620,000 to 3,380,000	
Ad+M – Adal	Adal alone dominates Adal+MTX			
Et+M – Etan	Etan alone dominates Etan+MTX			
Etan – Adal	41,000		40,400 to 41,700	
Et+M – Ad+M	35,100		34,600 to 35,600	
Ad+M – In+M	4,030		3,720 to 4,340	
Et+M – In+M	26,600		26,400 to 26,900	

TABLE 143 *Variation 13: TNF inhibitors third (early RA values) (200,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	47,317	70	6.2908	0.0106
Etan	60,211	85	6.8125	0.0112
Adal+MTX	47,436	70	6.4180	0.0106
Etan+MTX	60,434	85	6.9173	0.0113
Infl+MTX	47,044	67	6.3844	0.0105
Base	16,472	16	5.3751	0.0097
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	30,845	69	0.9158	0.0105
Etan – Base	43,739	82	1.4374	0.0111
Ad+M – Base	30,964	69	1.0429	0.0105
Et+M – Base	43,962	83	1.5422	0.0111
In+M – Base	30,572	66	1.0094	0.0104
Ad+M – Adal	120	93	0.1271	0.0110
Et+M – Etan	223	110	0.1048	0.0119
Etan – Adal	12,894	103	0.5216	0.0114
Et+M – Ad+M	12,997	103	0.4994	0.0115
Ad+M – In+M	393	92	0.0335	0.0109
Et+M – In+M	13,390	101	0.5329	0.0115
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	33,700		32,900 to 34,500	
Etan – Base	30,400		30,000 to 30,900	
Ad+M – Base	29,700		29,100 to 30,300	
Et+M – Base	28,500		28,100 to 28,900	
In+M – Base	30,300		29,700 to 30,900	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Et+M – Etan	2,120		Dominates to 4,280	
Etan – Adal	24,700		23,600 to 25,900	
Et+M – Ad+M	26,000		24,800 to 27,400	
Ad+M – In+M	11,700		6,500 to 59,200	
Et+M – In+M	25,100		24,000 to 26,300	

TABLE 144 *Variation 13: TNF inhibitors third (late RA values) (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	46,475	98	5.6051	0.0147
Etan	59,709	120	6.3171	0.0156
Adal+MTX	47,066	99	5.8852	0.0147
Etan+MTX	59,706	120	6.2940	0.0157
Infl+MTX	46,456	94	5.6372	0.0148
Base	16,473	23	5.3979	0.0138
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	30,002	96	0.2073	0.0142
Etan – Base	43,236	116	0.9192	0.0151
Ad+M – Base	30,593	97	0.4873	0.0143
Et+M – Base	43,232	116	0.8961	0.0153
In+M – Base	29,983	92	0.2393	0.0142
Ad+M – Adal	591	130	0.2801	0.0143
Etan – Et+M	3	155	0.0231	0.0160
Etan – Adal	13,234	143	0.7119	0.0151
Et+M – Ad+M	12,639	144	0.4088	0.0154
Ad+M – In+M	610	128	0.2480	0.0145
Et+M – In+M	13,249	142	0.6568	0.0154

continued

TABLE 144 *Variation 13: TNF inhibitors third (late RA values) (100,000 patients) (cont'd)*

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	145,000	127,000 to 168,000
Etan – Base	47,000	45,500 to 48,700
Ad+M – Base	62,800	59,300 to 66,700
Et+M – Base	48,200	46,600 to 50,000
In+M – Base	125,000	112,000 to 142,000
Ad+M – Adal	2,110	1,160 to 3,060
Etan – Et+M	Comparison is inconclusive	
Etan – Adal	18,600	17,700 to 19,500
Et+M – Ad+M	30,900	28,700 to 33,600
Ad+M – In+M	2,460	1,390 to 3,530
Et+M – In+M	20,200	19,200 to 21,300

TABLE 145 *Variation 13: TNF inhibitors last (20,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	35,094	216	1.8291	0.0217
Etan	48,150	264	2.9608	0.0267
Adal+MTX	35,380	219	2.1258	0.0225
Etan+MTX	48,416	265	2.9210	0.0270
Infl+MTX	35,066	210	1.8709	0.0224
Base	2,848	11	1.0178	0.0181
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	32,246	215	0.8113	0.0158
Etan – Base	45,302	262	1.9431	0.0230
Ad+M – Base	32,531	217	1.1080	0.0172
Et+M – Base	45,567	262	1.9032	0.0232
In+M – Base	32,217	208	0.8532	0.0168
Ad+M – Adal	285	298	0.2967	0.0204
Et+M – Etan	266	352	–0.0399	0.0299
Etan – Adal	13,056	325	1.1318	0.0253
Et+M – Ad+M	13,036	327	0.7952	0.0263
Ad+M – In+M	314	292	0.2548	0.0213
Et+M – In+M	13,350	321	1.0500	0.0260
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	39,700		38,200 to 41,400	
Etan – Base	23,300		22,700 to 23,900	
Ad+M – Base	29,400		28,400 to 30,400	
Et+M – Base	23,900		23,300 to 24,600	
In+M – Base	37,800		36,300 to 39,400	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Et+M – Etan	Comparison is inconclusive			
Etan – Adal	11,500		10,800 to 12,300	
Et+M – Ad+M	16,400		15,100 to 17,900	
Ad+M – In+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant			
Et+M – In+M	12,700		11,900 to 13,700	

Variation 14

In this variation, the probability of quitting TNF inhibitors in the short term was reduced by 50%.

TABLE 146 *Variation 14: TNF inhibitors first (1,000,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	50,542	32	8.9468	0.0053
Etan	64,418	39	9.2912	0.0055
Adal+MTX	50,660	33	8.5290	0.0051
Etan+MTX	64,608	39	8.9364	0.0054
Infl+MTX	49,980	31	8.3593	0.0051
Base	15,336	7	8.3177	0.0050
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	35,206	32	0.6291	0.0054
Etan – Base	49,083	38	0.9735	0.0055
Ad+M – Base	35,325	32	0.2112	0.0052
Et+M – Base	49,273	38	0.6187	0.0054
In+M – Base	34,645	30	0.0416	0.0052
Ad+M – Adal	118	44	–0.4178	0.0054
Et+M – Etan	190	52	–0.3547	0.0057
Etan – Adal	13,876	48	0.3444	0.0056
Et+M – Ad+M	13,948	48	0.4075	0.0055
Ad+M – In+M	680	43	0.1697	0.0052
Et+M – In+M	14,628	47	0.5771	0.0055
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	56,000		55,000 to 56,900	
Etan – Base	50,400		49,900 to 51,000	
Ad+M – Base	167,000		159,000 to 176,000	
Et+M – Base	79,600		78,300 to 81,100	
In+M – Base	833,000		666,000 to 1,110,000	
Ad+M – Adal		Adal alone dominates Adal+MTX		
Et+M – Etan		Etan alone dominates Etan+MTX		
Etan – Adal	40,300		39,000 to 41,700	
Et+M – Ad+M	34,200		33,300 to 35,200	
Ad+M – In+M	4,010		3,440 to 4,570	
Et+M – In+M	25,300		24,800 to 25,900	

TABLE 147 *Variation 14: TNF inhibitors third (early RA values) (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	49,271	98	6.3330	0.0150
Etan	61,438	119	6.8631	0.0159
Adal+MTX	49,332	98	6.4770	0.0149
Etan+MTX	61,790	119	6.9684	0.0160
Infl+MTX	49,095	95	6.4474	0.0149
Base	16,462	23	5.4046	0.0138
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	32,809	96	0.9284	0.0148
Etan – Base	44,977	115	1.4585	0.0157
Ad+M – Base	32,871	96	1.0724	0.0148
Et+M – Base	45,329	116	1.5638	0.0157
In+M – Base	32,633	92	1.0429	0.0148
Ad+M – Adal	62	130	0.1440	0.0154
Et+M – Etan	352	154	0.1053	0.0169
Etan – Adal	12,168	143	0.5301	0.0162

continued

TABLE 147 *Variation 14: TNF inhibitors third (early RA values) (100,000 patients) (cont'd)*

Et+M – Ad+M	12,458	143	0.4914	0.0162
Ad+M – In+M	238	127	0.0296	0.0154
Et+M – In+M	12,695	141	0.5209	0.0161

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	35,300	34,200 to 36,500
Etan – Base	30,800	30,200 to 31,500
Ad+M – Base	30,700	29,800 to 31,500
Et+M – Base	29,000	28,400 to 29,600
In+M – Base	31,300	30,400 to 32,200
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Et+M – Etan	3,340	234 to 6,450
Etan – Adal	23,000	21,500 to 24,600
Et+M – Ad+M	25,400	23,700 to 27,300
Ad+M – In+M	Comparison is inconclusive	
Et+M – In+M	24,400	22,900 to 26,100

TABLE 148 *Variation 14: TNF inhibitors third (late RA values) (40,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	48,510	154	5.6096	0.0234
Etan	60,764	187	6.3362	0.0247
Adal+MTX	48,682	154	5.8713	0.0232
Etan+MTX	61,084	187	6.2842	0.0248
Infl+MTX	48,029	148	5.6453	0.0235
Base	16,478	36	5.3700	0.0217

Comparison	Diff. cost (£)	QSE	Diff. QALY	QSE
Adal – Base	32,032	150	0.2396	0.0223
Etan – Base	44,286	181	0.9662	0.0237
Ad+M – Base	32,204	150	0.5013	0.0225
Et+M – Base	44,606	181	0.9141	0.0239
In+M – Base	31,551	144	0.2753	0.0224
Ad+M – Adal	172	202	0.2617	0.0227
Etan – Et+M	319	240	–0.0521	0.0252
Etan – Adal	12,255	224	0.7266	0.0239
Et+M – Ad+M	12,402	223	0.4128	0.0242
Ad+M – In+M	653	198	0.2260	0.0228
Et+M – In+M	13,054	220	0.6389	0.0241

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	134,000	113,000 to 164,000
Etan – Base	45,800	43,700 to 48,200
Ad+M – Base	64,200	58,900 to 70,600
Et+M – Base	48,800	46,300 to 51,500
In+M – Base	115,000	98,600 to 137,000
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Etan – Et+M	Etan+MTX more effective than Etan alone; diff. cost not significant	
Etan – Adal	16,900	15,700 to 18,200
Et+M – Ad+M	30,000	26,800 to 34,200
Ad+M – In+M	2,890	1,040 to 4,740
Et+M – In+M	20,400	18,900 to 22,300

TABLE 149 *Variation 14: TNF inhibitors last (20,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	37,360	214	1.8689	0.0219
Etan	49,845	262	2.9910	0.0267
Adal+MTX	37,334	215	2.1633	0.0223
Etan+MTX	50,136	263	2.9875	0.0272
Infl+MTX	37,314	208	1.9216	0.0226
Base	2,869	11	1.0236	0.0183
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	34,491	213	0.8453	0.0160
Etan – Base	46,976	259	1.9675	0.0229
Ad+M – Base	34,465	213	1.1398	0.0171
Et+M – Base	47,267	260	1.9639	0.0234
In+M – Base	34,445	206	0.8980	0.0170
Adal – Ad+M	26	292	–0.2945	0.0204
Et+M – Etan	291	348	–0.0035	0.0299
Etan – Adal	12,485	322	1.1222	0.0253
Et+M – Ad+M	12,802	323	0.8242	0.0263
Ad+M – In+M	20	289	0.2417	0.0213
Et+M – In+M	12,822	316	1.0659	0.0262
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	40,800		39,200 to 42,500	
Etan – Base	23,900		23,300 to 24,500	
Ad+M – Base	30,200		29,300 to 31,300	
Et+M – Base	24,100		23,500 to 24,700	
In+M – Base	38,400		36,900 to 39,900	
Adal – Ad+M	Adal+MTX more effective than Adal alone; diff. cost not significant			
Et+M – Etan	Comparison is inconclusive			
Etan – Adal	11,100		10,400 to 11,900	
Et+M – Ad+M	15,500		14,400 to 16,900	
Ad+M – In+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant			
Et+M – In+M	12,000		11,200 to 12,900	

Variation 15

In this variation, short-term quitters on TNF inhibitors were increased by 50% compared to the base case.

TABLE 150 *Variation 15: TNF inhibitors first (400,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	48,439	51	8.9461	0.0084
Etan	63,188	62	9.2858	0.0087
Adal+MTX	48,589	52	8.4953	0.0080
Etan+MTX	63,452	63	8.9254	0.0085
Infl+MTX	47,964	50	8.3522	0.0080
Base	15,293	10	8.2891	0.0079
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	33,146	50	0.6569	0.0085
Etan – Base	47,895	61	0.9967	0.0087
Ad+M – Base	33,296	51	0.2062	0.0083
Et+M – Base	48,159	61	0.6362	0.0086
In+M – Base	32,670	49	0.0631	0.0083
Ad+M – Adal	150	70	–0.4507	0.0085
Et+M – Etan	264	83	–0.3604	0.0090

continued

TABLE 150 *Variation 15: TNF inhibitors first (400,000 patients) (cont'd)*

Etan – Adal	14,749	77	0.3398	0.0088
Et+M – Ad+M	14,862	78	0.4301	0.0086
Ad+M – In+M	626	69	0.1431	0.0083
Et+M – In+M	15,488	76	0.5732	0.0086

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	50,500	49,200 to 51,800
Etan – Base	48,100	47,200 to 48,900
Ad+M – Base	161,000	149,000 to 176,000
Et+M – Base	75,700	73,700 to 77,800
In+M – Base	518,000	410,000 to 703,000
Ad+M – Adal	Adal alone dominates Adal+MTX	
Et+M – Etan	Etan alone dominates Etan+MTX	
Etan – Adal	43,400	41,200 to 45,800
Et+M – Ad+M	34,600	33,200 to 36,100
Ad+M – In+M	4,370	3,280 to 5,460
Et+M – In+M	27,000	26,200 to 27,900

TABLE 151 *Variation 15: TNF inhibitors third (early RA values) (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	47,414	99	6.3210	0.0149
Etan	60,282	119	6.8437	0.0159
Adal+MTX	47,500	99	6.4689	0.0149
Etan+MTX	60,789	120	6.9720	0.0159
Infl+MTX	47,191	95	6.4248	0.0148
Base	16,484	23	5.4070	0.0137

Comparison	Diff. cost (£)	QSE	Diff. QALY	QSE
Adal – Base	30,930	97	0.9140	0.0148
Etan – Base	43,798	116	1.4367	0.0156
Ad+M – Base	31,017	97	1.0619	0.0149
Et+M – Base	44,305	117	1.5650	0.0158
In+M – Base	30,708	93	1.0178	0.0147
Ad+M – Adal	86	132	0.1479	0.0155
Et+M – Etan	507	155	0.1283	0.0169
Etan – Adal	12,868	145	0.5228	0.0162
Et+M – Ad+M	13,288	145	0.5031	0.0163
Ad+M – In+M	309	129	0.0441	0.0115
Et+M – In+M	13,597	143	0.5472	0.0162

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	33,800	32,800 to 35,000
Etan – Base	30,500	29,800 to 31,200
Ad+M – Base	29,200	28,400 to 30,100
Et+M – Base	28,300	27,700 to 28,900
In+M – Base	30,200	29,300 to 31,100
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Et+M – Etan	3,950	1,310 to 6,590
Etan – Adal	24,600	23,100 to 26,300
Et+M – Ad+M	26,400	24,700 to 28,400
Ad+M – In+M	7,010	Dominates to 14,700
Et+M – In+M	24,900	23,400 to 26,500

TABLE 152 *Variation 15: TNF inhibitors third (late RA values) (40,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	46,642	154	5.6138	0.0232
Etan	59,704	188	6.3308	0.0246
Adal+MTX	46,901	155	5.9263	0.0232
Etan+MTX	60,076	189	6.3199	0.0249
Infl+MTX	46,267	148	5.6352	0.0233
Base	16,492	36	5.4140	0.0217
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	30,151	151	0.1998	0.0223
Etan – Base	43,213	182	0.9169	0.0237
Ad+M – Base	30,409	151	0.5123	0.0226
Et+M – Base	43,584	183	0.9059	0.0240
In+M – Base	29,775	145	0.2212	0.0225
Ad+M – Adal	259	206	0.3125	0.0228
Et+M – Etan	372	244	–0.0110	0.0253
Etan – Adal	13,062	226	0.7171	0.0237
Et+M – Ad+M	13,175	228	0.3936	0.0242
Ad+M – In+M	634	201	0.2911	0.0230
Et+M – In+M	13,809	223	0.6847	0.0242
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	151,000		123,000 to 194,000	
Etan – Base	47,100		44,800 to 49,700	
Ad+M – Base	59,400		54,500 to 65,200	
Et+M – Base	48,100		45,700 to 50,800	
In+M – Base	135,000		112,000 to 169,000	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Et+M – Etan	Comparison is inconclusive			
Etan – Adal	18,200		17,000 to 19,700	
Et+M – Ad+M	33,500		29,700 to 38,400	
Ad+M – In+M	2,180		758 to 3,600	
Et+M – In+M	20,200		18,700 to 21,900	

TABLE 153 *Variation 15: TNF inhibitors last (40,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	35,348	154	1.8651	0.0157
Etan	48,690	186	2.9900	0.0189
Adal+MTX	35,388	154	2.1386	0.0159
Etan+MTX	49,012	187	2.9827	0.0193
Infl+MTX	35,511	149	1.9051	0.0160
Base	2,865	8	1.0327	0.0130
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	32,482	153	0.8324	0.0115
Etan – Base	45,825	184	1.9573	0.0161
Ad+M – Base	32,523	152	1.1058	0.0122
Et+M – Base	46,147	185	1.9500	0.0167
In+M – Base	32,646	147	0.8724	0.0120
Ad+M – Adal	41	211	0.2734	0.0147
Et+M – Etan	322	247	–0.0073	0.0212
Etan – Adal	13,342	230	1.1249	0.0179
Et+M – Ad+M	13,624	232	0.8442	0.0189
In+M – Ad+M	123	207	–0.2334	0.0151
Et+M – In+M	13,501	227	1.0776	0.0187

continued

TABLE 153 *Variation 15: TNF inhibitors last (40,000 patients) (cont'd)*

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	39,000	37,900 to 40,200
Etan – Base	23,400	23,000 to 23,800
Ad+M – Base	29,400	28,700 to 30,100
Et+M – Base	23,700	23,200 to 24,100
In+M – Base	37,400	36,400 to 38,500
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Et+M – Etan	Comparison is inconclusive	
Etan – Adal	11,900	11,300 to 12,400
Et+M – Ad+M	16,100	15,300 to 17,100
In+M – Ad+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant	
Et+M – In+M	12,500	12,000 to 13,200

Variation 16

In this variation, short-term quitters on conventional DMARDs were reduced by 50%.

TABLE 154 *Variation 16: TNF inhibitors first (200,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	49,314	72	8.9243	0.0119
Etan	63,789	88	9.2683	0.0124
Adal+MTX	49,359	73	8.5292	0.0113
Etan+MTX	63,870	89	8.9366	0.0120
Infl+MTX	48,774	70	8.3809	0.0114
Base	15,059	15	8.2830	0.0112
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	34,255	71	0.6412	0.0119
Etan – Base	48,730	85	0.9853	0.0122
Ad+M – Base	34,300	72	0.2461	0.0116
Et+M – Base	48,811	86	0.6535	0.0121
In+M – Base	33,715	69	0.0978	0.0116
Ad+M – Adal	46	98	–0.3951	0.0120
Et+M – Etan	81	117	–0.3317	0.0126
Etan – Adal	14,475	107	0.3441	0.0124
Et+M – Ad+M	14,511	109	0.4074	0.0121
Ad+M – In+M	585	97	0.1483	0.0117
Et+M – In+M	15,096	107	0.5557	0.0121
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	53,400		51,500 to 55,500	
Etan – Base	49,500		48,200 to 50,700	
Ad+M – Base	139,000		127,000 to 154,000	
Et+M – Base	74,700		72,000 to 77,600	
In+M – Base	345,000		278,000 to 452,000	
Ad+M – Adal	Adal alone more effective than Adal+MTX; diff. cost not significant			
Et+M – Etan	Etan alone more effective than Etan+MTX; diff. cost not significant			
Etan – Adal	42,100		39,200 to 45,400	
Et+M – Ad+M	35,600		33,600 to 37,900	
Ad+M – In+M	3,940		2,500 to 5,390	
Et+M – In+M	27,200		26,000 to 28,500	

TABLE 155 *Variation 16: TNF inhibitors third (early RA values) (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	48,077	98	6.1839	0.0148
Etan	60,569	119	6.6881	0.0158
Adal+MTX	48,004	98	6.3123	0.0147
Etan+MTX	60,729	119	6.8202	0.0158
Infl+MTX	47,742	94	6.2718	0.0147
Base	16,282	23	5.2523	0.0135
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	31,796	96	0.9317	0.0144
Etan – Base	44,287	115	1.4358	0.0153
Ad+M – Base	31,723	95	1.0600	0.0145
Et+M – Base	44,447	115	1.5679	0.0155
In+M – Base	31,461	92	1.0195	0.0144
Adal – Ad+M	73	130	–0.1283	0.0152
Et+M – Etan	160	154	0.1321	0.0167
Etan – Adal	12,491	143	0.5041	0.0159
Et+M – Ad+M	12,725	143	0.5079	0.0161
Ad+M – In+M	262	127	0.0405	0.0151
Et+M – In+M	12,987	141	0.5484	0.0160
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	34,100		33,100 to 35,200	
Etan – Base	30,800		30,200 to 31,500	
Ad+M – Base	29,900		29,100 to 30,800	
Et+M – Base	28,300		27,800 to 28,900	
In+M – Base	30,900		30,000 to 31,800	
Adal – Ad+M	Adal+MTX more effective than Adal alone; diff. cost not significant			
Et+M – Etan	Etan+MTX more effective than Etan alone; diff. cost not significant			
Etan – Adal	24,800		23,200 to 26,600	
Et+M – Ad+M	25,100		23,500 to 26,900	
Ad+M – In+M	6,460		Dominates to 14,400	
Et+M – In+M	23,700		22,300 to 25,300	

TABLE 156 *Variation 16: TNF inhibitors third (late RA values) (40,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	47,168	153	5.4548	0.0229
Etan	59,981	187	6.1606	0.0243
Adal+MTX	47,513	154	5.7821	0.0230
Etan+MTX	59,811	187	6.1612	0.0248
Infl+MTX	47,179	148	5.5014	0.0232
Base	16,305	36	5.2680	0.0213
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	30,862	149	0.1869	0.0218
Etan – Base	43,676	181	0.8926	0.0233
Ad+M – Base	31,207	150	0.5141	0.0221
Et+M – Base	43,505	181	0.8932	0.0238
In+M – Base	30,874	144	0.2334	0.0221
Ad+M – Adal	345	203	0.3273	0.0223
Etan – Et+M	171	241	–0.0007	0.0252
Etan – Adal	12,814	224	0.7057	0.0234
Et+M – Ad+M	12,298	224	0.3791	0.0239
Ad+M – In+M	333	199	0.2807	0.0224
Et+M – In+M	12,631	219	0.6598	0.0240

continued

TABLE 156 *Variation 16: TNF inhibitors third (late RA values) (40,000 patients) (cont'd)*

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	165,000	134,000 to 215,000
Etan – Base	48,900	46,500 to 51,700
Ad+M – Base	60,700	55,900 to 66,400
Et+M – Base	48,700	46,200 to 51,500
In+M – Base	132,000	111,000 to 163,000
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Et+M – Etan	Comparison is inconclusive	
Etan – Adal	18,200	16,900 to 19,600
Et+M – Ad+M	32,400	28,700 to 37,300
Ad+M – In+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant	
Et+M – In+M	19,100	17,700 to 20,800

TABLE 157 *Variation 16: TNF inhibitors last (20,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	35,614	212	1.6384	0.0211
Etan	48,151	258	2.7369	0.0258
Adal+MTX	36,030	215	1.9330	0.0216
Etan+MTX	48,536	260	2.7245	0.0264
Infl+MTX	35,659	205	1.6827	0.0218
Base	2,746	11	0.8031	0.0171
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	32,867	210	0.8353	0.0156
Etan – Base	45,405	255	1.9338	0.0225
Ad+M – Base	33,284	213	1.1299	0.0169
Et+M – Base	45,790	257	1.9214	0.0231
In+M – Base	32,913	203	0.8796	0.0163
Ad+M – Adal	417	290	0.2946	0.0204
Et+M – Etan	385	339	–0.0124	0.0297
Etan – Adal	12,538	319	1.0985	0.0248
Et+M – Ad+M	12,506	320	0.7915	0.0262
Ad+M – In+M	371	286	0.2503	0.0210
Et+M – In+M	12,877	315	1.0417	0.0261
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	39,300		37,800 to 41,000	
Etan – Base	23,500		22,900 to 24,100	
Ad+M – Base	29,500		28,500 to 30,400	
Et+M – Base	23,800		23,200 to 24,500	
In+M – Base	37,400		36,000 to 38,900	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Et+M – Etan	Comparison is inconclusive			
Etan – Adal	11,400		10,600 to 12,200	
Et+M – Ad+M	15,800		14,600 to 17,200	
Ad+M – In+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant			
Et+M – In+M	12,400		11,600 to 13,300	

Variation 17

In this variation, short-term quitters on conventional DMARDs were increased by 50% compared to the base case.

TABLE 158 *Variation 17: TNF inhibitors first (10,000,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	49,715	10	8.9033	0.0017
Etan	64,017	12	9.2629	0.0018
Adal+MTX	50,012	10	8.4065	0.0016
Etan+MTX	64,298	12	8.8430	0.0017
Infl+MTX	49,330	10	8.2443	0.0016
Base	15,626	2	8.2329	0.0016
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	34,088	10	0.6704	0.0017
Etan – Base	48,391	12	1.0300	0.0018
Ad+M – Base	34,386	10	0.1736	0.0017
Et+M – Base	48,672	12	0.6101	0.0018
In+M – Base	33,704	10	0.0114	0.0017
Ad+M – Adal	298	14	–0.4968	0.0017
Et+M – Etan	281	16	–0.4199	0.0018
Etan – Adal	14,302	15	0.3596	0.0018
Et+M – Ad+M	14,286	15	0.4365	0.0018
Ad+M – In+M	683	14	0.1622	0.0017
Et+M – In+M	14,986	15	0.5987	0.0018

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	50,800	50,600 to 51,100
Etan – Base	47,000	46,800 to 47,100
Ad+M – Base	198,000	194,000 to 202,000
Et+M – Base	79,800	79,300 to 80,200
In+M – Base	2,950,000	2,270,000 to 4,180,000
Ad+M – Adal	Adal alone dominates Adal+MTX	
Et+M – Etan	Etan alone dominates Etan+MTX	
Etan – Adal	39,800	39,400 to 40,200
Et+M – Ad+M	32,700	32,500 to 33,000
Ad+M – In+M	4,210	4,020 to 4,400
Et+M – In+M	25,000	24,800 to 25,200

TABLE 159 *Variation 17: TNF inhibitors third (early RA values) (200,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	48,713	70	6.4132	0.0107
Etan	61,513	84	6.9711	0.0114
Adal+MTX	49,060	70	6.5622	0.0107
Etan+MTX	61,624	84	7.0722	0.0114
Infl+MTX	48,606	67	6.5343	0.0107
Base	16,575	16	5.4246	0.0099
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	32,138	69	0.9886	0.0107
Etan – Base	44,938	82	1.5465	0.0113
Ad+M – Base	32,485	69	1.1376	0.0108
Et+M – Base	45,048	82	1.6476	0.0114
In+M – Base	32,031	66	1.1097	0.0107
Ad+M – Adal	347	94	0.1490	0.0112
Et+M – Etan	110	110	0.1011	0.0121

continued

TABLE 159 *Variation 17: TNF inhibitors third (early RA values) (200,000 patients) (cont'd)*

Etan – Adal	12,800	103	0.5579	0.0117
Et+M – Ad+M	12,564	103	0.5100	0.0118
Ad+M – In+M	454	92	0.0279	0.0112
Et+M – In+M	13,017	101	0.5379	0.0117

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	32,500	31,800 to 33,200
Etan – Base	29,100	28,600 to 29,500
Ad+M – Base	28,600	28,000 to 29,100
Et+M – Base	27,300	27,000 to 27,700
In+M – Base	28,900	28,300 to 29,400
Ad+M – Adal	2,330	1,020 to 3,630
Et+M – Etan	Etan+MTX more effective than Etan alone; diff. cost not significant	
Etan – Adal	22,900	22,000 to 24,000
Et+M – Ad+M	24,600	23,500 to 25,900
Ad+M – In+M	16,300	8,560 to 161,000
Et+M – In+M	24,200	23,100 to 25,400

TABLE 160 *Variation 17: TNF inhibitors third (late RA values) (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	47,967	98	5.7255	0.0150
Etan	61,045	119	6.4486	0.0158
Adal+MTX	48,371	99	5.9809	0.0149
Etan+MTX	60,953	119	6.4212	0.0160
Infl+MTX	47,619	94	5.7371	0.0150
Base	16,602	23	5.4093	0.0140

Comparison	Diff. cost (£)	QSE	Diff. QALY	QSE
Adal – Base	31,366	96	0.3162	0.0145
Etan – Base	44,444	116	1.0393	0.0154
Ad+M – Base	31,769	97	0.5716	0.0147
Et+M – Base	44,351	116	1.0119	0.0156
In+M – Base	31,017	92	0.3278	0.0146
Ad+M – Adal	404	131	0.2554	0.0148
Etan – Et+M	93	155	0.0274	0.0163
Etan – Adal	13,078	143	0.7231	0.0154
Et+M – Ad+M	12,582	144	0.4402	0.0157
Ad+M – In+M	752	128	0.2438	0.0149
Et+M – In+M	13,334	141	0.6841	0.0157

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	99,200	90,800 to 109,000
Etan – Base	42,800	41,500 to 44,100
Ad+M – Base	55,600	52,800 to 58,600
Et+M – Base	43,800	42,500 to 45,200
In+M – Base	94,600	86,900 to 104,000
Ad+M – Adal	1,580	541 to 2,620
Etan – Et+M	Comparison is inconclusive	
Etan – Adal	18,100	17,300 to 19,000
Et+M – Ad+M	28,600	26,600 to 30,900
Ad+M – In+M	3,090	1,970 to 4,200
Et+M – In+M	19,500	18,600 to 20,500

TABLE 161 *Variation 17: TNF inhibitors last (40,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	37,083	155	2.2519	0.0167
Etan	50,402	189	3.3443	0.0198
Adal+MTX	37,492	157	2.5198	0.0170
Etan+MTX	50,589	190	3.3466	0.0201
Infl+MTX	37,150	150	2.2976	0.0171
Base	2,970	8	1.3602	0.0142
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	34,113	154	0.8917	0.0119
Etan – Base	47,431	187	1.9841	0.0165
Ad+M – Base	34,522	156	1.1596	0.0127
Et+M – Base	47,619	188	1.9864	0.0170
In+M – Base	34,180	148	0.9374	0.0125
Ad+M – Adal	409	213	0.2679	0.0150
Et+M – Etan	188	249	0.0024	0.0214
Etan – Adal	13,319	232	1.0924	0.0181
Et+M – Ad+M	13,097	234	0.8269	0.0190
Ad+M – In+M	342	208	0.2221	0.0154
Et+M – In+M	13,439	229	1.0490	0.0189
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	38,300		37,200 to 39,400	
Etan – Base	23,900		23,500 to 24,400	
Ad+M – Base	29,800		29,100 to 30,500	
Et+M – Base	24,000		23,500 to 24,400	
In+M – Base	36,500		35,500 to 37,500	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Et+M – Etan	Comparison is inconclusive			
Etan – Adal	12,200		11,600 to 12,800	
Et+M – Ad+M	15,800		15,000 to 16,800	
Ad+M – In+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant			
Et+M – In+M	12,800		12,200 to 13,500	

Variation 18

For the final variation, the use of offset costs was considered to account for joint replacement and hospitalisation. In the absence of an effective method of including this explicitly in the model, a cost of £860 per unit HAQ score was assumed, as used in previous work.[3]

TABLE 162 *Variation 18: TNF inhibitors first (400,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	57,939	54	8.9463	0.0084
Etan	71,889	65	9.3025	0.0088
Adal+MTX	58,353	54	8.5201	0.0080
Etan+MTX	72,424	65	8.9313	0.0085
Infl+MTX	57,933	52	8.3555	0.0080
Base	24,395	19	8.3149	0.0079
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	33,543	52	0.6314	0.0085
Etan – Base	47,494	62	0.9876	0.0087
Ad+M – Base	33,958	52	0.2051	0.0083
Et+M – Base	48,028	62	0.6163	0.0086
In+M – Base	33,537	50	0.0405	0.0083

continued

TABLE 162 *Variation 18: TNF inhibitors first (400,000 patients) (cont'd)*

Ad+M – Adal	414	70	–0.4263	0.0085
Et+M – Etan	534	83	–0.3712	0.0090
Etan – Adal	13,950	77	0.3562	0.0088
Et+M – Ad+M	14,071	77	0.4112	0.0087
Ad+M – In+M	420	69	0.1646	0.0083
Et+M – In+M	14,491	76	0.5758	0.0086

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	53,100	51,700 to 54,600
Etan – Base	48,100	47,200 to 49,000
Ad+M – Base	166,000	153,000 to 180,000
Et+M – Base	77,900	75,800 to 80,200
In+M – Base	827,000	587,000 to 1,400,000
Ad+M – Adal	Adal alone dominates Adal+MTX	
Et+M – Etan	Etan alone dominates Etan+MTX	
Etan – Adal	39,200	37,300 to 41,300
Et+M – Ad+M	34,200	32,800 to 35,800
Ad+M – In+M	2,550	1,680 to 3,420
Et+M – In+M	25,200	24,400 to 26,000

TABLE 163 *Variation 18: TNF inhibitors third (early RA values) (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	58,107	106	6.3065	0.0149
Etan	70,040	126	6.8371	0.0159
Adal+MTX	58,088	105	6.4506	0.0149
Etan+MTX	70,137	126	6.9344	0.0159
Infl+MTX	57,699	101	6.4264	0.0149
Base	27,448	43	5.3611	0.0137

Comparison	Diff. cost (£)	QSE	Diff. QALY	QSE
Adal – Base	30,659	101	0.9454	0.0148
Etan – Base	42,592	119	1.4760	0.0156
Ad+M – Base	30,639	100	1.0895	0.0148
Et+M – Base	42,689	119	1.5733	0.0157
In+M – Base	30,250	96	1.0653	0.0147
Adal – Ad+M	20	133	–0.1441	0.0155
Et+M – Etan	96	157	0.0973	0.0168
Etan – Adal	11,933	146	0.5306	0.0162
Et+M – Ad+M	12,049	146	0.4838	0.0163
Ad+M – In+M	389	130	0.0242	0.0155
Et+M – In+M	12,438	144	0.5080	0.0162

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	32,400	31,400 to 33,500
Etan – Base	28,900	28,200 to 29,500
Ad+M – Base	28,100	27,400 to 28,900
Et+M – Base	27,100	26,600 to 27,700
In+M – Base	28,400	27,600 to 29,200
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Et+M – Etan	Etan+MTX more effective than Etan alone; diff. cost not significant	
Etan – Adal	22,500	21,100 to 24,100
Et+M – Ad+M	24,900	23,200 to 26,800
Ad+M – In+M	Adal+MTX more costly than Infl+MTX; diff QALY not significant	
Et+M – In+M	24,500	22,900 to 26,300

TABLE 164 *Variation 18: TNF inhibitors third (late RA values) (100,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	58,576	109	5.5927	0.0147
Etan	70,549	129	6.3112	0.0156
Adal+MTX	58,583	107	5.8779	0.0147
Etan+MTX	70,423	128	6.2830	0.0157
Infl+MTX	58,374	105	5.6291	0.0148
Base	27,469	43	5.3622	0.0137
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	31,107	103	0.2305	0.0141
Etan – Base	43,080	121	0.9489	0.0151
Ad+M – Base	31,114	102	0.5156	0.0142
Et+M – Base	42,954	121	0.9208	0.0152
In+M – Base	30,906	99	0.2669	0.0142
Ad+M – Adal	7	136	0.2851	0.0144
Etan – Et+M	126	159	0.0281	0.0161
Etan – Adal	11,973	149	0.7184	0.0152
Et+M – Ad+M	11,840	148	0.4052	0.0153
Ad+M – In+M	209	134	0.2488	0.0145
Et+M – In+M	12,048	147	0.6540	0.0153
Comparison	**ICER (£ per QALY)**		**Quasi-CI**	
Adal – Base	135,000		120,000 to 154,000	
Etan – Base	45,400		44,000 to 46,900	
Ad+M – Base	60,300		57,200 to 63,900	
Et+M – Base	46,600		45,100 to 48,300	
In+M – Base	116,000		105,000 to 130,000	
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant			
Etan – Et+M	Comparison is inconclusive			
Etan – Adal	16,700		15,900 to 17,500	
Et+M – Ad+M	29,200		27,100 to 31,800	
Ad+M – In+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant			
Et+M – In+M	18,400		17,500 to 19,500	

TABLE 165 *Variation 18: TNF inhibitors last (20,000 patients)*

Option	Cost (£)	QSE	QALYs	QSE
Adal	50,104	239	1.8630	0.0220
Etan	61,587	282	2.9782	0.0267
Adal+MTX	49,663	234	2.1603	0.0223
Etan+MTX	61,732	283	2.9730	0.0271
Infl+MTX	50,066	231	1.9151	0.0226
Base	18,262	81	1.0336	0.0183
Comparison	**Diff. cost (£)**	**QSE**	**Diff. QALY**	**QSE**
Adal – Base	31,842	227	0.8293	0.0160
Etan – Base	43,325	267	1.9446	0.0228
Ad+M – Base	31,401	223	1.1267	0.0171
Et+M – Base	43,470	266	1.9393	0.0233
In+M – Base	31,804	220	0.8815	0.0169
Adal – Ad+M	440	303	–0.2974	0.0204
Et+M – Etan	144	352	–0.0053	0.0298
Etan – Adal	11,484	332	1.1153	0.0253
Et+M – Ad+M	12,068	330	0.8126	0.0264
In+M – Ad+M	402	297	–0.2452	0.0214
Et+M – In+M	11,666	325	1.0578	0.0262

continued

TABLE 165 *Variation 18: TNF inhibitors last (20,000 patients) (cont'd)*

Comparison	ICER (£ per QALY)	Quasi-CI
Adal – Base	38,400	36,900 to 40,000
Etan – Base	22,300	21,700 to 22,900
Ad+M – Base	27,900	27,000 to 28,800
Et+M – Base	22,400	21,800 to 23,000
In+M – Base	36,100	34,700 to 37,600
Ad+M – Adal	Adal+MTX more effective than Adal alone; diff. cost not significant	
Et+M – Etan	Comparison is inconclusive	
Etan – Adal	10,300	9,540 to 11,100
Et+M – Ad+M	14,900	13,700 to 16,200
In+M – Ad+M	Adal+MTX more effective than Infl+MTX; diff. cost not significant	
Et+M – In+M	11,000	10,200 to 11,900

Appendix 11

Ongoing research

Additional ongoing/unpublished trials

Source: ClinicalTrials.gov http://www.clinicaltrials.gov/ct

http://www.clinicaltrials.gov/ct/show/NCT00034060?order=1
The role of cytokines on growth hormone suppression in premenopausal women with rheumatoid arthritis and the effect of treatment with etanercept. Sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases

http://www.clinicaltrials.gov/ct/show/NCT00099554?order=2
Effectiveness and safety of Enbrel® (etanercept) in rheumatoid arthritis subjects who have failed Remicade® (infliximab). Sponsored by Abbott Laboratories

http://www.clinicaltrials.gov/ct/show/NCT00095147?order=4
Abatacept and infliximab in combination with methotrexate in subjects with rheumatoid arthritis. Sponsored by Bristol-Myers Squibb

http://www.clinicaltrials.gov/ct/show/NCT00056602?order=5
Clinically important changes in rheumatoid arthritis. Sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases

Source: Controlled-Trials.com http://www.controlled-trials.com/

http://www.controlled-trials.com/mrct/trial/INFLIXIMAB%7CADALIMUMAB%7CETANERCEPT%7CRHEUMATOID%20ARTHRITIS/1059/67577.html
Preference of rheumatoid arthritis (RA) patients of Enbrel® (etanercept) auto-injector versus Enbrel® pre-filled syringes. Sponsored by Amgen

http://www.controlled-trials.com/mrct/trial/INFLIXIMAB%7CADALIMUMAB%7CETANERCEPT%7CRHEUMATOID%20ARTHRITIS/1059/67629.html
OPPOSITE: Open-label, Pilot Protocol of Patients with Rheumatoid Arthritis who Switch to Infliximab after an Incomplete Response To Etanercept. Sponsored by Centocor

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The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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