NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of TA143 and TA 233)

Manufacturer submission of evidence:

Infliximab (Remicade®)

MSD

Submitted 3rd September 2014

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1. Executive Summary

Background

Ankylosing spondylitis (AS) is part of a clinically heterogeneous group of inflammatory rheumatologic diseases (spondyloarthropathies) which share common genetic, histological, and clinical features. AS is closely related to axial spondyloarthritis. Whereas axial spondyloarthritis includes both non-radiographic (radiographs of the sacroiliac joints and spine appear normal) and radiographically-evident disease, AS is only diagnosed when definite radiographic sacroiliitis (abnormalities seen in plain x-rays of the sacroiliac joints, such as erosions, sclerosis, and partial or total ankylosis) is present. Diagnostic criteria for AS also consider a number of clinical criteria relating to symptomatology.

Symptoms of AS can include back pain and stiffness, which is usually inflammatory in nature and can result in limited mobility or permanent disability, oligoarthritis (predominantly of the lower limbs), enthesitis, dactylitis ('sausage-like' digits), other skeletal manifestations such as kyphosis (a forward curvature of the spine) and osteoporosis, and extra-articular manifestations such as uveitis, inflammatory bowel disease, psoriasis, and cardiac conduction abnormalities.

AS usually occurs in patients aged between 15 years and 35 years, rarely commencing in old age. The condition is strongly associated with the presence of the Human Leukocyte Antigen (HLA)-B27 antigen. There is also a preponderance of AS in males; the condition is ~3 times more common in men than in women (symptoms present differently in each gender, with women experiencing more cervical spine and peripheral joint pain than men). Similar to rheumatoid arthritis and psoriatic arthritis, many patients with AS experience worsened symptoms during an acute flare, and little to no disease activity during remission periods. However, there is an overall gradual progression in the disease.

The prevalence of clinically-significant AS is estimated to range from 0.05% to 0.23%, which represents between 32,050 and 147,430 patients in the UK using current population figures. The annual incidence rate of AS is poorly reported but has been estimated to be 23 per 100,000 individuals, representing ~14,743 new cases annually.

Guidelines and recommendations for the management of patients with AS have been developed the Assessment of Spondyloarthritis International Society and the European League Against Rheumatism (updated in 2010). Treatment is tailored according to the manifestations of the

disease (i.e. whether gastrointestinal manifestations are present), level of symptoms, and general clinical status of patients. Typically treatment will comprise both non-pharmacological elements (patient education, regular exercise, physiotherapy) and pharmacological treatment, including non-steroidal anti-inflammatory drugs, analgesics, and glucocorticoids. Non-biologic disease-modifying antirheumatic drugs such as sulfasalazine and methotrexate have limited to no efficacy for the treatment of AS and are therefore not typically used. However, for patients with persistently high disease activity despite conventional therapy, biologic disease-modifying antirheumatic drugs (tumour necrosis factor [TNF]-alpha inhibitors) can be effective, having demonstrated statistically significant improvements in measures of disease activity in large randomised controlled trials. Surgery is only considered in specific situations and does not constitute routine treatment.

NICE has previously recommended three TNF-alpha inhibitors for the treatment of AS: adalimumab and etanercept (NICE TA143) and golimumab (NICE TA233) (infliximab was also considered in TA143 but was not recommended). The recommendation applies only to severe disease (estimated by NICE to represent approximately 29% of patients with AS in the UK).

The Technology

Infliximab (Remicade®) is a TNF-alpha inhibitor, which is part of the biologic disease-modifying antirheumatic drug (DMARD) class. It is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF-alpha but not to lymphotoxin alpha (TNF-beta). The European Commission granted a marketing authorisation valid throughout the European Union for golimumab for the AS indication on 21st May 2003. Infliximab is provided as a 100mg vial of powder for reconstitution. The dosing regimen is 5mg/kg given as an intravenous infusion followed by additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks.

Clinical Effectiveness

The efficacy and safety of infliximab has been evaluated in two randomised, double-blind, placebo-controlled clinical studies in adult patients with AS. As the pivotal infliximab studies for the AS indication are not active-controlled, a network meta-analysis (NMA) was conducted to satisfy the requirements of the NICE reference case.

P01522

Infliximab for the treatment of active AS was evaluated in a randomised, placebo-controlled, multi-centre study conducted in Germany. Included patients were diagnosed with AS according to the modified New York criteria for AS, and had active disease defined by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and spinal pain scores >4 on a 10 cm visual analogue scale (VAS). The primary endpoint of the trial was the proportion of patients who achieved a BASDAI50 response at week 12. Secondary efficacy measures included improvements in the VAS for spinal pain, in the functional index (Bath Ankylosing Spondylitis Functional Index [BASFI]), the metrology index (Bath Ankylosing Spondylitis Metrology Index [BASMI]), and quality of life (Short Form-36 [SF-36]), and laboratory parameters (erythrocyte sedimentation rate [ESR], c-reactive protein [CRP]). Disease-modifying antirheumatic drugs (DMARDs) and corticosteroids were discontinued >4 weeks prior to screening. Patients were permitted to take non-steroidal anti-inflammatory drugs (NSAIDs), but the dose could not be increased over the baseline value. Patients were randomised to receive infliximab 5mg/kg (n=35) or placebo (n=35) at weeks 0, 2, and 63.

Significantly more infliximab-treated patients achieved a BASDAI50 response at week 12, compared to placebo (53% vs. 9%; $p<0.0001$). A clear difference could be seen when mean changes were compared: in the infliximab group the BASDAI score improved significantly from 6.5 at baseline to 3.3 at week 12, whereas little improvement was recorded in the placebo group (from 6.3 to 5.7; difference 2.7; $p<0.0001$). Rapid improvement was observed in 41% of patients at week 2. Similar findings were observed with other efficacy measures, including the BASFI and BASMI indices. Fewer infliximab-treated patients had peripheral arthritis or enthesitis at week 12 compared to baseline, whereas no change was seen in the placebo group. Infliximab-treated patients also demonstrated significant improvement in physical function, bodily pain, general health, activities affected by physical function, and vitality, compared to no effect for placebo.

The study was extended and followed-up over a number of years. After 1 year, the significant improvement in disease activity (BASDAI) was maintained, with 47% of patients originally receiving infliximab and 51% of patients originally in the placebo group (i.e. crossover group) achieving a BASDAI50 response. After 2 years, significant improvement in disease activity was sustained in every outcome measure. At week 102, 58% of the patients (n=30) achieved a BASDAI50 response. Additionally, 25% of patients (n=13) achieved at least partial remission, according to Assessment in Ankylosing Spondylitis (ASAS) criteria. The productivity and number of hospitalisations in the 49 patients who completed 2 years of treatment was also

investigated: after 1 year of treatment, the proportion of patients on sick leave was reduced to 36% (10/28; p=0.031), with a further reduction to 14% after 2 years (4/28; p<0.001 vs. prior to treatment). Additionally, the number of inpatient days (hospitalisation) for each patient decreased from an average of 11.1 days (range 0-77 days) before treatment with infliximab to 0.6 days (range 0-15 days) after 1 year of treatment, and to 2.9 days (range 0-72 days) after 2 years of treatment (p<0.001 and p=0.007 vs. before treatment, respectively). After 3 years, the clinical efficacy of infliximab was sustained, with persistent decrease of disease activity and continuous improvement of clinical symptoms.

After 3 years of maintenance treatment with infliximab, all patients discontinued treatment and were eligible to enter another 2-year extension phase (total observation period of 5 years), which would allow them to be re-infused with infliximab upon relapse. All but one patient (41/42) had to be re-infused because of relapse. The mean time to relapse was 17.5 weeks (±7.9 weeks, range 7 to 45 weeks). Patients who were in partial remission and those with normal CRP levels at the time point of withdrawal had longer times to relapse after discontinuation of the treatment. Re-treatment with infliximab was well-tolerated and resulted in clinical improvement in all patients to a state similar to that before the treatment was stopped. At the end of year 4, 62.5% of patients achieved a BASDAI50 response (ASAS40 response rates were also similar to those observed at the end of years 1, 2, and 3). Infliximab provided sustained efficacy through 4 years with regard to signs and symptoms, physical function, and spinal mobility. After 5 years, partial clinical remission was achieved by 34.2% of patients and BASDAI scores were <4 in 79% of patients. The mean BASDAI score at year 5 was 2.5±1.9 (6.4 at baseline). ASAS20 and ASAS40 responses were achieved by 84% and 63% of patients, respectively. Finally, at 8 years, partial remission was achieved by 35.1% of patients, and the mean BASDAI score was low (2.3±1.6). A BASDAI50 response was achieved by 67.6% of patients, and ASAS20 and ASAS40 responses were reported in 81% and 62% of patients, respectively. There was no loss of response during the eighth year of infliximab therapy.

ASSERT

The efficacy and safety of infliximab in AS was further assessed in a larger patient population at 33 centres throughout Europe, US, and Canada: ASSERT was a Phase III, randomised, double-blind, placebo-controlled, multicentre study in 279 patients with active AS. Adult patients classified as having AS according to the modified New York criteria, and active disease with a BASDAI score ≥4 (range 0-10) and spinal pain ≥4 (VAS of 0-10 cm) were eligible for the study. Doses of infliximab 5mg/kg as monotherapy or placebo were administered intravenously at

weeks 0, 2, 6, 12, and 18. The primary endpoint of the ASSERT trial was the proportion of patients who achieved an ASAS20 response at week 24. ASAS criteria included patient's global assessment, spinal pain, function according to the BASFI, and morning stiffness. Patients were assessed at baseline and week 24 using standard AS performance scores and magnetic resonance imaging (MRI) of the spine. Additional endpoints evaluated included the BASDAI, BASFI, BASMI, and health-related quality of life, as measured by the SF-36.

Patients were randomly assigned to treatment with infliximab (n=201) or placebo (n=78). The study population was typical for patients with active AS, consisted mostly of men (81%), had a median age of 40 years, and median disease duration of 8.8 years. At 24 weeks, an ASAS20 response was observed in 61.2% of patients in the infliximab-treated group versus 19.2% of patients in the placebo group ($p<0.001$). The difference between the treatment groups was observed as early as week 2 and maintained through week 24. Significantly more patients in the infliximab group met the more rigorous ASAS40 response criteria at week 24: 47% versus 12% of patients who received placebo ($p<0.001$). ASAS partial remission, defined as a value <20 on a scale of 0-100mm in each of the four ASAS response parameters, was achieved in 22.4% of infliximab-treated patients versus 1.3% in placebo-treated patients ($p<0.001$). Additionally, the proportion of patients with BASDAI20, BASDAI50, and BASDAI70 responses through week 24 was 68%, 51%, and 35% in the infliximab group, compared to 27%, 11%, and 8% in the placebo group, respectively ($p<0.001$). These data confirmed the primary endpoint results of the first placebo-controlled study (P01522). Significant reductions from baseline BASDAI, BASFI, and BASMI scores were also demonstrated in infliximab-treated patients, compared to patients receiving placebo (in infliximab-treated group, BASDAI score decreased by -2.9, BASFI score decreased by -1.7, and BASMI score decreased by -1.0).

In a sub-analysis, investigators examined whether clinical benefits observed with infliximab were accompanied by improvement in productivity and reduction in time lost from work. The median percent change from baseline to week 24 in the productivity score in patients receiving infliximab was 62% versus 11% in the placebo group ($p<0.05$). In addition, patients in the infliximab group had an average 60% reduction in the number of workdays missed over a 6-week period compared to baseline (0.7 days vs. 1.7 days; $p<0.01$); in contrast, no significant reduction was observed in the placebo group (1.2 days vs. 1.7 days; $p=0.6$). The mean number of workdays missed per patient during the 24 week study period was 6.8 in the placebo group, compared with 2.8 in the infliximab group ($p=0.07$).

The study was extended to 2 years, with patients randomised to placebo crossed-over to infliximab at weeks 24, 26, 30, and every 6 weeks thereafter through week 96. By week 102, the crossover group and the continuous infliximab group were similar with regard to ASAS20 response (72.1% versus 73.9%); ASAS40 responses at week 102 were 45.9% versus 59.4%. No new safety issues were discerned. Infliximab therefore demonstrated sustained efficacy and safety over 2 years in a large cohort of patients with active AS.

Network Meta-Analysis

As the pivotal infliximab studies for the AS indication are not active-controlled for the AS indication, a NMA was performed to compare the efficacy and safety of conventional therapy, adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab for the treatment of adults with severe active AS. A systematic review was conducted to identify relevant studies for inclusion in the network. Twenty-six eligible studies were identified following the systematic review, of which 16 were suitable for inclusion into the network (studies were excluded if crossover occurred prior to data reporting or if no data were reported at relevant time points).

The following outcomes were included for analysis in the NMA: Efficacy outcomes at 12 weeks (+/-2 weeks): ASAS20, ASAS40, and BASDAI50. Safety outcomes at 24 weeks: any adverse events (AEs), any serious adverse events (SAEs), and injection (infusion)-site reactions (ISRs). Both fixed effects and random effects models were explored, with results presented for random effects models in line with recommendations for the accommodation of between-study heterogeneity.

For the efficacy outcomes, each TNF-alpha inhibitor was statistically significantly more efficacious than placebo, with the exception of certolizumab pegol 200mg for ASAS40. In the three efficacy analyses, infliximab was the most effective compared with placebo, and the ranking of other TNF-alpha inhibitors differed according to the efficacy outcome. Importantly, there were no significant differences in efficacy detected between the TNF-alpha inhibitors, as evidenced by overlapping credible intervals, with the exception of infliximab compared with golimumab for ASAS20 (where infliximab was very weakly significant). The findings of the NMA therefore indicate that all TNF-alpha inhibitors are similarly effective for the treatment of AS. This finding was also noted for the safety outcomes, with no significant differences detected both between TNF-alpha inhibitors and placebo (with the exception of etanercept compared with placebo for injection-site reactions) and between the different TNF-alpha inhibitors when compared with each other.

Cost-Effectiveness

TNF-alpha inhibitors result in increased QALYs when compared to conventional therapy, ranging from 1.09 for adalimumab to 1.17 for infliximab. This is achieved at an increased cost (from £20,153 when adalimumab is administered to £50,607 for infliximab). The estimated ICERs for each TNF-alpha inhibitor when compared with conventional therapy ranged from £18,508 to £43,432 per additional QALY gained (for adalimumab and infliximab versus conventional therapy, respectively). The incremental analysis of each treatment versus each other and based on the incremental cost demonstrated that etanercept is dominated by certolizumab pegol.

None of the assessed TNF-alpha inhibitors has more than 30% likelihood of being cost-effective. At a WTP threshold of £20,000, there is a 20% probability that golimumab and adalimumab are likely to be the most cost-effective treatments for AS with and a 30% probability that certolizumab pegol is likely to be cost-effective. However, the cost-effectiveness curves and the cost-effectiveness frontier highlight the considerable uncertainty in differentiating the cost-effectiveness of TNF-alpha inhibitors.

In summary, infliximab is associated with an ICER of £43,432 compared with conventional therapy. This value remained mostly robust when key assumptions in the model were tested through sensitivity analyses. An ICER lower than £30,000 was obtained when the upper bound of the long-term treatment costs of AS associated with the BASFI score were considered.

Conclusion

Through this analysis, infliximab has been demonstrated through a NMA to be as clinically efficacious as other TNF-alpha inhibitors which have been previously recommended by NICE. There are additional benefits of treatment with infliximab which are not captured in the current modelling (productivity gains and patient support schemes offered by MSD) and given appropriate local arrangements (i.e. vial sharing) infliximab could be considered a cost-effective resource for certain patients.

2. Description of Technology

2.1. Brand Name, Generic Name, and Therapeutic Class

Infliximab is a tumour necrosis factor (TNF)-alpha inhibitor and part of the biologic disease-modifying antirheumatic drug (DMARD) class. It is available in a 100mg vial of powder for reconstitution.

2.2. Mechanism of Action

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF-alpha but not to lymphotoxin alpha (TNF-beta).

2.3. Marketing Authorisation

The European Commission granted a marketing authorisation valid throughout the European Union for infliximab for the ankylosing spondylitis (AS) indication on 21st May 2003.

2.4. Indications

The approved indications for infliximab are as follows:

Ankylosing spondylitis:
Infliximab is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.

Rheumatoid arthritis:
Infliximab, in combination with methotrexate (MTX), is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:

- adult patients with active disease when the response to disease-modifying anti-rheumatic drugs (DMARDs), including MTX, has been inadequate
- adult patients with severe, active and progressive disease not previously treated with MTX or other DMARDs

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated.

Psoriatic arthritis:

Infliximab is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Infliximab should be administered:

- in combination with MTX
- or alone in patients who show intolerance to MTX or for whom MTX is contraindicated

Adult ulcerative colitis:

Infliximab is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies.

Paediatric ulcerative colitis:

Infliximab is indicated for treatment of severely active ulcerative colitis, in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies.

Adult Crohn's disease:

Infliximab is indicated for:

- treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies
- treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage, and immunosuppressive therapy)

Paediatric Crohn's disease:

Infliximab is indicated for treatment of severe, active Crohn's disease, in children and adolescents aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies.

Infliximab has been studied only in combination with conventional immunosuppressive therapy.

Psoriasis:

Infliximab is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, MTX, or psoralen combined with ultraviolet A.

2.5. Costs

Cost information is provided in Table 1.

Table 1: Cost information for infliximab

Pharmaceutical formulation	One 100mg vial of powder for reconstitution
Acquisition cost (excluding Value Added Tax [VAT])	£419.62
Method of administration	Intravenous infusion
Doses	5mg/kg
Dosing frequency	5mg/kg given as an intravenous infusion followed by additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks[1]
Average length of a course of treatment	If a patient does not respond by 6 weeks (i.e. after 2 doses), no additional treatment with infliximab should be given[1]
Average cost of a course of treatment	Average cost in year 1: £13,427.84 (assuming patient weight of 77.4kg, including vial wastage, and re-dosing every 8 weeks) to £16,784.80 (assuming patient weight of 77.4kg, including vial wastage, and re-dosing every 6 weeks) Average cost in subsequent years: £10,910.12 to £14,267.08 (dependent on 6 week or 8 week re-dosing)
Dose adjustments	None

2.6. Additional Tests, Investigations, and Monitoring

Tests, investigations, precautions, and monitoring for infliximab are consistent with those for all other TNF-alpha inhibitors. Treatment with infliximab is contraindicated in patients with tuberculosis (TB) or other severe infections such as sepsis, abscesses, and opportunistic infections and in patients with moderate or severe heart failure (New York Heart Association [NYHA] class III/IV) and in patients with a history of hypersensitivity to infliximab, to other murine proteins, or to any of the following excipients: sucrose, polysorbate 80, monobasic sodium phosphate, and dibasic sodium phosphate[1].

3. Context

The scope for this appraisal, informed by input from clinical specialists, defines spondyloarthritis as a clinically heterogeneous group of inflammatory rheumatologic diseases which share common genetic, histological, and clinical features. Diseases belonging to this group include AS, psoriatic arthritis, arthritis associated with inflammatory bowel disease (IBD), reactive arthritis, and undifferentiated spondyloarthritis. The clinical presentation can include back pain, usually inflammatory in nature, oligoarthritis (predominantly of the lower limbs), enthesitis, dactylitis ('sausage-like' digits), and extra-articular manifestations (EAMs) such as uveitis, IBD, and psoriasis.

Spondyloarthritis can be categorised as having predominantly axial (sacroiliac joints or spine) or peripheral involvement. In people with axial spondyloarthritis, the predominant symptom is back pain – with inflammation of the sacroiliac joints, the spine, or both – but they may also have peripheral joint involvement or extra-articular manifestations of spondyloarthritis. In the early stages of disease, radiographs of the sacroiliac joints and spine can be normal (so-called 'non-radiographic' disease) although sacroiliitis or inflammation of the spine may be visible on magnetic resonance imaging (MRI) before structural damage occurs. If definite radiographic sacroiliitis (abnormalities seen in plain x-rays of the sacroiliac joints, such as erosions, sclerosis, and partial or total ankylosis) is present, the disease can be classified as AS. Radiographic changes to the spine are not part of the classification criteria, but new bone formation (such as syndesmophytes and ankylosis of the vertebral column) is characteristic of AS.

Infliximab is indicated for the treatment of severe, active AS in adults who have responded inadequately to conventional therapy[1]. Infliximab is not licensed for axial spondyloarthritis. Therefore, this submission will focus only on AS.

3.1. Ankylosing Spondylitis

AS usually occurs in patients aged between 15 years and 35 years, rarely commencing in old age[2]. The condition has an unknown aetiology that involves the sacroiliac joints, axial skeleton, entheses, and peripheral joints. Symptoms include chronic pain and stiffness of the spine, which can result in limited mobility or permanent disability. Chronic inflammation of entheses can also lead to new bone formation, syndesmophytes, and ankylosis of joints, primarily in the axial skeleton. Other skeletal manifestations include kyphosis, a forward curvature of the spine, and osteoporosis. Non-skeletal manifestations of the disease include uveitis, carditis, pulmonary fibrosis, bowel inflammation, psoriasis, and cardiac conduction abnormalities. AS is strongly

associated with the presence of the Human Leukocyte Antigen (HLA)-B27 antigen. There is also a preponderance of AS in males; the condition is ~3 times more common in men than in women[2]. Symptoms present differently according to gender, with women experiencing more cervical spine and peripheral joint pain than men.

Similar to rheumatoid arthritis and psoriatic arthritis, many patients with AS experience worsened symptoms during an acute flare, and little to no disease activity during remission periods. However, there is an overall gradual progression in the disease.

3.1.1. Diagnosis and Classification

AS is diagnosed and classified using the modified New York criteria (described below). More recently the Assessment of Spondyloarthritis International Society has developed further classification criteria relating to axial spondyloarthritis (below).

Modified New York criteria[3]

A. Diagnosis

Clinical criteria:

- Low back pain and stiffness of ≥3 months duration that is improved by exercise and not relieved by rest
- Limitations of motion of the lumbar spine in both the sagittal and frontal planes
- Limitation of chest expansion relative to normal values corrected for sex and age

Radiologic criterion:

- Sacroiliitis grade ≥2 bilaterally or sacroiliitis grade 3 or 4 unilaterally

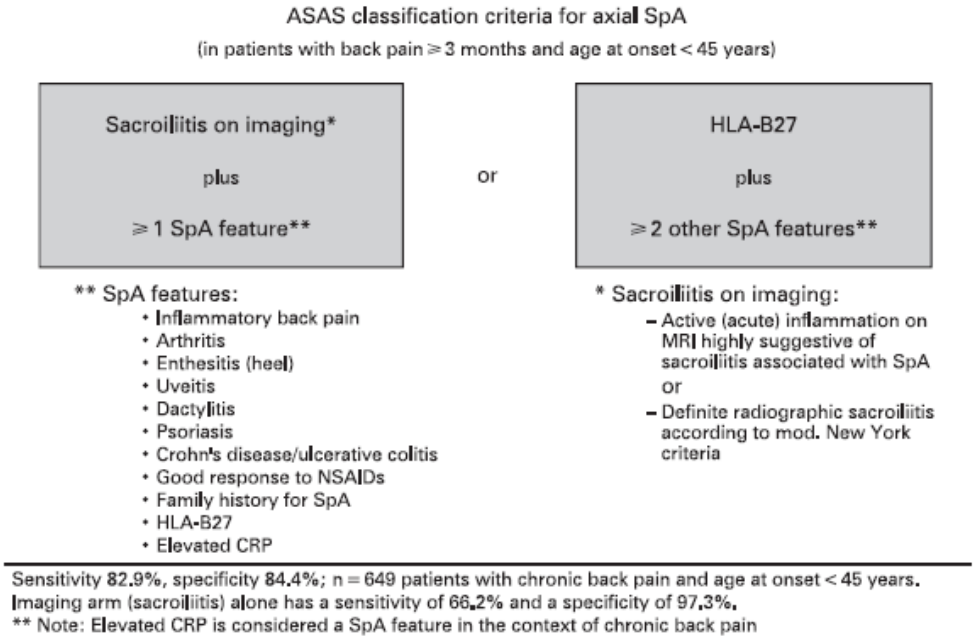
B. Grading

Definite AS if the radiologic criterion is associated with ≥1 clinical criterion. Probable AS if: 3 clinical criteria are present, and radiologic criterion is present without any signs/symptoms satisfying the clinical criteria

Assessment of Spondyloarthritis International Society criteria[4]

Criteria were recently updated through consensus discussion between Assessment of Spondyloarthritis International Society members. Refinement of the candidate criteria resulted in new classification criteria that are defined as: the presence of sacroiliitis by radiography or by MRI plus at least one spondyloarthritis feature (''imaging arm'') or the presence of HLA-B27 plus at least two spondyloarthritis features (''clinical arm'') (Figure 1).

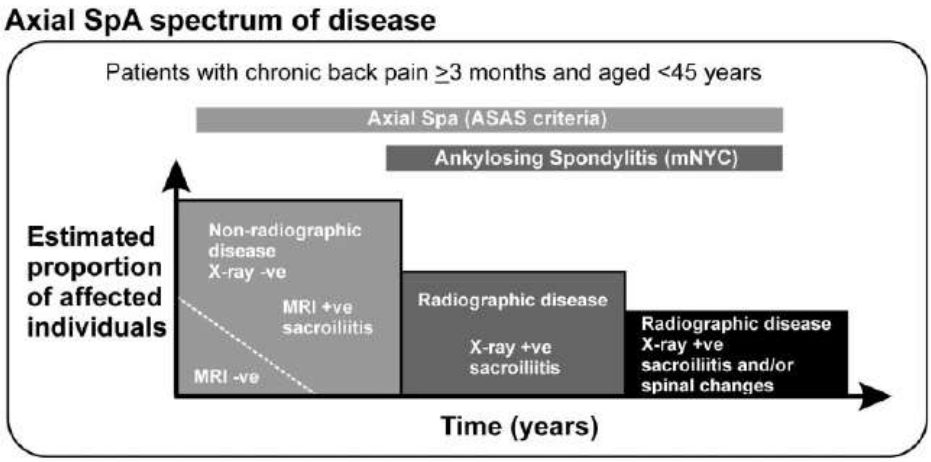
Figure 1: Assessment of Spondyloarthritis International Society criteria[4]



ASAS, Assessment in Ankylosing Spondylitis; CRP, c-reactive protein; HLA, Human Leukocyte Antigen; MRI, magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory drug; SpA, spondyloarthropathy.

Assessment of Spondyloarthritis International Society criteria are not directly relevant to the classification of AS, however; they are the most recently-developed criteria through which patients presenting with relevant symptoms will be assessed. The relevance of each classification criteria is outlined in Figure 2.

Figure 2: Disease spectrum showing classification of ankylosing spondylitis and axial spondyloarthritis[5]



ASAS, Assessment in Ankylosing Spondylitis; mNYC, modified New York criteria; MRI, magnetic resonance imaging; SpA, spondyloarthropathy.

3.1.2. Measures of Disease Activity and Function

Two key measures for the measurement of disease activity in AS include the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score and the Assessment in Ankylosing Spondylitis (ASAS) score. BASDAI is a validated instrument completed by the patients, consisting of six 10cm horizontal visual analogue scales (VAS) to measure severity of fatigue, spinal and peripheral joint pain, localised tenderness, and morning stiffness with the final BASDAI score ranging from 0 to 10 (Garrett *et al*. 1994)[6]. A 50% reduction in the BASDAI score has been recommended by the Assessment of Spondyloarthritis International Society as the response criteria used to determine treatment success. The ASAS score is a composite measure, comprising a 10cm horizontal VAS for pain, inflammation, well-being, and function. Improvement in three modalities by 20% or more, without deterioration in the fourth modality constitutes an ASAS20 response (Anderson *et al*. 2001)[7]. Functional ability is measured with the Bath Ankylosing Spondylitis Functional Index (BASFI) score, which consists of eight questions regarding patient functioning in AS and two questions around the patient's ability to cope with everyday life. The answers are based on a 10cm horizontal VAS, the mean of which gives the BASFI score (ranging from 0 to 10) (Calin *et al*. 1994)[8]. The BASDAI and BASFI scores are used together to determine disease progression.

3.2. Number of Patients Covered by the Indication in the UK

The prevalence of AS in the UK has not been well-quantified; however, the NICE scope estimates the prevalence of clinically significant AS to range from 0.05% to 0.23% in the UK[9]. Given the mid-2013 UK population estimate of 64.1 million[10] this represents between 32,050 and 147,430 patients in the UK. The annual incidence rate of AS is poorly reported but was estimated to be 23 per 100,000 individuals in NICE TA233 (described in following section). Based on the UK population estimate, this represents ~14,743 new cases annually.

The costing statement accompanying NICE TA233 states that: “the estimated prevalence of ankylosing spondylitis in England is 0.14%, equivalent to around 71,000 people. The number of these people who are eligible for treatment with biological drugs has been estimated as around 20,000. Expert clinical opinion suggests that biologic drugs may not be the most appropriate treatment for all eligible patients. According to expert clinical opinion, 30% or around 6800 of the 20,000 eligible patients will take up treatment”.

3.3. Relevant NICE Guidance

NICE has performed two technology appraisals of TNF-alpha inhibitors licensed for the treatment of severe active AS:

TA143: Adalimumab, etanercept, and infliximab for ankylosing spondylitis[11]

1.1 Adalimumab or etanercept are recommended as treatment options for adults with severe active ankylosing spondylitis only if all of the following criteria are fulfilled.

- The patient's disease satisfies the modified New York criteria for diagnosis of ankylosing spondylitis.
- There is confirmation of sustained active spinal disease, demonstrated by:
    - a score of at least 4 units on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) *and*
    - at least 4 cm on the 0 to 10 cm spinal pain visual analogue scale (VAS).
    - These should both be demonstrated on two occasions at least 12 weeks apart without any change of treatment.
- Conventional treatment with two or more non-steroidal anti-inflammatory drugs taken sequentially at maximum tolerated or recommended dosage for 4 weeks has failed to control symptoms.

1.2 When using BASDAI and spinal pain VAS scores to inform conclusions about whether or not sustained active spinal disease is present, healthcare professionals should be mindful of the need to secure equality of access to treatment for patients with disabilities and patients from different ethnic groups. There are circumstances in which it may not be appropriate for healthcare professionals to use a patient's BASDAI and spinal pain VAS scores to inform their conclusion about the presence of sustained active spinal disease. These are:

- where the BASDAI or spinal pain VAS score is not a clinically appropriate tool to inform a clinician's conclusion on the presence of sustained active spinal disease because of a patient's learning or other disabilities (for example, sensory impairments) or linguistic or other communication difficulties

  or
- where it is not possible to administer the BASDAI or spinal pain VAS questionnaire in a language in which the patient is sufficiently fluent for it to be an appropriate tool to inform a conclusion on the presence of sustained active spinal disease, or there are similarly exceptional reasons why use of a patient's BASDAI or spinal pain VAS score

would be an inappropriate tool to inform a conclusion on the presence of sustained active spinal disease in that individual patient's case.

In such cases, healthcare professionals should make use of another appropriate method of assessment, which may include adapting the use of the questionnaire to suit the patient's circumstances.

The same approach should apply in the context of a decision about whether to continue the use of the drug in accordance with sections 1.3 and 1.4.

1.3 It is recommended that the response to adalimumab or etanercept treatment should be assessed 12 weeks after treatment is initiated, and that treatment should be only continued in the presence of an adequate response as defined in section 1.4.

1.4 For the purposes of this guidance, an adequate response to treatment is defined as a:

- reduction of the BASDAI score to 50% of the pre-treatment value or by 2 or more units *and*
- reduction of the spinal pain VAS by 2 cm or more.

1.5 Patients who have experienced an adequate response to adalimumab or etanercept treatment, as defined in section 1.4, should have their condition monitored at 12-week intervals. If the response to treatment, as defined in section 1.4, is not maintained, a repeat assessment should be made after a further 6 weeks. If at this 6-week assessment the response defined in section 1.4 has not been maintained, treatment should be discontinued.

1.6 For patients who have been shown to be intolerant of adalimumab or etanercept before the end of the 12-week initial assessment period, as in section 1.3, the other one of this pair of TNF-alpha inhibitor treatments is recommended as an alternative treatment.

1.7 Prescription of an alternative TNF-alpha inhibitor is not recommended in patients who have either not achieved an adequate initial response to treatment with adalimumab or etanercept, as defined in section 1.4, or who experience loss of the initially adequate response during treatment.

1.8 It is recommended that the use of adalimumab or etanercept for severe active ankylosing spondylitis should be initiated and supervised only by specialist physicians experienced in the diagnosis and treatment of this condition.

1.9 Infliximab is not recommended for the treatment of ankylosing spondylitis.

1.10 Patients currently receiving infliximab for the treatment of ankylosing spondylitis should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

TA233: Golimumab for the treatment of ankylosing spondylitis[12]

1.1 Golimumab is recommended as an option for the treatment of severe, active ankylosing spondylitis in adults only if:

- it is used as described for adalimumab and etanercept in 'Adalimumab, etanercept and infliximab for ankylosing spondylitis' (NICE TA143) and
- the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose in accordance with the patient access scheme.

1.2 People currently receiving golimumab for the treatment of severe, active ankylosing spondylitis who do not fulfil the criteria for treatment with adalimumab and etanercept described in NICE TA143 should have the option to continue golimumab until they and their clinician consider it appropriate to stop.

3.4. Current Clinical Practice

Guidelines and recommendations for the management of patients with AS have been developed by the Assessment of Spondyloarthritis International Society and the European League Against Rheumatism (updated in 2010)[13]. The key recommendations are as follows:

1. General treatment

The treatment of patients with AS should be tailored according to:

- The current manifestations of the disease (axial, peripheral, entheseal, extra-articular symptoms and signs)
- The level of current symptoms, clinical findings, and prognostic indicators
- The general clinical status (age, gender, comorbidity, concomitant medications, psychosocial factors)

2. Disease monitoring

The disease monitoring of patients with AS should include: patient history (e.g. questionnaires); clinical parameters; laboratory tests; imaging; all according to the clinical presentation as well

as the ASAS core set. The frequency of monitoring should be decided on an individual basis depending on: course of symptoms; severity; treatment.

3. Non-pharmacological treatment

- The cornerstone of non-pharmacological treatment of patients with AS is patient education and regular exercise
- Home exercises are effective. Physical therapy with supervised exercises, land or water based, individually or in a group, should be preferred as these are more effective than home exercises
- Patient associations and self-help groups may be useful

4. Extra-articular manifestations and comorbidities

- The frequently observed extra-articular manifestations, for example, psoriasis, uveitis and IBD, should be managed in collaboration with the respective specialists
- Rheumatologists should be aware of the increased risk of cardiovascular disease and osteoporosis

5. Non-steroidal anti-inflammatory drugs

- NSAID, including Coxibs, are recommended as first-line drug treatment for AS patients with pain and stiffness
- Continuous treatment with NSAID is preferred for patients with persistently active, symptomatic disease
- Cardiovascular, gastrointestinal and renal risks should be taken into account when prescribing NSAIDs

6. Analgesics

- Analgesics, such as paracetamol and opioid (like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated

7. Glucocorticoids

- Corticosteroid injections directed to the local site of musculoskeletal inflammation may be considered
- The use of systemic glucocorticoids for axial disease is not supported by evidence

8. Disease-modifying antirheumatic drugs

- There is no evidence for the efficacy of DMARDs, including sulfasalazine and methotrexate, for the treatment of axial disease
- Sulfasalazine may be considered in patients with peripheral arthritis

9. Anti-TNF therapy

- Anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments according to the ASAS recommendations
- There is no evidence to support the obligatory use of DMARD before or concomitant with anti-TNF therapy in patients with axial disease
- There is no evidence to support a difference in efficacy of the various TNF inhibitors on the axial and articular/entheseal disease manifestations; but in the presence of IBD a difference in gastrointestinal efficacy needs to be taken into account
- Switching to a second TNF blocker might be beneficial especially in patients with loss of response
- There is no evidence to support the use of biological agents other than TNF inhibitors in AS

10. Surgery

- Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age
- Spinal corrective osteotomy may be considered in patients with severe disabling deformity
- In patients with AS and an acute vertebral fracture a spinal surgeon should be consulted

11. Changes in the disease course

- If a significant change in the course of the disease occurs, other causes than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed

3.5. Issues Relating to Current Practice

NICE guidance and Assessment of Spondyloarthritis International Society/European League Against Rheumatism recommendations recognise the benefits of TNF-alpha inhibitors, and in-line with this, patients can receive treatment with adalimumab, etanercept, and golimumab. However, infliximab has not been recommended by NICE and therefore patients cannot access

this treatment. Treatment is also restricted only to those with severe AS, and although more moderate disease is outside the scope of this appraisal, it is worth noting that this restricted access means that patients cannot benefit from efficacious TNF-alpha inhibitors at an early stage of their disease to prevent structural damage with long-term consequences.

3.6. Comparators

Relevant comparators, as listed in the scope for this appraisal, are TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, and infliximab) and established clinical management without TNF-alpha inhibitors (henceforth referred to as conventional therapy).

3.6.1. Conventional Therapy

Non-biologic DMARDs such as methotrexate, leflunomide, and sulfasalazine have demonstrated limited to no efficacy in AS[13]. Therefore, conventional therapy primarily comprises NSAIDs and physiotherapy, in addition to COX-2 inhibitors, steroids, gastro-protectants, and bisphosphonates. NSAIDs have demonstrated significant improvements in spinal pain, peripheral joint pain, and physical function in patients with AS and are used as part of conventional therapy in current clinical practice[13].

3.6.2. TNF-Alpha Inhibitor Therapy

Patients failing conventional therapy are likely to be offered TNF-alpha inhibitor therapy. These biologic DMARDs have represented a major advancement in the management of AS patients for whom NSAIDs provide inadequate relief. The TNF-alpha inhibitors currently recommended by NICE for use in AS are adalimumab, etanercept, and golimumab; these agents have demonstrated significant improvements in disease activity as assessed by the BASDAI and/or the ASAS response criteria, function, and active inflammation in the sacroiliac joints and spine[13].

4. Identification of Equality Issues

No equality issues are anticipated during this appraisal.

5. Clinical Evidence

5.1. Key Clinical Trial Data

5.1.1. P01522[14,15,16,17,18,19,20,21]

A study by Braun and colleagues evaluated the use of infliximab in the treatment of active AS in a randomised, placebo-controlled, multi-centre study conducted in Germany. Included patients were diagnosed with AS according to the modified New York criteria for AS, and had active disease defined by BASDAI and spinal pain scores >4 on a 10 cm visual analogue scale (VAS). The primary endpoint of the trial was the proportion of patients who achieved a BASDAI50 response at week 12. Secondary efficacy measures included improvements in the VAS for spinal pain, in the functional index (BASFI), the metrology index (Bath Ankylosing Spondylitis Metrology Index [BASMI]), and quality of life (Short Form-36 [SF-36]), and laboratory parameters (erythrocyte sedimentation rate [ESR], c-reactive protein [CRP]). DMARDs and corticosteroids were discontinued >4 weeks prior to screening. Patients were permitted to take NSAIDs, but the dose could not be increased over the baseline value. Patients were randomised to receive infliximab 5mg/kg (n=35) or placebo (n=35) at weeks 0, 2, and 63.

Significantly more infliximab-treated patients achieved a BASDAI50 response at week 12, compared to placebo (53% vs. 9%; p<0.0001). A clear difference could be seen when mean changes were compared: in the infliximab group the BASDAI score improved significantly from 6.5 at baseline to 3.3 at week 12, whereas little improvement was recorded in the placebo group (from 6.3 to 5.7; difference 2.7; p<0.0001). Rapid improvement was observed in 41% of patients at week 2. Similar findings were observed with other efficacy measures, including the BASFI and BASMI indices. Forty-four percent of patients (15/34) had both peripheral arthritis and enthesitis at baseline compared with 17% who had peripheral arthritis and 27% with enthesitis at week 12, whereas no changes were seen in the placebo group. NSAIDs were discontinued in 41% of infliximab-treated patients versus 13% of patients in the placebo group (p=0.02). Moreover, NSAID doses were reduced by >50% of baseline in 56% of patients (18/34) receiving infliximab, compared to 19% of patients (6/35) receiving placebo (p=0.004). At week 12, CRP and ESR decreased significantly from baseline in the infliximab group (p<0.001), compared to the placebo group (p=0.77). Infliximab-treated patients also demonstrated significant improvement in physical function, bodily pain, general health, activities affected by physical function, and vitality, compared to no effect in placebo-treated patients.

Infliximab was generally well-tolerated and no infusion-related reactions were observed through 12 weeks. The most common adverse event (AE) was upper respiratory tract infection. A total of 35% of patients treated with infliximab had an infection compared with 51% of patients treated with placebo (p=0.227). Three infliximab-treated patients discontinued therapy secondary to a serious adverse event (SAE), compared to none in the placebo group. One patient in the infliximab group developed systemic TB after the third infusion. Another patient experienced bronchiocentric allergic granulomatosis of the lung, which resolved 8 weeks after cessation of infliximab and treatment with corticosteroids. A third patient developed transient leukopenia after the third infusion and did not experience further complications.

Twenty patients were included in a sub-study to evaluate three MRI scoring systems for spinal changes in AS. At baseline, active spinal lesions were observed in 75% of patients (15/20). With all three systems, active lesions improved markedly more in the infliximab group compared with the placebo group (40% vs. 6%; 60% vs. -21%; 7% vs. -35%). The significant regression of spinal inflammation corresponded with improvement in disease activity.

One-Year Open-Label Extension

Patients enrolled in the 12-week, controlled portion of this trial were eligible to continue in an open-label, observational follow-up phase up to 54 weeks. Seventy-eight percent of patients (54/69) were enrolled in the 54-week extension and continued to receive infliximab 5mg/kg at week 18 and every 6 weeks thereafter. Significant improvement in disease activity (BASDAI) was maintained through 54 weeks. At week 54, 47% of patients originally receiving infliximab and 51% of patients originally in the placebo group (i.e. crossover group) achieved a BASDAI50 response. Additionally, 72% and 67% of patients in the infliximab group and crossover group, respectively, reduced their NSAID doses by >50% from baseline; 59% of the patients in both groups were able to discontinue NSAIDs.

The AEs reported during the 54-week extension were similar to those reported in the first 12 weeks and consistent with those observed in previous clinical trials. Twenty-two percent of patients discontinued the study due to lack of efficacy (n=2), noncompliance (n=2), and adverse events (n=11). No deaths were reported. Three anti-nuclear antibody (ANA) positive patients developed musculoskeletal symptoms, including polyarthritis: two patients recovered after discontinuation of infliximab and short-term treatment with methylprednisolone, and one patient developed chronic polyarthritis. The authors concluded that treatment with infliximab resulted in rapid, clinical improvement for one year in patients with active AS.

Two-Year Open-Label Extension

All patients who completed 54 weeks of infliximab therapy were eligible to continue in the open-label, observational follow-up to 102 weeks. The long-term efficacy and safety of infliximab treatment and the impact on socioeconomic outcomes was assessed. Of the 54 patients who completed the first year of the study, 52 patients continued to receive infliximab 5mg/kg every 6 weeks to week 102. Seventy-one percent of the original study population (49/69) and 94% of patients (49/52) who started the second year completed the study, while 29% of the original study population (20/69) discontinued treatment due to AEs, lack of efficacy, or other reasons. Significant improvement in disease activity was sustained in every outcome measure through week 102. At week 102, 58% of the patients (n=30) achieved a BASDAI50 response. Additionally, 25% of patients (n=13) achieved at least partial remission, according to ASAS criteria. The most frequently reported AEs included upper respiratory tract infection (17%), rhinitis (13%), and herpes simplex (12%). SAEs were reported in six patients (12%): four reactions (osteoporosis, euphoria/syncope, pancreatitis, and menorrhagia) were considered by the investigator to be unrelated to the study drug, while two reactions (infusion-related reaction and musculoskeletal pain) were considered possibly related to the study drug.

The productivity and number of hospitalisations in the 49 patients who completed 2 years of treatment was investigated[22]. Fifty-seven percent of patients (28/49) were employed at baseline and were evaluated for reduction in the frequency of sick leave from work. Fifty-seven percent of employed patients (16/28) had been on sick leave within 12 months prior to the start of the trial. After 1 year of treatment, the proportion of patients on sick leave was reduced to 36% (10/28; p=0.031), with a further reduction to 14% after 2 years (4/28; p<0.001 vs. prior to treatment). Additionally, of the 49 patients who completed 2 years of treatment, 41% (20/49) had been admitted to a hospital within 12 months before the start of the trial. After 1 and 2 years of treatment, 10% (5/49) had been admitted to a hospital at each of the two time points (p=0.001 vs. prior to treatment), respectively. Importantly, the number of inpatient days for each patient decreased from an average of 11.1 days (range 0-77 days) before treatment with infliximab to 0.6 days (range 0-15 days) after 1 year of treatment, and to 2.9 days (range 0-72 days) after 2 years of treatment (p<0.001 and p=0.007 vs. before treatment, respectively).

Three-Year Open-Label Extension

A total of 43 patients (62% of the original study population) completed 3 years of follow-up. The clinical efficacy of infliximab was sustained through 3 years of therapy, with persistent decrease

of disease activity and continuous improvement of clinical symptoms (Table 2). Additionally, there were no significant safety issues and no major side effects observed.

Table 2: Assessment of response after 54, 102, and 156 weeks of therapy

	Baseline	**Week 54**	**Week 102**	**Week 156**	**p value†**
BASDAI score 0-10*	6.4+1.3	2.4+1.6	2.6+2.0	2.7+2.0	<0.0001
BASFI score 0-10*	5.2+1.9	3.1+2.2	3.1+2.3	3.1+2.5	<0.0001
BASMI score 0-10*	3.7+2.0	2.4+1.9	2.7+2.1	2.8+2.2	0.001
CRP median, mg/l (range)	21.5 (0.9-74.0)	3.8 (0-17.8)	3.0 (0-12.2)	1.5 (0-41.2)	<0.0001
ESR median, mm/h (range)	25.0 (3-88)	7.0 (1-50)	6.0 (2-35)	7.5 (2-9.0)	<0.0001
SF-36 physical component*	29.6+7.4	40.2+10.8	40.5+11.4	41.6+11.7	<0.0001
SF-36 mental component*	242.5+11.9	51.5+8.6	51.4+8.9	48.8+10.4	0.002

* Results presented as mean ±standard deviation; † week 0 versus week 156. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SF-36, Short Form-36.

Response to Discontinuation after 3 Years and Re-Administration

After 3 years of maintenance treatment with infliximab, all patients discontinued treatment and were eligible to enter another 2-year extension phase (total observation period of 5 years), which would allow them to be re-infused with infliximab upon relapse. Forty-two patients were included in this extension and visited regularly at 6-week intervals to assess their clinical disease state. Relapse was defined as a BASDAI score ≥4 points and a PGA score ≥4 (according to the recommendations of the Assessment of Spondyloarthritis International Society). All but one patient (41/42) had to be re-infused because of relapse. The mean time to relapse was 17.5 weeks (±7.9 weeks, range 7 to 45 weeks). Patients who were in partial remission and those with normal CRP levels at the time point of withdrawal had longer times to relapse after discontinuation of the treatment. Re-treatment with infliximab was well tolerated and resulted in clinical improvement in all patients to a state similar to that before the treatment was stopped.

The primary outcome of this longer-term extension was the safety of the patients over 1 year after re-administration of infliximab. The overall incidence of AEs was similar to the results of the first 3 years of therapy. No new patients developed infusion reactions after infliximab re-administration. One patient discontinued therapy due to AEs (repeated local infections). Efficacy outcomes included the BASDAI50 response rate 24 and 48 weeks after re-administration of infliximab. Of the 42 patients who enrolled in the fourth year of this study, 41 patients completed 4 years of treatment (59.4% of the original study population). At the end of year 4, 62.5% of patients achieved a BASDAI50 response. In addition, ASAS40 response rates were similar to those observed at the end of years 1, 2, and 3. Infliximab provided sustained

efficacy through 4 years with regard to signs and symptoms, physical function, and spinal mobility.

Table 3: Assessment of clinical response after 4 years of therapy

Assessment	**Infliximab 5mg/kg**
BASDAI (mean±SD)	2.6±2.0
BASFI (mean±SD)	3.2±2.5
BASMI (mean±SD)	2.7±2.0
CRP median, mg/l (range)	1.8 (0-17)
ESR median, mm/h (range)	11 (1-66)
PatGA 0-10 (mean±SD)	2.8±2.3
PhysGA 0-10 (mean±SD)	2.0±1.9
ASAS40, %	62.5
ASAS5/6, %	70.0
ASAS partial remission, %	30.0

ASAS, Assessment in Ankylosing Spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PatGA, Patient Global Assessment; PhysGA, Physician Global Assessment; SD, standard deviation.

Persistent Clinical Efficacy and Safety over 5 Years

The results of the 5-year follow-up to this trial were reported. The primary outcome of this further extension of the study was the proportion of patients in clinical remission according to ASAS criteria at the end of the fifth study year. Of the 43 patients who completed year 3, 42 agree to continue, 38 of which (90.5%) finished year 5 (55% of the patients who were initially included). Partial clinical remission was achieved by 34.2% of patients at year 3 and 5. BASDAI scores <4 were seen in 79% of patients at both 3 and 5 years. Mean BASDAI score at year 5 was 2.5±1.9 (6.4 at baseline). ASAS20 and ASAS40 responses were achieved by 84% and 63% of patients, respectively. No major side effects occurred during year 4 and year 5 of infliximab therapy. Authors concluded that infliximab was well-tolerated and efficacious in AS patients over 5 years. The majority of the patients remained on treatment and had rather persistent levels of low disease activity.

The authors identified three distinctive patient populations according to their level and degree of response. Group A patients (26%) were in remission at most time-points (≥20 of the 25 visits). Group B patients (32%) were in a state of low disease activity (BASDAI <3) at most time-points (≥20 of the 25 visits). The rest of the patients were classified as Group C. When analysing those populations, some differences were found: patients in Group A were younger (mean age was 31.2, 39.5, 42.9 years, respectively) and had less disease duration than other groups (mean

disease duration was 6.1, 16.2, 17.0 years, respectively). The main difference between Group B and Group C was function at baseline (mean BASFI score was 4.8 and 6.7, respectively).

Persistent Clinical Efficacy and Safety over 8 Years

Clinical efficacy and safety results were reported after 8 years of infliximab therapy. The primary outcome of the 8-year extension was the proportion of patients on partial remission according to the ASAS criteria at the end of the eighth study year in comparison to baseline and to the end of year 3. Of the 43 patients who completed year 3, 42 agreed to continue infliximab treatment, and 37 (88.1%) of those patients finished year 8 (53.6% of the initial 69 patients). At the end of year 8, partial remission was achieved by 35.1% of patients, and the mean BASDAI score was low (2.3±1.6). A BASDAI50 response was achieved by 67.6% of patients, and ASAS20 and ASAS40 responses were reported in 81% and 62% of patients, respectively. There was no indication of loss of response, and no major side effects occurred during the eighth year of infliximab therapy.

5.1.2. ASSERT[23]

The efficacy and safety of infliximab in AS was further assessed in a larger patient population at 33 centres throughout Europe, US, and Canada: ASSERT was a Phase III, randomised, double-blind, placebo-controlled, multicentre study in 279 patients with active AS. Adult patients classified as having AS according to the modified New York criteria, and active disease with a BASDAI score ≥4 (range 0-10) and spinal pain ≥4 (VAS of 0-10 cm) were eligible for the study.

Patients with complete ankylosis of the spine were excluded, and the use of DMARDs and systemic corticosteroids were prohibited. Doses of infliximab 5mg/kg as monotherapy or placebo were administered intravenously at weeks 0, 2, 6, 12, and 18. The primary endpoint of the ASSERT trial was the proportion of patients who achieved an ASAS20 response at week 24. ASAS criteria included patient's global assessment, spinal pain, function according to the BASFI, and morning stiffness. Patients were assessed at baseline and week 24 using standard AS performance scores and magnetic resonance imaging (MRI) of the spine. Additional endpoints evaluated included the BASDAI, BASFI, BASMI, and HRQoL, as measured by the SF-36.

Patients were randomly assigned to treatment with infliximab (n=201) or placebo (n=78). The study population was typical for patients with active AS, consisted mostly of men (81%), had a median age of 40 years, and median disease duration of 8.8 years. At 24 weeks, an ASAS20 response was observed in 61.2% of patients in the infliximab-treated group versus 19.2% of

patients in the placebo group (p<0.001). The difference between the treatment groups was observed as early as week 2 and maintained through week 24. Significantly more patients in the infliximab group met the more rigorous ASAS40 response criteria at week 24: 47% versus 12% of patients who received placebo (p< 0.001). ASAS partial remission, defined as a value <20 on a scale of 0-100mm in each of the four ASAS response parameters, was achieved in 22.4% of infliximab-treated patients versus 1.3% in placebo-treated patients (p<0.001).

Additionally, the proportion of patients with BASDAI20, BASDAI50, and BASDAI70 responses through week 24 was 68%, 51%, and 35% in the infliximab group, compared to 27%, 11%, and 8% in the placebo group, respectively (p<0.001). These data confirm the primary endpoint results of the first placebo-controlled study (P01522). Significant reductions from baseline BASDAI, BASFI, and BASMI scores were demonstrated in infliximab-treated patients, compared to patients receiving placebo (Table 4).

Table 4: Summary of major clinical outcomes from baseline to week 24*

		Placebo	**Infliximab 5mg/kg**	**p value**
BASDAI, score 0-10		-0.4 (-1.4, 0.7)	-2.9 (-4.9, -0.9)	<0.001
BASFI, score 0-10		0.0 (-1.0, 1.0)	-1.7 (-3.6, -0.6)	<0.001
BASMI, score 0-10		0.0 (-1.0, 0.0)	-1.0 (-1.0, 0.0)	0.019
CRP level, mg/dl		0.0 (-31.7, 25.0)	-68.7 (-85.2, -16.7)	<0.001
SF-36 summary scores	Physical component	0.8 (-1.9, 6.0)	10.2 (3.9, 17.1)	<0.001
	Mental component	2.0 (-2.6, 7.5)	2.7 (-2.9, 8.8)	0.547

* values are median (interquartile range) change from baseline except CRP, which is median (interquartile range) percent change from baseline. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; SF-36, Short Form-36.

The median improvement from baseline in the general health-related quality of life questionnaire SF-36 physical component summary (PCS) score at week 24 was 10.2 for the infliximab group versus 0.8 for the placebo group (p<0.001). There was no change in the SF-36 mental component summary (MCS) score in either the infliximab group or the placebo group; however, the patients participating in this study had approximately normal MCS at baseline.

One or more AEs were reported in 82% and 72% of patients receiving infliximab and placebo, respectively, and most were mild to moderate in severity. The most frequently-reported AE was upper respiratory tract infection, which occurred at similar rates in the infliximab group (13.9%) and the placebo group (14.7%). Infections were reported in 43% and 36% of patients receiving infliximab and placebo, respectively. Increases in levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were reported in 9.4% (n=19) and 5.4% (n=11) of

the infliximab-treated patients, respectively, and in 4.0% (n=3) and 2.7% (n=2) of the patients receiving placebo, respectively. None of the patients developed symptoms of clinical hepatitis. SAEs were reported in 3.5% (n=7) and 2.7% (n=2) of patients in the infliximab and placebo groups, respectively. No discontinuations due to SAEs were seen among infliximab patients. There were no reports of deaths, malignancies, or tuberculosis in the study. Additionally, the proportion of infusions with infusion-related reactions was the same for both treatment groups (2.7%). The proportion of patients who experienced an infusion-related reaction was slightly higher in the infliximab treatment group (11%) versus placebo (9.3%). Importantly, there were no serious infusion-related reactions, anaphylactic reactions, or possible delayed hypersensitivity reactions in infliximab-treated patients or placebo-treated patients.

At week 24, positive ANA and anti-dsDNA antibodies were found in 40.7% and 12.7%, respectively, of patients who were treated with infliximab and who were negative at baseline, compared to 9.2% and 0.0%, respectively, in the placebo group. Additionally, among the 199 patients in the infliximab group with appropriate serum samples, 6 patients (3%) were positive for antibodies to infliximab.

Twelve infliximab-treated patients (5.9%) had post-baseline ALT or AST values that were ≥2 times greater than the baseline value and ≥3 times greater than the upper limit of the normal range. No patients in the placebo group met these criteria. None of the infliximab-treated patients with increased ALT or AST values had their treatment discontinued or had their enzyme increases reported as SAEs. Additionally, none of the patients developed symptoms of clinical hepatitis. As of week 24, 33% of the mentioned patients (4/12) had liver enzyme levels that had returned to normal or were decreasing.

ASSERT Sub-Analyses[24,25,26]

Van der Heijde and colleagues examined whether clinical benefits observed with infliximab were accompanied by improvement in productivity and reduction in time lost from work. At both baseline and week 24, 122 patients (n=94, infliximab; n=28, placebo) were employed full-time. The median percent change from baseline to week 24 in the productivity score (VAS, range 0-10) in patients receiving infliximab was 62% versus 11% in the placebo group ($p<0.05$). In addition, patients in the infliximab group had an average 60% reduction at week 24 in the number of workdays missed over a 6-week period compared to baseline (0.7 days vs. 1.7 days; $p<0.01$); in contrast, no significant reduction was observed in the placebo group (1.2 days vs. 1.7 days; $p=0.6$). The mean number of workdays missed per patient during the 24 week study

period was 6.8 in the placebo group, compared with 2.8 in the infliximab group (p=0.07). The authors concluded that treatment with infliximab resulted in a substantial improvement in productivity among patients with AS.

Braun and colleagues evaluated the effect of infliximab (n=194) compared to placebo (n=72) on spinal inflammation assessed by MRI. Patients receiving infliximab had a highly significant decrease in spinal inflammation, while patients receiving placebo showed almost no change. Specifically, the mean change from baseline in MRI activity scores at week 24 was -5.0 with infliximab versus -0.6 with placebo (p<0.001).

Visvanathan *et al*. evaluated the relationship between biomarker levels and disease activity and the spinal inflammation detected by MRI and demonstrated that significant reductions in interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), and CRP were observed with infliximab compared with placebo. High levels of baseline IL-6 and CRP were associated with clinical response after infliximab treatment. Early reductions in IL-6 were significantly associated with improvements in disease activity and the spinal inflammation detected by MRI.

ASSERT 2-Year Extension[27,28,29,30,31]

Patients randomised to placebo in ASSERT were crossed-over to infliximab 5mg/kg at weeks 24, 26, 30, and every 6 weeks thereafter through week 96. Starting at week 36, patients randomised to infliximab who had a BASDAI score of ≥3 at two consecutive visits had their dose increased to 7.5mg/kg through the remainder of the study. By week 102, the crossover group and the continuous infliximab group were similar with regard to ASAS20 response (72.1% versus 73.9%); ASAS40 responses at week 102 were 45.9% versus 59.4%. No new safety issues were discerned. The finding of the 2 year extension was that infliximab demonstrated sustained efficacy and safety over 2 years in a large cohort of patients with active AS.

Infliximab-treated patients maintained a gradual improvement in BASMI and chest expansion after week 24, which was sustained at week 102. After switching to infliximab at week 24, patients who were originally randomised to placebo showed similar improvements in BASMI and in chest expansion as the infliximab group when evaluated at weeks 54, 78, and 102. Moreover, similar positive and sustained changes were seen in BASFI scores, as well as daily productivity among the actively employed patients. The improvement in productivity was statistically significantly correlated with improvement in physical function at all time points (p<0.01).

Pre- and post-treatment gadolinium T1 and STIR images of the spine were acquired at baseline, week 24, and week 102 to determine the effect of infliximab on the spinal inflammation detected by MRI. Images were evaluated independently by two readers, who were blinded to the treatment allocation and time sequence of the images. Scores according to the Ankylosing Spondylitis MRI spinal score for activity (ASspiMRI-a) were applied. Patients in the infliximab group showed improvement in MRI activity scores at week 24; the mean change from baseline (standard deviation [SD]) in ASspiMRI-a was -4.44 (6.16), which was sustained through week 102 (-4.87 [6.42]). Patients in the placebo group showed no change in MRI activity scores at week 24 (0.38 [3.97]), but improved after crossing over to infliximab (-4.89 [6.85]).

Radiographs were taken at baseline and week 102 to determine the effect of infliximab on radiographic progression in patients with AS included in the ASSERT trial. Radiographs of the lateral cervical and lumbar spine were scored using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) (range 0 to 72). Radiographic changes in the patients who received infliximab for 2 years (ASSERT infliximab group) were compared to patients from the Outcome in AS International Study (OASIS) cohort, a population of consecutive AS patients followed according to a fixed protocol who did not receive TNF-alpha inhibitor therapy. Radiographs of both cohorts of patients were digitised, and the origin of the films and the true time order were blinded to the two readers. Mean change in mSASSS between baseline and 2 years was used as the primary endpoint. There was no statistically significant difference between the ASSERT infliximab cohort and the entire OASIS cohort in the mean (SD) mSASSS score change from baseline to week 102 (0.9 [2.6] and 1.0 [3.2], respectively]. The results were similar when the ASSERT infliximab cohort was compared with a cohort of OASIS patients who met the eligibility criteria for the ASSERT study (OASIS matched): 0.9 (2.6) among the ASSERT infliximab cohort and 1.2 (3.9) among the OASIS matched cohort.

5.2. Identification of Relevant Studies through a Systematic Review

The objective for this submission is to assess the clinical and cost-effectiveness of infliximab for the treatment of people with severe active AS whose disease has responded inadequately to, or who are intolerant to, NSAIDs.

Relevant comparators, as listed in the NICE scope for this appraisal, are conventional therapy (comprising NSAIDs, COX-2 inhibitors, steroids, gastro-protectants, bisphosphonates, and physiotherapy) and other TNF-alpha inhibitors: adalimumab, certolizumab pegol, etanercept, and golimumab. As the pivotal infliximab studies for the AS indication are not active-controlled

for the AS indication, a network meta-analysis (NMA) was performed to compare the efficacy and safety of conventional therapy, adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab for the treatment of adults with severe active AS (described in the following sections).

5.2.1. Searching for Relevant Studies

To identify data to inform the NMA, two reviewers working independently, in duplicate, conducted a systematic literature search. MEDLINE®, Embase®, and the Cochrane Library (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Methodology Register, Database of Abstracts of Reviews of Effects) were searched via OVID (from inception to February 2014). The search facets included disease terms (ankylosing spondylitis), intervention terms (adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab), and study design terms (randomised controlled trials [RCTs] and controlled clinical trials [CCTs]). For each search facet, a list of search terms using appropriate indexing and free text terms were developed. The syntax/search commands and search terms necessarily varied between databases, even when using the OVID platform (Table 5, Table 6, and Table 7). Searches were limited to studies in humans and studies written in English. A search of health technology assessment (HTA) documents produced by NICE (i.e. manufacturers' submissions, Evidence Review Group reports, Technology Appraisal Guidance documents) was also undertaken to identify any additional evidence.

Table 5: Embase® search strategy – OVID database, February 2014

No.	Search terms	Hits
1	randomised controlled trial/	349455
2	clinical trial/	839908
3	(clinical trial$).mp	1061076
4	randomization/	61231
5	random$.mp.	972245
6	(crossover$ or cross over$ or cross over$).mp.	70373
7	double blind procedure/ or single blind procedure/ or crossover procedure/	152263
8	factorial design/ or factorial analysis/ or factorial$.mp.	41196
9	(doubl$ adj blind$).mp.	158722
10	(doub$ adj mask$).mp.	2821
11	(open$ label$).mp.	38351
12	placebo$.tw. or placebo/	279825
13	(singl$ adj blind$).mp.	25360
14	(singl$ adj mask$).mp.	338
15	assign$.mp.	226571
16	allocate$.mp.	48001
17	(randomi?ed control$ trial$).tw	103039
18	rct.tw	13485
19	((treble or triple) adj blind$).tw	322

20	or/1-19	1889570
21	Ankylosing Spondylitis/	13280
22	(ankyl$ adj2 spondyl$).mp.	14839
23	Rheumat$ spondyl$.mp.	27
24	(ankyl$ adj3 (spine$ or spinal or vertebra$)).mp.	2296
25	(bechterew or bekhtere$ or mariestru?mpell or Marie Stru?mpell).mp.	325
26	or/21-25	15174
27	(golimumab or simponi or cnto148 or cnto 148 or 476181 74 5).af.	1810
28	(etanercept or enbrel or 185243 69 0 or 200013 86 1).af.	18558
29	(adalimumab or humira or trudexa or 331731 18 1).af.	14253
30	(infliximab or remicade or 170277 31 3).af.	28550
31	(certolizumab or cimzia or 428863 50 7).af.	2820
32	or/27-31	39223
33	20 and 26 and 32	1453
34	LIMIT 33 to ENGLISH LANGUAGE	1353
35	LIMIT 34 to human	1287

Table 6: MEDLINE® search strategy – OVID database, February 2014

No.	Search terms	Hits
1	Randomised Controlled Trial.pt.	360539
2	Randomised Controlled Trials as Topic/	88658
3	Controlled Clinical Trial.pt.	87004
4	Clinical trial.pt	481718
5	Randomi?ed.mp	559542
6	exp Clinical trials as Topic/	271916
7	Random$.mp	860495
8	Random allocation/	78711
9	Trial.ti,ab.	344879
10	Clinical trial, phase ii.pt	21781
11	Clinical trial, phase iii.pt	8380
12	Clinical trial, phase iv.pt	871
13	Multicenter study.pt	163138
14	placebo.mp. or placebos/	167113
15	Double blind method/	122333
16	Single blind method/	18312
17	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw	125756
18	(Clinical adj trial$).tw	205935
19	(open$ label$).mp.	24362
20	or/1-19	1509168
21	animals/ not (animals/ and humans/)	10031
22	20 not 21	1508267
23	Spondylitis, Ankylosing/	11433
24	(ankyl$ adj2 spondyl$).mp.	13821
25	rheumat$ spondyl$.mp.	134
26	(ankyl$ adj3 (spine$ or spinal or vertebra$)).mp.	595
27	(bechterew or bekhtere$ or mariestru?mpell or Marie Stru?mpell).mp.	550
28	or/23-27	14185
29	(golimumab or simponi or cnto148 or cnto 148 or 476181 74 5).af.	290
30	(etanercept or enbrel or 185243 69 0 or 200013 86 1).af.	5263
31	(adalimumab or humira or trudexa or 331731 18 1).af.	3458
32	(infliximab or remicade or 170277 31 3).af.	8684
33	(certolizumab or cimzia or 428863 50 7).af.	445
34	or/29-33	13178
35	22 and 28 and 34	449

36	LIMIT 35 to ENGLISH LANGUAGE	406

Table 7: Cochrane Library search strategy – OVID database, February 2014

No.	Search terms	Hits
1	Spondylitis, Ankylosing/	348
2	(ankyl$ adj2 spondyl$).af.	617
3	(ankyl$ adj3 (spine$ or spinal or vertebra$)).af.	38
4	(rheumat$ adj2 spondyl$).af.	49
5	(bechterew or bekhtere$ or (marie adj stru?mpell) or (Marie adj Stru?mpell) or mariestru?mpell).af.	33
6	or/1-5	648
7	(golimumab or simponi or cnto148 or cnto 148 or 476181 74 5).af.	69
8	(etanercept or enbrel or 185243 69 0 or 200013 86 1).af.	516
9	(adalimumab or humira or trudexa or 331731 18 1).af.	319
10	(infliximab or remicade or 170277 31 3).af.	612
11	(certolizumab or cimzia or 428863 50 7).af.	68
12	or/7-11	1266
13	6 and 12	152

5.2.2. Study Selection

All identified citations were scanned by two independent reviewers for eligibility according to the types of patients, interventions, comparisons, and outcomes outlined in Table 8. The researchers then obtained the full-text publications of those citations potentially matching the eligibility criteria. After obtaining these full-text publications, the same two researchers independently assessed for eligibility again, with disagreements assessed by a third adjudicator.

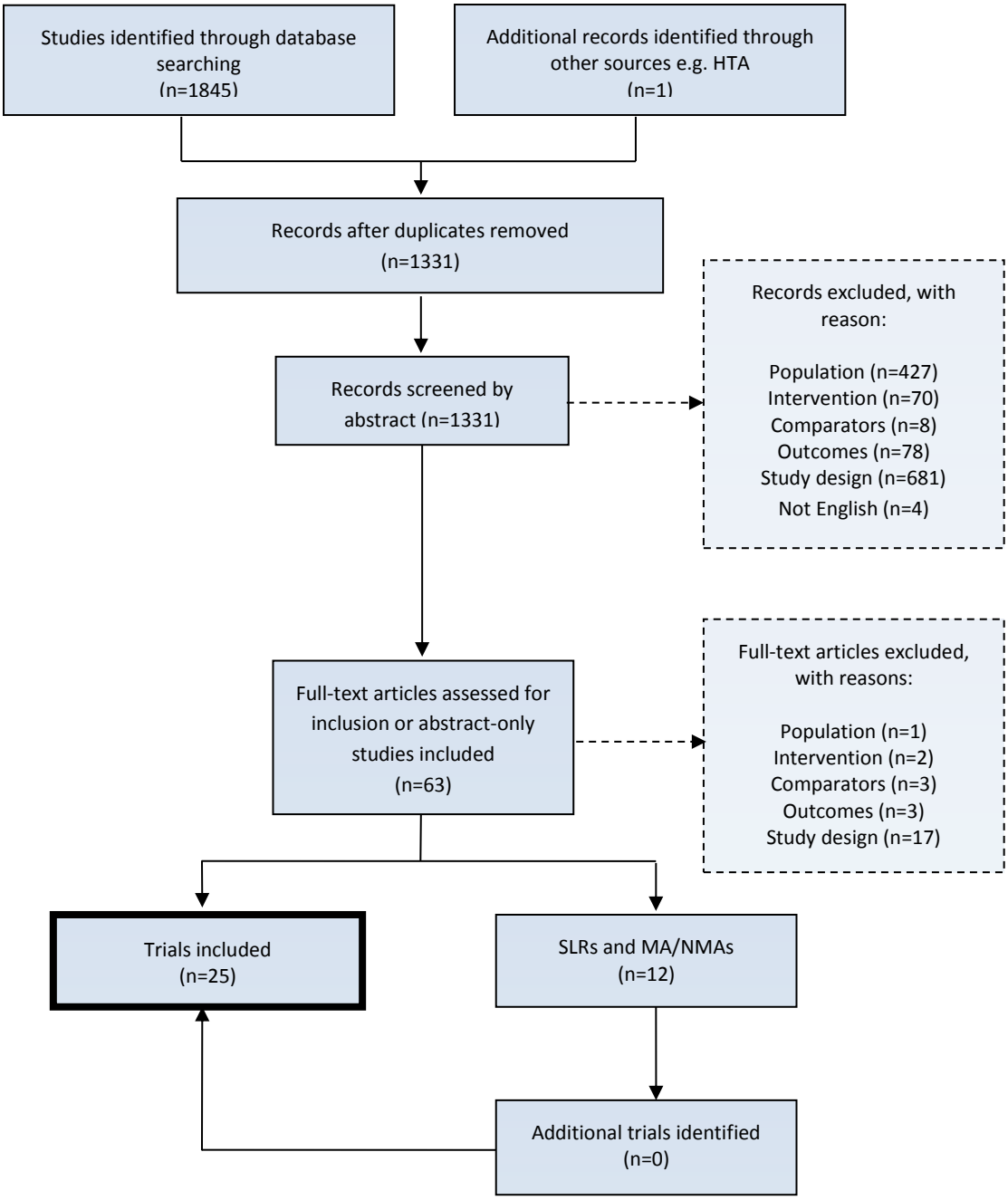
Table 8: Types of patients, interventions, controls, and outcomes considered

Component	Eligibility criteria
Population	Human patients with AS (including patients with juvenile AS but excluding patients with axial spondyloarthritis without radiographic evidence of AS)
Interventions	• Adalimumab • Certolizumab pegol • Etanercept • Golimumab • Infliximab
Comparisons (controls)	Interventions were to be compared with active comparators or placebo (conventional therapy) and were to be taken alone or in combination with MTX
Efficacy outcomes	• Assessment in Ankylosing Spondylitis (ASAS) • Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
Safety outcomes	• Any AE • Any SAE • Injection (infusion)-site reactions
Time points	Efficacy (12 +/-2 weeks), safety (24 weeks)
	RCTs and CCTs (including blinded and open-label studies), meta-analyses, network meta-analyses, and systematic literature reviews were included (the purpose of the latter three was to search their reference lists for any missing RCTs or CCTs)
Restrictions	Abstracts must be in English

AE, adverse event; AS, ankylosing spondylitis; ASAS, Assessment in Ankylosing Spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CCT, controlled clinical trial; MTX, methotrexate; RCT, randomised controlled trial; SAE, serious adverse event.

The flow of citations through the screening process is outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram in Figure 3. In total, the search yielded 1846 hits including one study identified through the HTA review, of which 515 were duplicates, leaving 1331 records to be reviewed against the eligibility criteria. After screening 1331 titles and abstracts, 63 studies were selected for full-text review. Of these 63 publications, 12 were published systematic review and/or NMAs. The hand search of the primary papers included in these systematic reviews and NMAs did not yield any extra references. The systematic reviews and NMAs were excluded as they are not a primary source of evidence. After full-text review of all 51 remaining publications, 25 studies were retained for data extraction. Data were extracted from the included studies by two reviewers working independently and recorded in a Microsoft Excel® spreadsheet. A third reviewer checked all data extraction.

Figure 3: Schematic of the publication selection process



HTA, health technology assessment; MA, meta-analysis; NMA, network meta-analysis; SLR, systematic literature review.

5.3. List of Relevant Studies from Systematic Review

Of the 25 eligible studies (summarised in Table 9), five assessed adalimumab[11,32,33,34,35,36], one evaluated certolizumab pegol[37], ten considered etanercept[38,39,40,41,42,43,44,45,46,47], two assessed golimumab[48,49,50,51], and seven appraised infliximab[52,53,54,55,56,57,58,59]. (Please note that some included studies are associated with more than one reference, for instance Clinical Study Reports [CSRs]). The majority of identified studies compared a TNF-alpha inhibitor with a placebo arm where patients were receiving background conventional therapy, though seven studies compared different doses of the TNF-alpha inhibitor being studied, and one study compared two separate TNF-alpha inhibitors (infliximab and etanercept).

The study identified through the HTA review was a Canadian AS study of adalimumab 40mg every other week versus placebo[60]. It was only reported in abstract format for the American College of Rheumatology Annual Meeting in 2005. However, the abstract is no longer publicly available. The journal (Arthritis & Rheumatology), the American College of Rheumatology, and the first author were contacted but none had access to this abstract, and access could not be obtained through a back stock agent. Certain outcomes (not in the scope of this appraisal) from this study were reported in Lambert *et al*. 2007. Outcomes of interest from this study were reported in NICE TA143. Therefore, Lambert *et al*. 2007 was referred to for information on the study design and baseline patient characteristics and NICE TA143 informed the relevant outcomes.

The 38 full-text articles excluded following the full-text screening are listed in Table 10, with the justification for their exclusion.

Table 9: Summary of included studies

Trial identifier	Type of study	Intervention	Comparator	Population	Study duration
Golimumab					
GO-RAISE (Inman *et al*. 2008 & CSR)	Double-blind randomised, placebo controlled trial	Golimumab 50mg (n=138) and 100mg (n=140) every 4 weeks	Placebo (n=78) every 4 weeks	Adult patients with AS (diagnosed according to the modified New York Criteria) for ≥3 months before the first administration of the study agent (n=356)	16 weeks (before crossover)
Bao *et al*. 2012*	Randomised, placebo controlled trial (blinding not reported)	Golimumab 50mg every 4 weeks (n=108)	Placebo every 4 weeks (n=105)	Active AS (n=213)	16 weeks (before crossover)
Infliximab					
Perez-Guijo *et al*. 2007	Open-label non-randomised trial	Infliximab 5mg/kg + MTX 7.5mg (n=9)	Infliximab 5mg/kg (n=10)	Patients were adults diagnosed as having AS defined by the modified New York criteria (n=19)	30 weeks
Giardina *et al*. 2010	Open-label randomised study	Infliximab 5mg/kg at week 0, 2, 6 and every 6 weeks for 102 weeks (n=25)	Etanercept 50mg once weekly (n=25)	Patients were adults diagnosed as having AS defined by the modified New York criteria (n=50)	2 years
Braun *et al*. 2002	Double-blind randomised, placebo controlled trial	Infliximab 5mg/kg at weeks 0, 2, 6 (n=34)	Placebo at weeks 0, 2, 6 (n=35)	Patients who fulfilled modified New York criteria for AS, and who had severe active disease that was defined by a BASDAI of 4 or greater, and spinal pain of 4 or greater (n=70)	12 weeks
ASSERT (van der Heijde *et al*. 2005 & CSR)	Double-blind randomised, placebo controlled trial	Infliximab 5mg/kg at weeks 0, 2, 6, 12, 18 (n=201)	Placebo at weeks 0, 2, 6, 12, 18 (n=78)	Patients were adults diagnosed as having AS defined by the modified New York criteria for at least 3 months prior to screening (n=279)	18 weeks
Marzo-Ortega *et al*. 2005	Double-blind randomised, placebo controlled trial	Infliximab 5mg/kg (5 infusions over 30 weeks) + MTX 7.5mg (n=28)	Placebo (5 infusions over 30 weeks) + MTX 7.5mg (n=14)	Patients were adults diagnosed as having AS defined by the modified New York criteria (n=42)	30 weeks
Breban *et al*. 2008	Open-label randomised trial	Infliximab 5mg/kg (starting dose) every 6 weeks until week 52 (n=124)	Infliximab 5mg/kg (starting dose) on demand treatment + MTX 2.5mg (starting dose) (n=62), infliximab 5mg/kg (starting dose) on demand treatment (n=61)	Patients who had diagnosed with AS and had to fulfil the clinical part of the modified New York criteria for the diagnosis of AS and have evidence of active inflammation in the 3 months prior to enrolment (n=247)	58 weeks
CANDLE (Inman *et al*.	Double-blind randomised,	Infliximab 3mg/kg at weeks	Placebo at weeks 0, 2, 6	Patients were adults diagnosed	12 week double-

Trial identifier	Type of study	Intervention	Comparator	Population	Study duration
2010)	placebo controlled trial	0, 2, 6 and every 8 weeks thereafter (n=39)	and every 8 weeks thereafter (n=37)	as having AS defined by the modified New York criteria (n=76)	blind period (crossover starting in week 14)
Adalimumab					
ATLAS (van der Heijde *et al*. 2006)	Double-blind randomised, placebo controlled trial	Adalimumab 40mg EOW (n=208)	Placebo EOW (n=107)	Patients were adults diagnosed as having AS defined by the modified New York criteria (n=315)	12 weeks (before crossover)
Canadian AS (Lambert *et al*. 2007 & NICE TA143)	Double-blind randomised, placebo controlled trial	Adalimumab 40mg EOW (n=38)	Placebo EOW (n=44)	Patients were adults diagnosed as having AS defined by the modified New York criteria (n=82)	12 weeks (before crossover)
Horneff *et al*. 2012	Double-blind randomised, placebo controlled trial	Adalimumab 40mg EOW (n=17)	Placebo EOW for 12 weeks, then patients could start adalimumab 40mg EOW (n=15)	Patients with severe, active and refractory juvenile onset AS (n=32)	12 weeks (before crossover)
Hu *et al*. 2012	Double-blind randomised, placebo controlled trial	Adalimumab 40mg EOW (n=26)	Placebo EOW for 12 weeks then adalimumab 40mg EOW (n=20)	Patients were adults diagnosed as having AS defined by the modified New York criteria (n=46)	12 weeks (before crossover)
Huang *et al*. 2013	Double-blind randomised, placebo controlled trial	Adalimumab 40mg EOW (n=229)	Placebo EOW (n=115)	Patients were adults diagnosed as having AS defined by the modified New York criteria (n=344)	12 weeks (before crossover)
Etanercept					
Brandt *et al*. 2003	Double-blind randomised, placebo controlled trial	Etanercept 25mg twice weekly (n=14)	Placebo twice weekly then etanercept 25mg after 6 weeks (n=16)	Patients diagnosed as having AS defined by the modified New York criteria (n=30)	6 weeks (before crossover)
Calin *et al*. 2004	Double-blind randomised, placebo controlled trial	Etanercept 25mg twice weekly (n=45)	Placebo twice weekly (n=39)	Patients were adults diagnosed as having AS defined by the modified New York criteria (n=84)	12 weeks
Cantini *et al*. 2013	Open-label randomised trial	Etanercept 50mg EOW (n=22)	Etanercept 50mg once weekly (n=21)	Patients diagnosed as having AS defined by the modified New York criteria (n=43)	22 months mean follow-up
SPINE (Dougados *et al*. 2011)	Double-blind randomised placebo controlled trial	Etanercept 50mg once weekly (n=39)	Placebo once weekly (n=43)	Active AS (n=82)	12 weeks
Davis *et al*. 2003	Double-blind randomised, placebo controlled trial	Etanercept 25mg twice weekly (n=138)	Placebo twice weekly (n=139)	Patients were adults diagnosed as having AS defined by the modified New York criteria (n=277)	24 weeks
Gorman *et al*. 2002	Double-blind randomised,	Etanercept 25mg twice	Placebo twice weekly	Patients were adults diagnosed	4 months (before

Trial identifier	Type of study	Intervention	Comparator	Population	Study duration
	placebo controlled trial	weekly (n=20)	(n=20)	as having AS defined by the modified New York criteria (n=40)	crossover)
van der Heijde *et al*. 2006	Double-blind randomised, placebo controlled trial	Etanercept 50mg once weekly (n=155) and 25mg twice weekly (n=150)	Placebo (n=51)	Patients were adults diagnosed as having AS defined by the modified New York criteria (n=356)	24 weeks
Huang *et al*. 2010*	Double-blind randomised, placebo controlled trial	Etanercept (n=74), dose not reported	Placebo (n=78)	Chinese adults with active AS who had an inadequate response or were intolerant to ≥1 NSAIDs (n=152)	6 weeks (before crossover)
LOADET (Navarro Sarabia *et al*. 2011)	Double-blind randomised controlled trial	Etanercept 50mg (n=54) twice weekly	Etanercept 50mg plus placebo (n=54), etanercept was given once weekly plus a second injection of placebo	Patients were adults diagnosed as having AS defined by the modified New York criteria (n=108)	12 weeks
Zhang *et al*. 2009*	Double-blind randomised, placebo controlled trial	Etanercept (n=43), dose not reported	Placebo (n=43)	Active AS (n=86)	6 weeks (before crossover)
Certolizumab pegol					
Landewé *et al*. 2014 (AS subgroup)	Double-blind randomised placebo controlled trial	Certolizumab pegol (CZP) 400mg every 2 weeks at weeks 0, 2 and 4 (loading dose) followed by either CZP 200mg every 2 weeks (n=65) or CZP 400mg every 4 weeks (n=56), n corresponds to the AS subgroup only	Placebo every 2 weeks (n=57), n corresponds to the AS subgroup only	Patients were diagnosed as having axial spondyloarthritis (axSpA) (n=325) including a subgroup of patients with AS (n=178)	16 weeks (before crossover)

* These studies are only available in abstract form – the full text articles are in Chinese. AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CSR, clinical study report; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug.

Table 10: Studies excluded after full-text screening

Principal reason for exclusion	Study
Population	Dougados *et al*. 2010
Intervention	Krzysiek *et al*. 2009; Li *et al*. 2008
Outcomes	Baraliakos *et al*. 2005; Horneff *et al*. 2011; Braun *et al*. 2008
Comparators	de Vries *et al*. 2009; Haibel *et al*. 2008; Lubrano *et al*. 2006
Study design	Braun *et al*. 2009; Braun *et al*. 2010; Braun *et al*. 2012a; Braun *et al*. 2012b; Davis *et al*. 2005; Davis *et al*. 2008; Haibel *et al*. 2006; Kobayashi *et al*. 2012; Revicki *et al*. 2008; Rudwaleit *et al*. 2004; van der Heijde *et al*. 2008; van der Heijde *et al*. 2008; Wanger *et al*. 2012; Sieper *et al*. 2012; Braun *et al*. 2009; Rudwaleit *et al*. 2009; Gottlieb *et al*. 2011; Fouque Aubert *et al*. 2010; Zhi han *et al*. 2013; McLeod *et al*. 2007; Migliore *et al*. 2012; Ren *et al*. 2013; Baraliakos *et al*. 2012; Betts *et al*. 2013; Ubago *et al*. 2011; Braun *et al*. 2007; Machado *et al*. 2013; Shu *et al*. 2013; Baraliakos *et al*. 2005

An additional study was identified after the systematic review was completed. Barkham *et al*. 2010[61] is a double-blind, placebo-controlled trial of etanercept 25mg twice weekly. This study was excluded at the abstract screening stage on the basis that it reported outcomes that were not of interest; however, an additional data supplement to this study was later identified which reported some of the outcomes of interest. As a result, Barkham *et al*. 2010 was included and data were extracted. A summary of the features of Barkham *et al*. 2010 is provided in Table 11 (information provided in Table 9 for other studies).

Table 11: Summary of Barkham *et al*. 2010

Trial identifier	Type of study	Intervention	Comparator	Population	Study duration
Barkham *et al*. 2010	Double-blind randomised, placebo controlled trial	Etanercept 25mg (n=20) twice weekly	Placebo (n=20)	Patients were adults diagnosed as having AS defined by the modified New York criteria and active disease (n=40)	12 weeks

Due to the fact that the database searches were conducted on 3rd February 2014, the full manuscript associated with the abstract by Bao *et al*. 2012 was not identified at that time. Bao *et al*. 2014[62] contains some of the information that was missing from the abstract of Bao *et al*. 2012. Both Bao *et al*. 2012 and Bao *et al*. 2014 are considered together as one reference. Bao *et al*. 2014 reported additional details to those stated in Table 9: the trial was double-blinded and recruited patients who were adults with a diagnosis of AS for at least 3 months defined as definite by the 1984 modified New York criteria, a BASDAI score ≥4, and a visual analogue scale score for total back pain ≥4.

5.4. Summary of Methodology, Participants, and Outcomes of Relevant Studies

Eligibility criteria for enrolment into the included studies were similar. It should be noted that not all studies included patients who had failed two DMARDs in line with the marketing authorisation for TNF-alpha inhibitors (Table 12). Baseline patient characteristics (including age, disease severity [BASDAI and BASFI scores], and disease duration) were reasonably similar across all included studies (Table 12).

The included studies followed similar methodology and the study outcomes were relevant to clinical practice in the UK (Table 13). Common primary outcomes were the proportion of patients with 20% or 40% improvement in ASAS score and/or the proportion of patients achieving 50% improvement in BASDAI score. Secondary outcomes included the proportion of patients achieving 40%, 50%, or 70% improvement in ASAS; 20% improvement in 5 of 6 ASAS domains (ASAS5/6); or achieving improvement in the BASFI score. Due to the fact that in many trials the disease activity was evaluated using BASDAI, the secondary outcomes were often reported as the proportion of patients achieving 20% or 50% in BASDAI scores.

Fourteen of the studies had early escape or crossover study designs, including two golimumab studies[48,49,50,51,62], one infliximab study[59], five adalimumab studies[11,32,33,34,35,36], five etanercept studies[38,40,43,45,47], and the one certolizumab pegol study[37]. (Please note that some included studies are associated with more than one reference). In three of these studies, crossover or early escape could occur as early as 6 weeks. In the majority of these studies, crossover or early escape was allowed beginning in week 12 to week 16. In Cantini *et al*. 2013 patients in the etanercept every other week arm could cross over onto etanercept once weekly at relapse.

Table 12: Baseline patient characteristics of included studies

Trial identifier	Interventions	Number of patients (n)	Female patients (%)	Mean age (years)	Mean disease duration (years)	Concomitant therapy	Prior drug failure	TNF-alpha inhibitor failure	TNF-alpha inhibitor naïve	Mean BASFI (SD, SE)	Mean BASDAI score (SD, SE)
Golimumab											
GO-RAISE (Inman *et al.* 2008 & CSR)	Golimumab 50mg	138	26.1	39.2	7.9	21.0%	NSAIDs or DMARDs	No	Yes	5.001 (2.37, 0.202)	6.498 (1.56, 0.134)
	Golimumab 100mg	140	30.0	38.6	8.1	20.0%				5.168 (2.55, 0.216)	6.893 (1.50, 0.127)
	Placebo	78	29.5	40.6	10.8	19.2%				5.098 (2.25, 0.255)	6.608 (1.52, 0.172)
Bao *et al.* 2012/Bao *et al.* 2014	Golimumab 50mg	108	16.7	30.5	4.2	MTX (19.4%), SSZ (53.7%), steroids (4.6%), NSAIDs (66.7%)	NR	NR	Yes	5.0 (2.35, NR)	6.6 (1.31, NR)
	Placebo	105	17.1	30.6	3.7	MTX (21.9%), SSZ (53.3%), steroids (4.8%), NSAIDs (72.4%)				5.0 (2.38, NR)	6.5 (1.54, NR)
Infliximab											
Perez-Guijo *et al.* 2007	Infliximab 5mg/kg plus MTX 7.5mg	9	NR	Median: 33.0	Median: 10.0	Yes (MTX)	NSAIDs, MTX, sulfasalazine	NR	NR	4.95 (NR, NR)	7.35 (NR, NR)
	Infliximab 5mg/kg	10		Median: 41.5	Median: 18.0	No				5.45 (NR, NR)	7.38 (NR, NR)
Giardina *et al.* 2010	Infliximab 5mg/kg	25	24.0	31.9	15.4	No	NSAIDs	No	Yes	6.1 (0.9, 0.18)	6.5 (1.1, 0.22)
	Etanercept 50mg	25	20.0	32.6	15.7					6.5 (1.2, 0.24)	6.6 (1.1, 0.22)

Trial identifier	Interventions	Number of patients (n)	Female patients (%)	Mean age (years)	Mean disease duration (years)	Concomitant therapy	Prior drug failure	TNF-alpha inhibitor failure	TNF-alpha inhibitor naïve	Mean BASFI (SD, SE)	Mean BASDAI score (SD, SE)
Braun *et al.* 2002	Infliximab 5mg/kg	34	32.0	40.6	16.4	No	NR	No	NR	5.5* (1.8, 20.31)	6.5 (1.2, 0.21)
	Placebo	35	37.0	39.0	14.9					5.1 (2.2, 0.37)	6.3 (1.4, 0.24)
ASSERT (van der Heijde *et al.* 2005 & CSR)	Infliximab 5mg/kg	201	21.9	39.6	10.1	No	NSAIDs	No	Yes	5.7 (1.9, 0.134)	5.8 (2.2, 0.2507)
	Placebo	78	12.8	40.3	11.9					6.5 (1.5, 0.105)	6.2 (1.6, 0.1811)
Marzo-Ortega *et al.* 2005	Infliximab 5mg/kg + MTX	28	18.0	41.0	Median: 8.0	Yes	≥1 NSAID	NR	NR	Median: 6.68	Median: 6.00
	Placebo + MTX	14	21.0	39.0	Median: 10.0					6.45 (1.87, 0.353)	6.57 (2.05, 0.548)
Breban *et al.* 2008	Infliximab (continuous)	124	25.0	41.4	14.6	No	No	NR	NR	5.4 (2.0, 0.18)	6.2 (1.5, 0.134)
	Infliximab + MTX (on demand)	62	19.4	42.7	16.4	Yes				5.6 (1.9, 0.241)	6.3 (1.3, 0.165)
	Infliximab alone (on demand)	61	26.2	40.0	13.8	No				6 (1.8, 0.230)	6.1 (1.3, 0.166)
CANDLE (Inman *et al.* 2010)	Infliximab 3mg/kg	39	18.0	42.9	11.7	Yes	Yes	No	No	NR	NR
	Placebo	37	22.0	39.3	11.1						
Adalimumab											
ATLAS (van der Heijde *et al.* 2006)	Adalimumab 40mg	208	24.5	41.7	11.3	9.6%	DMARDs, NSAIDs	No	Yes	5.2 (2.2, 0.153)	6.3 (1.7, 0.118)
	Placebo	107	26.2	43.4	10.0	7.5%				5.6 (2.2, 0.123)	6.3 (1.7, 0.164)

Trial identifier	Interventions	Number of patients (n)	Female patients (%)	Mean age (years)	Mean disease duration (years)	Concomitant therapy	Prior drug failure	TNF-alpha inhibitor failure	TNF-alpha inhibitor naïve	Mean BASFI (SD, SE)	Mean BASDAI score (SD, SE)
Canadian AS (Lambert *et al*. 2007 & NICE TA143)	Adalimumab 40mg	38	23.7	41.9	14.5	Yes	≥1 NSAID	NR	NR	5.3 (2.0, 0.324)	6.2 (1.7, 0.276)
	Placebo	44	18.2	40.0	12.1					5.6 (2.2, 0.357)	6.5 (1.6, 0.241)
Horneff *et al*. 2012	Adalimumab 40mg	17	41.2	15.1	0.9	No	NR	NR	Patients treated with infliximab, etanercept, adalimumab not eligible	3.85 (1.8, 0.437)	4.75 (1.3, 0.315)
	Placebo then adalimumab 40mg	15	53.3	15.5	2.5					4.17 (2.3, 0.596)	5.45 (1.5, 0.387)
Hu *et al*. 2012	Adalimumab 40mg	26	7.7	28.2	7.4	Continue SSZ, MTX, prednisone +/or equiv., +/or NSAIDs if stable for 4 weeks before baseline	≥1 NSAID	NR	NR	3.7 (2.1, 0.421)	5.9 (1.4, 0.275)
	Placebo then adalimumab 40mg	20	0.0	27.4	7.6					3.9 (2.0, 0.447)	6.2 (1.1, 0.246)
Huang *et al*. 2013	Adalimumab 40mg	229	19.0	30.1	8.1	SSZ (52.4%), MTX (22.7%)	NR	NR	NR	4.3 (2.3, 0.152)	6 (1.4, 0.093)
	Placebo	115	17.0	29.6	7.7					4.4 (2.3, 0.214)	6.2 (1.4, 0.131)
Etanercept											
Barkham *et al*. 2010	Etanercept 25mg	20	25.0	40.8	11.0	Stable dose SSZ or MTX +/or NSAID (no steroids, other DMARDs)	NR	NR	NR	5.60 (1.98, NR)	6.05 (1.71, NR)
	Placebo	20	15.0	39.4	20.0					5.27 (1.81, NR)	5.46 (1.74, NR)

Trial identifier	Interventions	Number of patients (n)	Female patients (%)	Mean age (years)	Mean disease duration (years)	Concomitant therapy	Prior drug failure	TNF-alpha inhibitor failure	TNF-alpha inhibitor naïve	Mean BASFI (SD, SE)	Mean BASDAI score (SD, SE)
Brandt *et al.* 2003	Etanercept 25mg	14	28.6	39.8	14.9	No	NR	NR	NR	6.2 (1.8, 0.481)	6.5 (1.2, 0.32)
	Placebo then etanercept 25mg after 6 weeks	16	25.0	32.0	11.4					5.3 (2.3, 0.575)	6.6 (1.0, 0.25)
Calin *et al.* 2004	Etanercept 25mg	45	20.0	45.3	15.0	13.0%	NR	No	Yes	6.0 (NR, NR)	6.1 (NR, NR)
	Placebo	39	23.0	40.7	9.7	13.0%				5.72 (NR, NR)	5.86 (NR, NR)
Cantini *et al.* 2013	Etanercept 50mg (EOW)	22	18.1	Median: 37.0	13.0	No	NR	Prior use of etanercept	No	2.6 (1.4, 0.298)	2.4 (0.3, 0.064)
	Etanercept 50mg (once weekly)	21	23.8	Median: 38.0	12.0					2.5 (1.3, 0.284)	2.3 (0.4, 0.087)
SPINE (Dougados *et al.* 2011)	Etanercept 50mg	39	5.0	46.0	19.0	Yes	NR	No	No	6.3 (2.0, 0.32)	6.4 (1.2, 0.192)
	Placebo	43	9.0	48.0	23.0					5.7 (1.9, 0.29)	5.8 (1.5, 0.229)
Davis *et al.* 2003	Etanercept 25mg	138	24.0	42.1	10.1	NR	11.0%	No	Yes	5.17 (2.1, 0.18)	5.81 (1.8, 0.15)
	Placebo	139	24.0	41.9	10.5		12.0%			5.63 (2.0, 0.17)	5.96 (1.7, 0.14)
Gorman *et al.* 2002	Etanercept 25mg	20	35.0	Median: 38.0	Median: 15.0	Yes	Yes	NR	NR	Median: 4.5 (2.1, 0.47)	NR
	Placebo	20	10.0	Median: 39.0	Median: 12.0					Median: 3.2 (2.5, 0.56)	
van der Heijde *et al.* 2006	Etanercept 50mg	155	30.3	41.5	9.0	MTX if stable >4 weeks before baseline	NR	No	Yes	6.06 (2.03, 0.163)	6.24 (1.70, 0.137)
	Etanercept 25mg	150	26.0	39.8	10.0					5.77 (2.01, 0.164)	5.94 (1.67, 0.136)

Trial identifier	Interventions	Number of patients (n)	Female patients (%)	Mean age (years)	Mean disease duration (years)	Concomitant therapy	Prior drug failure	TNF-alpha inhibitor failure	TNF-alpha inhibitor naïve	Mean BASFI (SD, SE)	Mean BASDAI score (SD, SE)
	Placebo	51	21.6	40.1	8.5					5.97 (1.93, 0.27)	6.11 (1.37, 0.192)
Huang *et al*. 2010	Etanercept	74	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	78									
LOADET (Navarro-Sarabia *et al*. 2011)	Etanercept 50mg	54	20.4	40.2	7.0	DMARDs (n=16)	≥2 NSAIDs	No	Yes	5.87 (1.96, 0.267)	6.10 (1.70, 0.231)
	Etanercept 50mg + placebo	54	20.4	42.6	7.3	DMARDs (n=15)				5.66 (2.04, 0.278)	6.48 (1.61, 0.219)
Zhang *et al*. 2009	Etanercept	43	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	43									
Certolizumab pegol											
Landewé *et al*. 2014 (AS subgroup)	Certolizumab pegol 200mg	65	NR	NR	NR	DMARDs (35.4%)	NR	NR	n=36	NR	NR
	Certolizumab pegol 400mg	56									
	Placebo	57									

* A discrepancy was noted regarding the BASFI score at baseline. The tabulated value was 5.4, reported in the text as 5.5 (p. 1189). AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CSR, clinical study report; DMARD, disease modifying anti-rheumatic drug; EOW, every other week; MTX, methotrexate; NR, not reported, NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; SE, standard error; SSZ, sulfasalazine; TNF, tumour necrosis factor.

Table 13: Primary and secondary outcomes of included studies

Trial identifier	Primary outcomes	Secondary outcomes	Crossover, early escape, and dose escalation
Golimumab			
GO-RAISE (Inman *et al*. 2008 & CSR)	ASAS20 at week 14	ASAS40, ASAS partial remission, ASAS5/6	Early escape to golimumab 50mg at week 16 for 41 placebo patients; early escape to golimumab 100mg at week 16 for 25 patients. Placebo group patients could crossover to receive open-label infliximab starting in week 14; all patients could receive dose-escalation of infliximab to 5mg/kg at weeks 22 or 38 if the patient had an absolute BASDAI score >3 and a relative decrease of <50% in BASDAI from baseline
Bao *et al*. 2012/Bao *et al*. 2014	ASAS20	BASDAI, BASFI, BASMI, ASAS40, ASAS5/6, ASAS partial remission, SF-36, JSEQ	At week 16, all patients randomised to placebo that met early escape criteria (<20% improvement from baseline in both total back pain and morning stiffness measures) began receiving golimumab 50mg SC injections in a blinded fashion at week 16 and every 4 weeks thereafter through week 48; all other patients still receiving placebo injections began receiving golimumab 50mg SC injection at week 24 and every 4 weeks thereafter through week 48
Infliximab			
Perez-Guijo *et al*. 2007	BASDAI50 at week 30	ASAS, BASDAI, BASFI, ESR, CRP, pain, inflammation, physician's global assessment	NR
Giardina *et al*. 2010	ASAS, BASDAI, BASFI, BASMI	NR	NR
Braun *et al*. 2002	BASDAI50	Improvements in VAS for spinal pain, BASFI, BASMI, SF-36, working group response criteria, concentration of CRP in serum, sedimentation rate	NR
ASSERT (van der Heijde *et al*. 2005 & CSR)	ASAS20 at week 24	ASAS40, BASDAI, BASFI, BASMI, chest expansion, Mander enthesis index, total swollen joint level, SF-36	Starting with the week 36 infusion and continuing through the week 96 infusion, if subjects in the placebo group had a BASDAI ≥3 at both the current visit and the prior visit (i.e. 2 consecutive visits) they were to receive a 7.5mg/kg infliximab infusion and were to continue to receive 7.5mg/kg infliximab infusions every 6 weeks thereafter through week 96
Marzo-Ortega *et al*. 2005	Change from baseline in BASDAI at weeks 4, 10, and 30	ASAS	Placebo patients crossed over onto adalimumab after 12 weeks
Breban *et al*. 2008	ASAS20 at week 58	ASAS20, ASAS40, ASAS partial remission	Infliximab was administered at a standard dose of 5mg/kg. The dose of infliximab was increased to 7.5mg/kg per infusion in the continuous

Trial identifier	Primary outcomes	Secondary outcomes	Crossover, early escape, and dose escalation
			treatment group, starting not earlier than week 40, for those patients in relapse at 2 consecutive visits. Likewise, the infusion dose was increased to 7.5mg/kg in the on-demand group, starting no earlier than the fourth on-demand infusion, if relapse occurred as early as 3 weeks after an infusion
CANDLE (Inman *et al*. 2010)	ASAS20 at week 12	ASAS40, ASAS50, ASAS70, change from baseline in BASDAI, BASFI, and BASGI, BASDAI50, BASMI, SF-36, ESR, CRP	Placebo group patients could crossover to receive open-label infliximab starting in week 14; all patients could receive dose-escalation of infliximab to 5mg/kg at weeks 22 or 38 if the patient had an absolute BASDAI score >3 and a relative decrease of <50% in BASDAI from baseline
Adalimumab			
ATLAS (van der Heijde *et al*. 2006)	ASAS20 at week 12	ASAS40, ASAS5/6	Patients who did not achieve ASAS20 at weeks 12, 16, or 20 were eligible for early-escape open-label treatment with adalimumab 40mg every other week
Canadian AS (Lambert *et al*. 2007 & NICE TA143)	ASAS20 at week 12	SPARCC scores	Those who had not reached an ASAS20 response on assessment at weeks 12, 16, or 20 were offered the option of early-escape open-label treatment with adalimumab. Participants who chose this option were counted only as 'non-responders' in the analysis of primary and secondary endpoints
Horneff *et al*. 2012	ASAS40 at week 12	ASAS20, paediatric ACR30, paediatric ACR70 at 4, 8, 12 weeks	NR
Hu *et al*. 2012	NR	NR	Placebo patients crossed over onto adalimumab after 12 weeks
Huang *et al*. 2013	ASAS20 at week 13	ASDAS, spinal mobility, disease activity, physical function, QoL	Patients were allowed to crossover onto open label adalimumab after the 12 week double-blind phase
Etanercept			
Barkham *et al*. 2010	Change in work instability of patients (AS-WIS) at week 12	BASDAI, ASQoL, BASFI, HAQ-DI	NR
Brandt *et al*. 2003	≥50% improvement in BASDAI	Spinal pain, BASFI, BASMI, SF-36, ASAS, serum CRP, ESR	Patients in the placebo group were switched to etanercept from weeks 6 to 18
Calin *et al*. 2004	ASAS20	ASAS50, ASAS70, individual ASAS components, BASDAI, acute phase reactants, spinal mobility tests	NR
Cantini *et al*. 2013	Patients maintaining clinical remission	Patients achieving clinical remission at end of first phase,	Escalation of the etanercept dose to 50mg weekly was prescribed for patients who relapsed on etanercept 50 mg every other week

Trial identifier	Primary outcomes	Secondary outcomes	Crossover, early escape, and dose escalation
		ASAS20, ASAS50, ASAS70, BASDAI, BASMI, BASFI	
SPINE (Dougados *et al*. 2011)	Net incremental AUC for the BASDAI over 12 weeks	Improvement in ASDAS	NR
Davis *et al*. 2003	ASAS20 at weeks 12 and 24	Percentage of patients achieving higher ASAS responses, safety	NR
Gorman *et al*. 2002	Composite treatment response: ≥20% improvement in 3 of 5 measures [morning stiffness, nocturnal spinal pain, BASFI, patient's global assessment, joint swelling], 1 of which had to be morning stiffness or nocturnal spinal pain, with no worsening in any of the measures. If swollen joint score was 0 throughout, improvement needed in 2 of the 4 other outcome measures	Physician's global assessment, measures of spinal mobility, scores for enthesitis and peripheral joint tenderness, ESR, CRP	After study completion at 4 months, patients were given the opportunity to crossover onto open-label etanercept
van der Heijde *et al*. 2006	ASAS20 at week 12	ASAS40, ASAS5/6 at all time points, patient and physician global assessments, nocturnal/total back pain assessments, BASDAI, patients achieving partial remission, time to partial remission, spinal mobility (modified Schober's test, chest expansion measurement, and occiput to wall distance), joint assessment (70 points), serum CRP	NR
Huang *et al*. 2010	ASAS 20	ASAS40, ASAS50, ASAS70, ASAS5/6, improvement in subject and physician global assessment, nocturnal and total back pain, BASFI, BASDAI, spinal mobility, joint assessment, QoL, safety	Placebo patients crossed over onto etanercept after 6 weeks

Trial identifier	Primary outcomes	Secondary outcomes	Crossover, early escape, and dose escalation
LOADET (Navarro Sarabia *et al*. 2011)	ASAS20 at week 12	ASAS40, ASAS50, ASAS70, ASAS5/6, partial remission at week 12, nocturnal/overall spine pain, physician global assessment, BASDAI, BASMI, complete peripheral joint count (ACR64/66), tenderness of enthesis, CRP, ESR	NR
Zhang *et al*. 2009	ASAS 20	Patients achieving higher ASAS responses, change from baseline in BASDAI and BASFI, morning stiffness, and nocturnal spinal pain	Placebo patients crossed over onto etanercept after 6 weeks
Certolizumab pegol			
Landewé *et al*. 2014 (AS subgroup)	ASAS20 at week 12	Change from baseline in BASFI, BASDAI, BASMI (linear)	Placebo patients who did not achieve an ASAS20 response at weeks 14 and 16 underwent mandatory escape at week 16 and were randomised to active treatment in a dose-blind manner

ACR, American College of Rheumatology; AS, ankylosing spondylitis; ASAS, Assessments in Ankylosing Spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life; AS-WIS, Ankylosing Spondylitis Work Instability Scale; AUC, area under the curve; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; JSEQ, Jenkins Sleep Evaluation Questionnaire; NR, not reported; QoL, quality of life; SC, subcutaneous; SF-36: Short Form-36.

5.5. Critical Appraisal of Included Studies

The NICE guidance quality checklist was used to assess the quality of each study included in the systematic review with respect to methodological criteria for experimental studies. The framework assesses the potential for studies to be impacted by biases affecting validity, including:

- Selection bias, arising from systematic differences between comparison groups in terms of performance and prognosis;
- Performance bias, relative to the provision of systematically different care other than the intervention between comparison groups;
- Measurement bias, arising from systematic differences in how outcomes are ascertained and measured;
- Attrition bias arising from systematic differences between comparison groups in how participants are withdrawn or excluded from the study groups

Please see Appendix A for the critical appraisal of included studies.

5.6. Inclusion of Studies in the Network Meta-Analysis

From the 26 studies identified, 16 were considered eligible for evidence synthesis. These totals include Barkham *et al*. 2010 which was identified after the systematic review was completed.

Since the most relevant and highly-reported time point for the measurement of efficacy outcomes was 12 weeks, Zhang *et al*. 2009, Huang *et al*. 2010, and Brandt *et al*. 2003 were not suitable for inclusion in the NMA base case due to the fact that patients crossed over at 6 weeks. Crossover or early escape reduces the relative treatment effect between arms and may therefore lead to biased results. All the studies included in the NMA base case reported at least one outcome at or close to week 12 (i.e. within +/-2 weeks), otherwise were excluded (for example, Breban *et al*. 2008 was excluded since outcomes were only reported at 58 weeks). As relative treatment effects may change over time, the risk of bias is reduced by including only outcomes measured at similar time points.

Regarding safety outcomes, studies reporting AEs or discontinuation over durations of 24 weeks were included, providing that the outcomes were reported prior to any crossover.

Table 14 summarises the studies identified in the systematic review (plus Barkham *et al*. 2010) and of those, the included studies in the NMA base case. Where a study was excluded, the reason for exclusion is given.

Table 14: Inclusion of studies in the NMA

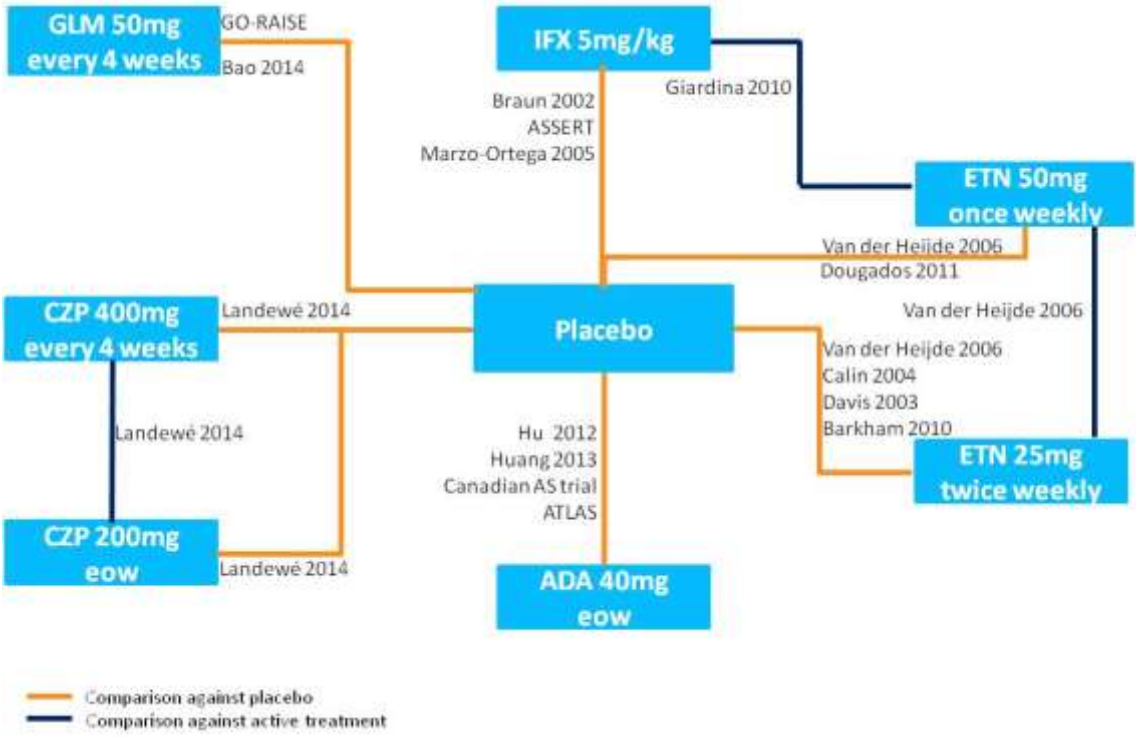
Studies	Status	Reason for exclusion
Golimumab		
GO-RAISE (Inman *et al*. 2008 & CSR)	Included	N/A
Bao *et al*. 2012/Bao *et al*. 2014	Included	N/A
Infliximab		
Perez-Guijo *et al*. 2007	Excluded	Non-randomised study
Giardina *et al*. 2010	Included	N/A
Braun *et al*. 2002	Included	N/A
ASSERT (van der Heijde *et al*. 2005 & CSR)	Included	N/A
Marzo-Ortega *et al*. 2005	Included	N/A
Breban *et al*. 2008	Excluded	No outcomes at 12 +/-2 weeks; unlicensed dose regimen
CANDLE (Inman *et al*. 2010)	Excluded	Unlicensed dose regimen
Adalimumab		
ATLAS (van der Heijde *et al*. 2006)	Included	N/A
Canadian AS (Lambert *et al*. 2007 & NICE TA143)	Included	N/A
Horneff *et al*. 2012	Excluded	Juvenile population
Hu *et al*. 2012	Included	N/A
Huang *et al*. 2013	Included	N/A
Etanercept		
Barkham *et al*. 2010	Included	N/A
Brandt *et al*. 2003	Excluded	Crossover before 12 weeks
Calin *et al*. 2004	Included	N/A
Cantini *et al*. 2013	Excluded	No outcomes at 12 +/-2 weeks; unlicensed dose regimen
SPINE (Dougados *et al*. 2011)	Included	N/A
Davis *et al*. 2003	Included	N/A
Gorman *et al*. 2002	Excluded	No outcomes at 12 +/-2 weeks
van der Heijde *et al*. 2006	Included	N/A
Huang *et al*. 2010	Excluded	Crossover before 12 weeks
LOADET (Navarro Sarabia *et al*. 2011)	Excluded	Unlicensed etanercept regimen
Zhang *et al*. 2009	Excluded	Crossover before 12 weeks
Certolizumab pegol		
Landewé *et al*. 2014 (AS subgroup)	Included	N/A

CSR, clinical study report; N/A, not applicable.

The full network of evidence is shown in Figure 4. Dark blue lines denote comparisons against active treatments, whilst orange lines denote comparisons against placebo. Note: across studies there was some heterogeneity in the use of concomitant MTX; however, there is no connected network if treatments are separated based on whether or not patients could be taking concomitant MTX (consistent with the approach taken in NICE TA233). This network differs

from that used in NICE TA233 in that the different dosing regimens of etanercept have been separated, and certolizumab pegol has been added.

Figure 4: NMA network



ADA, adalimumab; CZP, certolizumab pegol; eow, every other week; ETN, etanercept; GLM, golimumab; IFX, infliximab.

The following outcomes were included for analysis in the NMA: Efficacy outcomes at 12 weeks (+/-2 weeks): ASAS20, ASAS40, and BASDAI50. Safety outcomes at 24 weeks: any AEs, any SAEs, and ISRs.

In addition, absolute probabilities for efficacy outcomes were calculated by pooling the placebo arms of trials included in the evidence network. Absolute probabilities for safety outcomes were calculated by pooling the placebo arms of studies reporting the relevant outcomes up to 24 weeks prior to crossover. The absolute treatment effect was used to calculate relative risk (RR) from odds ratios (ORs), for use in the economic model.

5.7. Extracted Data from Studies Included in Network Meta-Analysis

Data were extracted from the 16 studies suitable for inclusion in the NMA for each of the outcomes to be analysed (Table 15).

Table 15: Extracted data included in NMA

Trial identifier	Interventions	ASAS20 (n)	ASAS40 (n)	BASDAI50 (n)	AEs (n)	SAEs (n)	ISRs (n)
Golimumab							
GO-RAISE (Inman *et al.* 2008 & CSR)	Golimumab 50mg (n=138)	81 (of 133)	62*	61*	109[a]	5[a]	9[a]
	Placebo (n=78)	20 (of 76)	12*	12*	57 (of 77)[a]	4 (of 77)[a]	2 (of 77)[a]
Bao *et al.* 2012/Bao *et al.* 2014	Golimumab 50mg (n=108)	48	28	32	Not included in NMA (reported post-crossover)		
	Placebo (n=105)	25	10	8			
Infliximab							
Giardina *et al.* 2010	Infliximab 5mg/kg (n=25)	19	14	NR	Not included (evaluation period over 2 years)		
	Etanercept 50mg (n=25)	15	11				
Braun *et al.* 2002	Infliximab 5mg/kg (n=34)	24	NR	18	NR	3 (of 35)[b]	NR
	Placebo (n=35)	10		3		0 (of 36)[b]	
ASSERT (van der Heijde *et al.* 2005 & CSR)	Infliximab 5mg/kg (n=201)	124	98	NR	166 (of 202)	7 (of 202)	22 (of 202)
	Placebo (n=78)	15	10		54 (of 75)	2 (of 75)	7 (of 75)
Marzo-Ortega *et al.* 2005	Infliximab 5mg/kg + MTX (n=28)	20‡	NR	NR	Not included in NMA (reported at 30 weeks)		
	Placebo + MTX (n=14)	4‡					
Adalimumab							
ATLAS (van der Heijde *et al.* 2006)	Adalimumab 40mg (n=208)	121	83	94	Not included in NMA (not reported prior to crossover)		
	Placebo (n=107)	22	14	17			
Canadian AS (Lambert *et al.* 2007 & NICE TA143)	Adalimumab 40mg (n=38)	18	NR	NR	NR		
	Placebo (n=44)	9					
Hu *et al.* 2012	Adalimumab 40mg (n=26)	NR	NR	NR	NR		

Trial identifier	Interventions	ASAS20 (n)	ASAS40 (n)	BASDAI50 (n)	AEs (n)	SAEs (n)	ISRs (n)
	Placebo then adalimumab 40mg (n=20)						
Huang *et al.* 2013	Adalimumab 40mg (n=229)	154	102	114	81	1	NR
	Placebo (n=115)	35	11	19	26	1	
Etanercept							
Barkham *et al.* 2010	Etanercept 25mg (n=20)	NR	Not included in NMA (only a proportion of patients [~50%] measured for this outcome)	7	19	NR	NR
	Placebo (n=20)			1	16		
Calin *et al.* 2004	Etanercept 25mg (n=45)	27	NR	NR	NR	NR	15
	Placebo (n=39)	9					6
SPINE (Dougados *et al.* 2011)	Etanercept 50mg (n=39)	25	17	18	24	2	3 (of 40)[b]
	Placebo (n=43)	14	10	10	28	1	0 (of 44)[b]
Davis *et al.* 2003	Etanercept 25mg (n=138)	82	NR	NR	NR	NR	41
	Placebo (n=139)	39					13
van der Heijde *et al.* 2006	Etanercept 50mg (n=155)	115	90	93	55	NR	32
	Etanercept 25mg (n=150)	107	80	87	66		34
	Placebo (n=51)	19	11	10	18		6
Certolizumab pegol							
Landewé *et al.* 2014 (AS subgroup)	Certolizumab 200mg (n=65)	37	26	50 (of 111)†	NR		
	Certolizumab 400mg (n=56)	36	28	47 (of 107)†			
	Placebo (n=57)	21	11	14 (of 107)†			

All efficacy data at 12 weeks unless otherwise stated. ‡ 10 weeks; * 14 weeks; † data from the full axial spondyloarthritis population has been used in the absence of data from the AS subgroup; [a] safety data were obtained from the GO-RAISE CSR (at 16 weeks); [b] studies with zero events tend to produce problems in the NMA due to the discontinuity in the odds ratio, therefore a continuity correction of 0.5 is introduced which can itself increase bias. AS, ankylosing spondylitis; ASAS, Assessments in Ankylosing Spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ISR, injection (infusion)-site reaction; MTX, methotrexate; NMA, network meta-analysis; NR, not reported; SAE, serious adverse event.

5.8. Methodology of Network Meta-Analysis

5.8.1. The Bayesian Framework

The analysis was conducted using WinBUGS version 1.4.3[63]: Bayesian analysis software that, through the use of Monte Carlo Markov Chains, calculates posterior distributions for the parameters of interest, given likelihood functions derived from data and prior probabilities. The Monte Carlo Markov Chain simulation begins with an approximate distribution and, if the model is a good enough fit to the data, the distribution converges to the true distribution.

The analyses conducted consisted of binary outcomes. All baseline and intervention effect parameters were given flat (uninformative) normal (0, 1000) priors and the between-study SD flat uniform distributions with an appropriately large range given the scale of measurement. A binomial likelihood with logit link function was used for binary data. The WinBUGS codes used were based on the NICE Decision Support Unit (DSU) Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials[64]. The methodology also follows guidance from the International Society For Pharmacoeconomics and Outcomes Research Task Force on Indirect Treatment Comparisons[65,66]. In addition, correlations induced by multi-arm trials were taken into account using the methods and WinBUGS codes recommended by the DSU[64]. For the calculation of absolute treatment effect, probabilities were pooled by logistic regression in WinBUGS using methods outlined by the NICE DSU[64]. The WinBUGS codes used are detailed in Appendix B.

5.8.2. Assessment of Convergence

Convergence was assessed using the Brooks-Gelman-Rubin diagnostic[67] in WinBUGS along with visual inspection of the trace and density plots and the autocorrelation. A burn-in of at least 20,000 simulations was discarded and three chains were used. Thinning of the chains with a larger number of iterations was required to achieve convergence in some cases. All results presented are based on a further sample of at least 50,000 simulations or until convergence is achieved. We observed the Monte Carlo error, which can be interpreted as the standard error (SE) of the posterior mean adjusted for autocorrelation. A Monte Carlo error of less than 5% of the posterior SD is the standard rule of thumb that was used to test convergence[68]. All models used in the base case and sensitivity analyses converged.

5.8.3. Rare Events

A continuity correction was applied in the case of zero events occurring in one of the treatment arms for the binary outcomes. A value of 0.5 was added to the number of events and non-events in each arm[69].

5.8.4. Assessment of Model Fit

The value of total residual deviance was compared to the number of independent data points to check model fit. Each data point should contribute approximately one unit to the total residual deviance; hence, the total residual deviance should be approximately equal to the number of unconstrained data points for a model that fits well. Most models fitted well in terms of this criterion. Fit, as assessed by the difference between the total residual deviance and the number of data points, was similar for the fixed effects and random effects models.

5.8.5. Model Comparison

Both fixed effects and random effects models were conducted. Fixed effects models make the assumption that studies investigating the same treatment comparison are estimating the same true treatment effect, subject only to sampling error. A random effects model assumes that the treatment effects for studies investigating the same treatment comparison come from a distribution with a common variance parameter estimated from the variation in treatment effects. The main difference between these two types of models is that the latter allows for additional variation caused by between study heterogeneity, thereby producing wider confidence intervals. The Deviance Information Criterion (DIC) and the total residual deviance can be considered in order to choose the appropriate model for the data as it provides a measure of model fit that penalises model complexity – lower values of the DIC suggest a more parsimonious model (differences of less than 3 are not considered to be important)[70].

Recently, the ISPOR-AMCP-NPC Good Practice Task Force has published guidelines on network meta-analyses[71]. These guidelines state that a random effects model should be generally be chosen unless there is substantial reasoning to support a fixed effects model. This is based on the underlying assumption of the fixed effect model that the trials for a particular comparison are estimating the same true treatment effect. These guidelines state that this is unlikely to be a plausible assumption because study characteristics and the distribution of treatment effect

modifiers generally differ across studies. Random effects models were therefore selected for all indirect comparisons – to account for any heterogeneity between included studies.

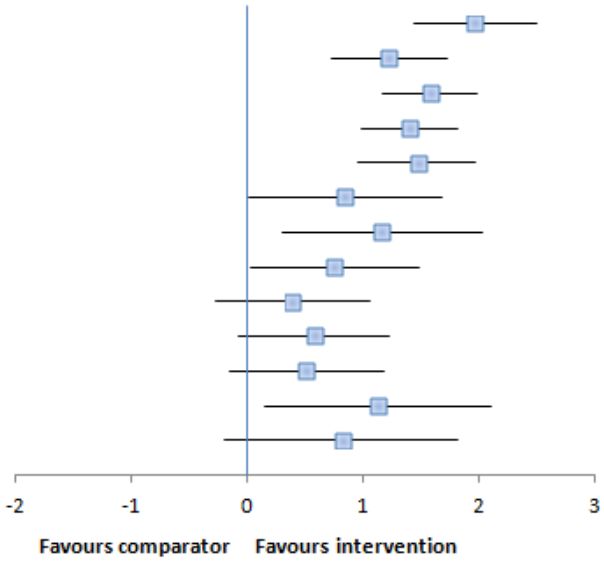
5.9. Results of Network Meta-Analysis

5.9.1. ASAS20

Figure 5 presents the relative efficacy estimates between golimumab, adalimumab, certolizumab pegol, etanercept, and infliximab in ASAS20 response at week 12 (+/-2 weeks). Each TNF-alpha inhibitor had significantly greater efficacy compared to placebo, with the greatest treatment effect noted for infliximab, followed by adalimumab, etanercept, golimumab, and certolizumab pegol. For most of the comparisons between TNF-alpha inhibitors there were no significant differences detected as evidenced by overlapping credible intervals, with the exception of infliximab compared with golimumab which was very weakly significant (median log odds ratio [LOR]: 0.74; 95% CrI: 0.02, 1.47) and infliximab compared with certolizumab pegol 200mg (median LOR: 1.12; 95% CrI: 0.14, 2.10).

Figure 5: NMA for ASAS20 (random effects model)

Comparison	Median LOR	[95% CrI]
IFX vs. PBO	1.95	[1.43, 2.49]
GLM vs. PBO	1.21	[0.71, 1.72]
ADA vs. PBO	1.57	[1.16, 1.98]
ETN 25mg vs. PBO	1.38	[0.97, 1.81]
ETN 50mg vs. PBO	1.46	[0.95, 1.95]
CZP 200mg vs. PBO	0.83	[0.01, 1.68]
CZP 400mg vs. PBO	1.14	[0.30, 2.03]
IFX vs. GLM	0.74	[0.02, 1.47]
IFX vs. ADA	0.38	[-0.28, 1.05]
IFX vs. ETN 25mg	0.57	[-0.08, 1.22]
IFX vs. ETN 50mg	0.49	[-0.15, 1.17]
IFX vs. CZP 200mg	1.12	[0.14, 2.10]
IFX vs. CZP 400mg	0.81	[-0.21, 1.81]



ADA, adalimumab; CrI, credible interval; CZP, certolizumab pegol; ETN, etanercept; GLM, golimumab; IFX, infliximab; LOR, log odds ratio; PBO, placebo; vs., versus.

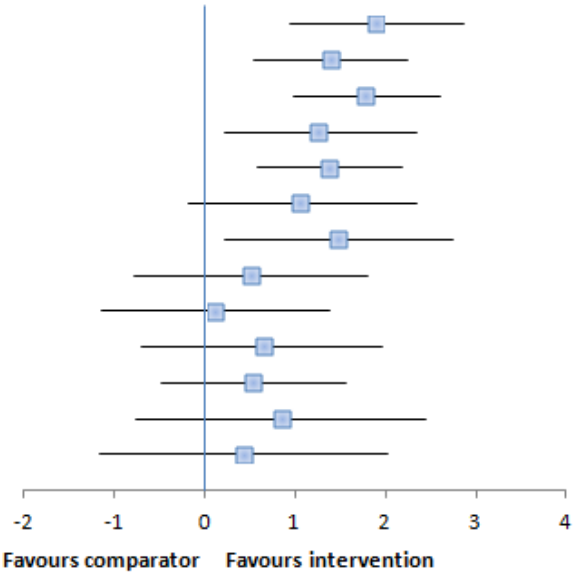
5.9.2. ASAS40

Figure 6 presents the relative efficacy estimates between golimumab, adalimumab, certolizumab pegol, etanercept, and infliximab in ASAS40 response at week 12 (+/-2 weeks).

Each TNF-alpha inhibitor had significantly greater efficacy compared to placebo, with the exception of certolizumab pegol 200mg. The greatest treatment effect compared with placebo was noted for infliximab, followed by adalimumab, certolizumab pegol 400mg, golimumab, and etanercept. There were no significant differences detected between the TNF-alpha inhibitors as evidenced by overlapping credible intervals.

Figure 6: NMA for ASAS40 (random effects model)

Comparison	Median LOR	[95% CrI]
IFX vs. PBO	1.89	[0.93, 2.87]
GLM vs. PBO	1.38	[0.54, 2.24]
ADA vs. PBO	1.78	[0.98, 2.60]
ETN 25mg vs. PBO	1.25	[0.21, 2.35]
ETN 50mg vs. PBO	1.37	[0.56, 2.18]
CZP 200mg vs. PBO	1.05	[-0.19, 2.34]
CZP 400mg vs. PBO	1.46	[0.21, 2.74]
IFX vs. GLM	0.50	[-0.79, 1.80]
IFX vs. ADA	0.11	[-1.16, 1.38]
IFX vs. ETN 25mg	0.64	[-0.72, 1.95]
IFX vs. ETN 50mg	0.52	[-0.50, 1.56]
IFX vs. CZP 200mg	0.84	[-0.77, 2.43]
IFX vs. CZP 400mg	0.43	[-1.17, 2.02]



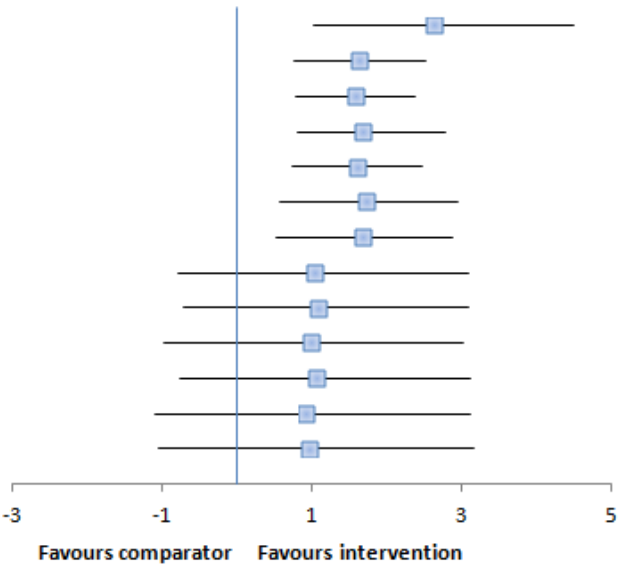
ADA, adalimumab; CrI, credible interval; CZP, certolizumab pegol; ETN, etanercept; GLM, golimumab; IFX, infliximab; LOR, log odds ratio; PBO, placebo; vs., versus.

5.9.3. BASDAI50

Figure 7 presents the relative efficacy estimates between golimumab, adalimumab, certolizumab pegol, etanercept, and infliximab in BASDAI50 response at week 12 (+/-2 weeks). Each TNF-alpha inhibitor had significantly greater efficacy compared to placebo, with the greatest treatment effect noted for infliximab, followed by certolizumab pegol, etanercept 25mg, golimumab, etanercept 50mg, and adalimumab. There were no significant differences detected between the TNF-alpha inhibitors as evidenced by overlapping credible intervals. Please note that although BASDAI50 data are not reported for the AS-specific subgroup by Landewé *et al.* 2014, due to the importance of BASDAI50 in the cost-effectiveness model, data relating to the full AxSpA population were considered in the NMA in order to be able to include certolizumab pegol for this outcome.

Figure 7: NMA for BASDAI50 (random effects model)

Comparison	Median LOR	[95% CrI]
IFX vs. PBO	2.62	[1.01, 4.49]
GLM vs. PBO	1.61	[0.75, 2.50]
ADA vs. PBO	1.56	[0.76, 2.36]
ETN 25mg vs. PBO	1.66	[0.78, 2.77]
ETN 50mg vs. PBO	1.59	[0.71, 2.46]
CZP 200mg vs. PBO	1.72	[0.54, 2.92]
CZP 400mg vs. PBO	1.67	[0.50, 2.87]
IFX vs. GLM	1.02	[-0.81, 3.09]
IFX vs. ADA	1.07	[-0.73, 3.08]
IFX vs. ETN 25mg	0.96	[-1.01, 3.00]
IFX vs. ETN 50mg	1.04	[-0.79, 3.10]
IFX vs. CZP 200mg	0.91	[-1.11, 3.11]
IFX vs. CZP 400mg	0.95	[-1.06, 3.14]

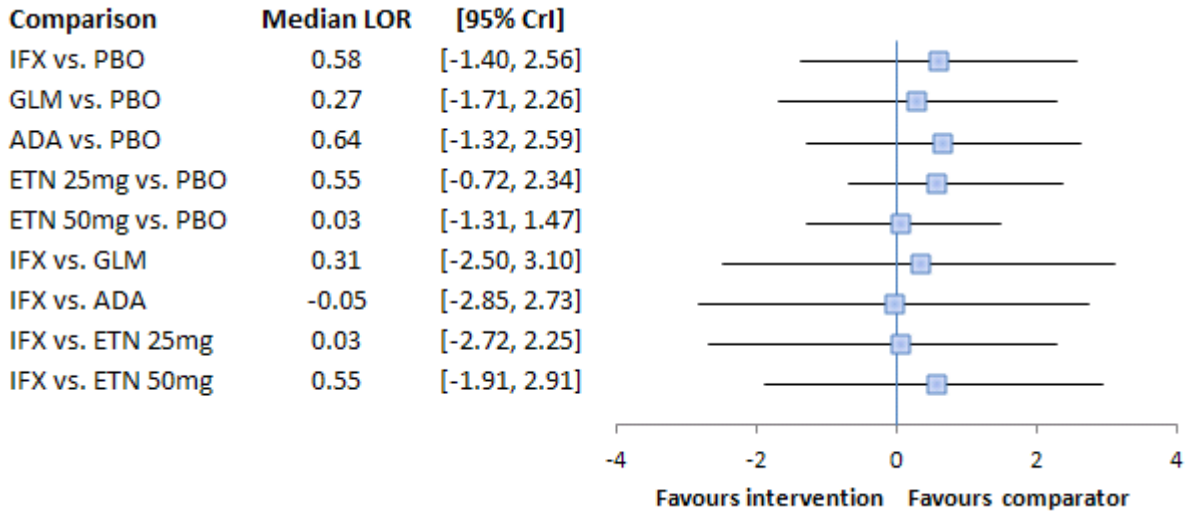


ADA, adalimumab; CrI, credible interval; CZP, certolizumab pegol; ETN, etanercept; GLM, golimumab; IFX, infliximab; LOR, log odds ratio; PBO, placebo; vs., versus.

5.9.4. Adverse Events

Figure 8 presents the relative estimates between golimumab, adalimumab, etanercept, and infliximab for AEs at week 24. No data were reported for the certolizumab pegol study. Each TNF-alpha inhibitor had a similar safety profile to placebo, with no significant differences noted. There were also no significant differences detected between the TNF-alpha inhibitors as evidenced by overlapping credible intervals.

Figure 8: NMA for AEs (random effects model)

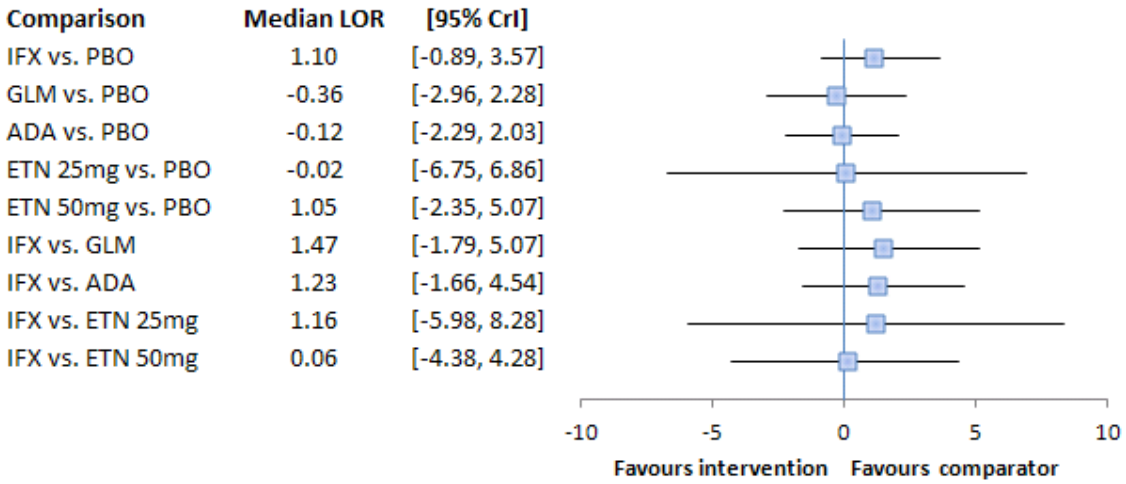


ADA, adalimumab; CrI, credible interval; ETN, etanercept; GLM, golimumab; IFX, infliximab; LOR, log odds ratio; PBO, placebo; vs., versus.

5.9.5. Serious Adverse Events

Figure 9 presents the relative estimates between golimumab, adalimumab, etanercept, and infliximab for SAEs at week 24. No data were reported by the included certolizumab pegol study. Each TNF-alpha inhibitor had a similar safety profile to placebo, with no significant differences noted. There were also no significant differences detected between the TNF-alpha inhibitors as evidenced by overlapping credible intervals.

Figure 9: NMA for SAEs (random effects model)

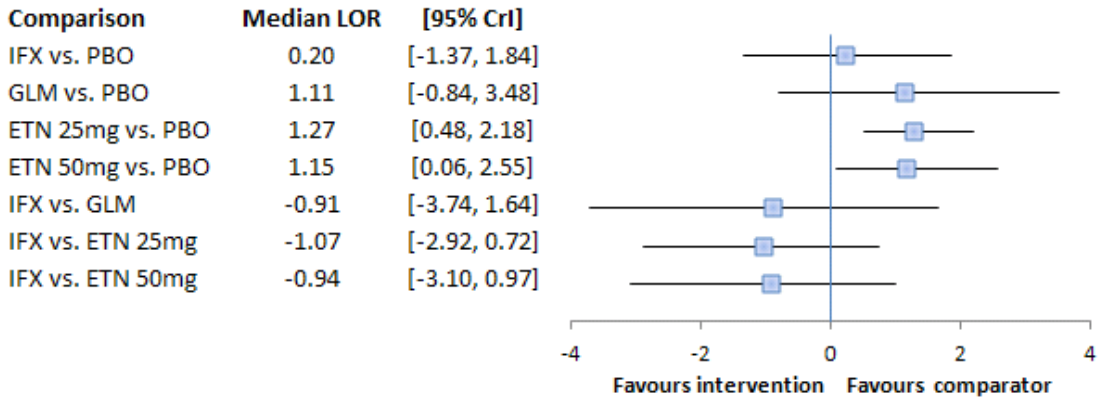


ADA, adalimumab; CrI, credible interval; ETN, etanercept; GLM, golimumab; IFX, infliximab; LOR, log odds ratio; PBO, placebo; vs., versus.

5.9.6. Injection (Infusion)-Site Reactions

Figure 10 presents the relative estimates between golimumab, etanercept, and infliximab for ISRs at week 24. No data were reported by the adalimumab and certolizumab pegol studies. Golimumab and infliximab had similar safety profiles to placebo (no significant differences) but etanercept was associated with significantly greater odds of ISRs compared with placebo (etanercept 25mg median LOR: 1.27; 95% CrI: 0.48, 2.18 and etanercept 50mg median LOR: 1.15; 95% CrI: 0.06, 2.55). No significant differences were detected between the TNF-alpha inhibitors as evidenced by overlapping credible intervals. Please note adalimumab is not included because ATLAS (van der Heijde *et al*. 2006) allowed early escape at 12 weeks but reports ISRs at 24 weeks.

Figure 10: NMA for ISRs (random effects model)



CrI, credible interval; ETN, etanercept; GLM, golimumab; IFX, infliximab; LOR, log odds ratio; PBO, placebo; vs., versus.

5.9.7. Absolute Treatment Effect

The absolute treatment effect for each of the outcomes explored in the NMA is shown in Table 16. Results were reported as baseline probabilities (following a predictive distribution as recommended by the NICE DSU[64]). Please note that ASAS40 was not calculated as this outcome is not considered in the economic modelling.

Table 16: Baseline probabilities of absolute treatment effect

	Mean	SD	Median	Lower CrI	Upper CrI
ASAS20	0.27	0.04	0.27	0.19	0.37
BASDAI50	0.15	0.05	0.14	0.06	0.27
AEs	0.56	0.26	0.58	0.05	0.98
SAEs	0.04	0.09	0.02	0.00	0.25
ISRs	0.10	0.12	0.07	0.00	0.46

AE, adverse event; ASAS, Assessment in Ankylosing Spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CrI, credible interval; ISR, injection (infusion)-site reaction; SAE, serious adverse event; SD, standard deviation.

5.10. Summary of Comparative Efficacy Data

For the efficacy outcomes, each TNF-alpha inhibitor was statistically significantly more efficacious than placebo, with the exception of certolizumab pegol 200mg for ASAS40. In the three efficacy analyses, infliximab was the most effective compared with placebo, and the ranking of other TNF-alpha inhibitors differed according to the efficacy outcome. For ASAS20 there were no significant differences detected between the TNF-alpha inhibitors as evidenced by overlapping credible intervals, with the exception of infliximab compared with golimumab, where infliximab was very weakly significant. For ASAS40 and BASDAI50 there were no statistically significant differences between TNF-alpha inhibitors supporting the conclusion that all TNF-alpha inhibitors are similarly effective for the treatment of AS (this conclusion is considered in the economic modelling, as BASDAI50 is the key driver of response considered in the model).

For safety outcomes, there were no significant differences in AEs or SAEs both between TNF-alpha inhibitors and placebo and between the different TNF-alpha inhibitors when compared with each other. For ISRs, golimumab and infliximab had similar safety profiles to placebo (no significant differences) but etanercept was associated with significantly greater odds of ISRs compared with placebo. No significant differences were noted between TNF-alpha inhibitors for the ISR outcome.

5.10.1. Strengths and Limitations of NMA

The network was well-informed, containing data from numerous well-conducted studies, with data reported for appropriate outcomes and at appropriate time points. The application of a random effects model was able to manage the limited heterogeneity in the studies.

Limitations to the approach taken were fairly minor. First, in order to include certolizumab pegol in the network for BASDAI50, the BASDAI50 results for the full axial spondyloarthritis population were used as these results were not reported for the AS subgroup. In addition, certolizumab pegol was not included in the network for safety outcomes because these outcomes were reported only post-crossover. Secondly, despite contacting the first author, the conference organisers, and the journal, it was not possible to obtain the conference abstract

associated with the Canadian AS study. This study was also reported in Lambert *et al*. 2007; however none of the outcomes of interest were reported. Therefore, the Lambert *et al*. publication was used for information about the study design and patient baseline characteristics and NICE TA143 (which reports some of the results of the Canadian AS study) was referenced for data on the outcomes of interest.

6. Cost-Effectiveness

6.1. Published Cost-Effectiveness Evaluations

Searches were conducted in Embase® and PubMed® (searched together via the ProQuest® platform) and the National Health Service Economic Evaluation Database (NHSEED) (from 2003 [the date of the first biologic to be licensed in AS] to week 20, 2014) to identify published economic evaluations in AS to help inform the model structure and relevant parameters. The search strategies developed for each of these databases are shown in Table 17 and Table 18.

Table 17: Embase® and MEDLINE® search strategy – ProQuest database, May 2014

No.	Search terms	Hits
1	Spondylitis, Ankylosing	39,724
2	ankyl* NEAR/2 spondyl*	40,139
3	rheumat* spondyl*	36,916
4	(ankyl* NEAR/3 (spine* OR spinal OR vertebra*))	3076
5	(bechterew OR bekhtere* OR mariestru?mpell OR Marie Stru?mpell)	2245
6	1 OR 2 OR 3 OR 4 OR 5	50,583
7	(golimumab OR simponi OR cnto148 OR "cnto 148")	2385
8	(etanercept or enbrel)	25,167
9	(adalimumab or humira or trudexa)	20,834
10	(infliximab or remicade)	41,192
11	(certolizumab or cimzia)	3310
12	7 OR 8 OR 9 OR 10 OR 11	58,317
13	cost benefit analysis	173,072
14	cost utility analysis	21,346
15	economic evaluation	60,298
16	cost-effectiveness analysis	138,971
17	QALY	15,110
18	cost*	1,345,770
19	util*	1,485,755
20	pharmacoeconomics	83,621
21	monte carlo simulation	46,059
22	decision support techniques	24,935
23	markov*	53,828
24	13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23	2,833,954
25	6 AND 12 AND 24	611
26	25 AND [2004-2014]	583
27	26 AND [ENGLISH]	552

Table 18: NHSEED search strategy – Cochrane Library, May 2014

No.	Search terms	Hits
1	(ankylosing spondylitis) AND (cost-effectiveness)	10

Publication titles and abstracts identified through the searches were scanned for inclusion/exclusion by a single reviewer and the full-texts of selected relevant studies were again reviewed for inclusion/exclusion prior to data extraction. Studies were included if they met the following criteria: Cost-effectiveness model/analysis in AS; UK setting/National Health Service (NHS) perspective; interventions: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, conventional care. Studies were excluded if they were not in English.

The flow of citations through the screening process is shown in Figure 11. Searches in Embase® and MEDLINE® identified 552 publications, and the search in NHSEED identified 10 publications. Of the total of 555 identified publications after the removal of duplicates, 21 were deemed relevant to the decision problem during the title and abstract screening and 8 studies were finally included after full-text review. In addition to these 8 studies, 11 systematic reviews were identified for bibliographic searching. No new relevant studies were identified from the systematic reviews. The cost-effectiveness models described in the included studies are listed in Table 19.

Figure 11: Schematic of the publication selection process

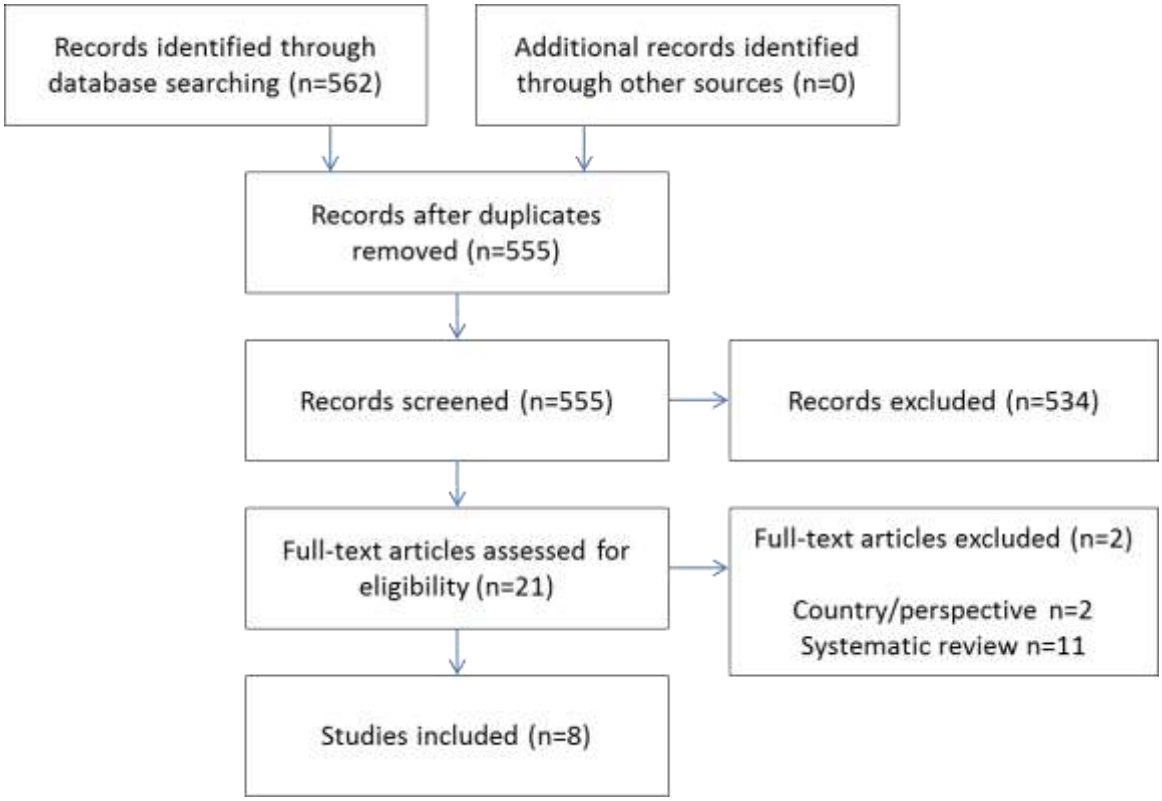


Table 19: Summary of published cost-effectiveness models

Study	Country/ perspective	Popn.	Model structure	Data	Time horizon/ cycle length	Intervention/ comparator	Health states	Key outcomes (cost/QALY)
Ara *et al.* 2007 [72]	UK, NHS	Severe AS	Decision analytic model (1000 patients)	Van der Heijde *et al.* 2006; Davis *et al.* 2003 Resource use estimated using a retrospective audit of 147 patients attending a UK rheumatology centre	25 years (2, 5, 15 years); cycle length: N/A	ETN vs. NSAIDs	N/A	£22,700 (£27,600, £23,600, £22,600 at 2, 5, 15 years)
Botteman *et al.* 2007 [73]	UK, NHS	Active AS	Decision analytic model	ATLAS; Canadian AS study Resource use estimated in OASIS	48 weeks (5, 30 years); cycle length: N/A	ADA vs. conventional care	N/A	£47,083 (£26,332, £23,097 at 5, 30 years)
Kobelt *et al.* 2004* [74]	UK, NHS/PSS	AS	Non-parametric model (patient-level data) for 2 year model Markov model for extension to 30 years	Braun *et al.* 2002; cohort of 700 patients followed in clinical practice at the Bath Royal National Hospital for Rheumatic Diseases; cross-sectional survey mailed to 3000 AS patients in UK Resource use estimated using survey of 1413 AS patients	2 years (30 year extension); cycle length: N/A (annual cycles until <5% patients remain on treatment in long-term model)	IFX vs. conventional care	'On treatment'; 'Off treatment'; 'Dead'	1 year: £35,400; 2 years: £32,800; 30 years: £9,600
Kobelt *et al.* 2007* [75]	UK, NHS/PSS	AS	As above	Braun *et al.* 2002; ASSERT (other inputs as above)	Lifetime; cycle length as above	As above	As above	Braun *et al.* 2002: no progression on treatment £28,332; 50% progression on treatment £35,332; same progression in both groups £49,417. ASSERT: £26,751, £30,067, £46,167

* Both Kobelt studies are based on the same underlying model. AS, ankylosing spondylitis; ADA, adalimumab; ETN, etanercept; IFX, infliximab; N/A, not applicable; NHS, National Health Service; NSAID, non-steroidal anti-inflammatory drug; Popn., population; PSS, Personal Social Services; QALY, quality-adjusted life year; UK, United Kingdom; vs., versus.

The models from the four studies detailed in Table 19 were submitted as part of NICE TA143 and are further described in the publication by McLeod *et al*. 2007[76] (also identified in the systematic search). The model submitted by Abbott (manufacturer of adalimumab) was the model by Botteman and colleagues. The model submitted by Wyeth (manufacturer of etanercept) was that described by Ara and colleagues; however, the reported incremental cost-effectiveness ratios (ICERs) differed between the two publications (McLeod *et al*. report the ICER of adalimumab versus conventional care as ranging from £44,684 at 1 year to £13,201 at 25 years). Finally, the model submitted by Schering-Plough (manufacturer of infliximab) is that described in Kobelt *et al*. 2007 (based on the same underlying model as Kobelt *et al*. 2004). None of the models considered in NICE TA143 make direct or indirect comparisons between TNF-alpha inhibitors and therefore are not suitable for use in this appraisal.

Three other studies identified in the systematic search reported on the manufacturer model submitted as part of NICE TA233 (Muszbek *et al*. 2010[77]; Farrell *et al*. 2011[78]; Armstrong *et al*. 2013[79]). The model compared golimumab with conventional care, adalimumab, and etanercept, and comprised a decision tree followed by a Markov component (health states: 'On treatment'; 'Not on TNF-α inhibitor'; 'Just discontinued' [tunnel]; 'Discontinued' [tunnel]). An NHS perspective was utilised. Long-term efficacy data informing the model were based on regressions estimated from the GO-RAISE trial and the literature. Short-term comparative efficacy was derived from a NMA. Utilities were estimated through use of an algorithm translating BASFI and BASDAI progression to EuroQoL-5 Domain (EQ-5D). Costs were based on the literature (long-term) and expert opinion (short-term). In the base case model a 20 year time horizon was employed (which could be extended to a maximum of 60.1 years) and the cycle length was 12 weeks. The results of the analysis were that all biologics were similarly cost-effective compared to conventional care.

This review of previously published cost-effectiveness analyses indicates that none of the identified studies compare all interventions specified in the scope for the current appraisal. We have chosen to use the most recent economic model submitted as part of NICE TA233 for the current appraisal, after adaptation to include certolizumab pegol and infliximab. Additional adaptations are described in the following sections.

6.2. De Novo Analysis

The economic model used in this appraisal is based on the model described in NICE TA233; however, the model has been extended to facilitate the comparison of adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and conventional therapy as specified by the scope for this appraisal. The objective of the model is to estimate the incremental cost-effectiveness of each TNF-alpha inhibitor relative to conventional therapy for the treatment of severe AS, from an NHS and Personal Social Services (PSS) perspective (only direct costs are included). The decision problem addressed in this submission and its relation to the final scope specified by NICE is outlined in Table 20. Where possible, the economic model fulfils the requirements of the NICE reference case and applies the guidelines for conducting an economic evaluation in AS described by Bansback *et al*. 2007[80] and recommended by Wailoo *et al*. 2008[81].

Please note that the model for infliximab is identical to that submitted for golimumab. Key inputs in the model are informed by golimumab data from the 5-year GO-RAISE extension.

Table 20: Description of decision problem addressed in submission

	Final scope	**Decision problem in submission**	**Rationale if different from the scope**
Population	Adults with severe active AS whose response to conventional therapy has been inadequate	Adults with severe active AS whose response to conventional therapy has been inadequate	N/A
Interventions	• Adalimumab • Certolizumab pegol • Etanercept • Golimumab • Infliximab • Management without TNF-alpha inhibitors (conventional treatment)	• Adalimumab • Certolizumab pegol • Etanercept • Golimumab • Infliximab • Management without TNF-alpha inhibitors (conventional treatment)	N/A
Outcomes	The outcome measures to be considered include: • Disease activity • Functional capacity • Disease progression • AEs with treatment • Health-related QoL	The outcome measures included are: • Disease activity • Functional capacity • Disease progression • AEs with treatment • Health-related QoL	N/A
Economic analysis	Reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY The reference case stipulates that	Cost-utility analysis. Cost-effectiveness of treatments expressed in terms of incremental cost per QALY A lifetime time horizon	N/A N/A

	the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and PSS perspective	(60.2 years) is applied. Patients are followed up until the age of 99 years (12 week cycle length with half-cycle correction) Costs are considered from an NHS and PSS perspective	
Other considerations	Guidance will only be issued in accordance with the marketing authorisation If evidence allows, the appraisal should consider the sequential use of TNF-alpha inhibitors	Included patient population is in accordance with the marketing authorisation Sequential use of TNF-alpha inhibitors not considered	N/A Insufficient evidence

AE, adverse event; AS, ankylosing spondylitis; N/A, not applicable; NHS, National Health Service; PSS, Personal Social Service; QALY, quality-adjusted life year; QoL, quality of life; TNF, tumour necrosis factor.

6.2.1. Patients

Infliximab is indicated for the treatment of severe, active AS in adults who have responded inadequately to conventional therapy. The target population in the model follows this indication.

6.2.2. Model Structure

The model comprises two structural components: an initial decision tree followed by a Markov model. The initial decision tree was considered to model the potential continuation/discontinuation of patients from TNF-alpha inhibitors based on response at 12 weeks. This was based on the fact that the summary of product characteristics for the relevant technologies to be assessed as part of the cost-effectiveness model state that clinical response is usually achieved at 12 weeks; otherwise, discontinuation should be considered (for infliximab, response is assessed at 6 weeks and there is the option to adjust the dose in cases of no response, however this has not been considered in the model for simplicity). The decision tree provides estimates of the expected costs and outcomes based on response to treatment over the short-term, which is assessed at 12 weeks following initiation of treatment. Criteria of response to treatment are described in the context section of this submission. The Markov model provides estimates of expected costs and outcomes over the long-term (e.g. lifetime; patients are followed up until 99 years old, at which point 0.2% of the patients remained alive) with a

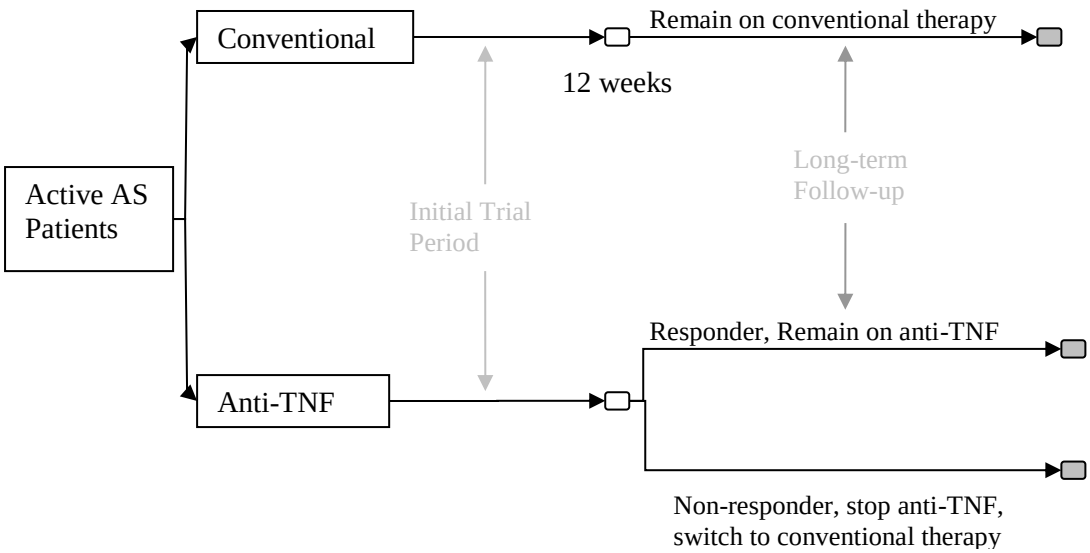
cycle length of 12 weeks. The Markov model comprises defined, mutually exclusive health states through which patients transition at a rate that is dependent on the rates of disease progression and the standardised mortality rate (SMR) for people with AS. Disease progression for conventional therapy and TNF-alpha inhibitors is based on the BASFI and BASDAI scores as described in Section 6.3.2. Mortality is described in Section 6.3.5.

Decision Tree

The initial short-term decision tree is shown in Figure 12 and represents the clinical decision that can be taken at 12-14 weeks to either continue or discontinue treatment with TNF-alpha inhibitors (as described in the summary of product characteristics for the included interventions). Patients entered the decision tree on either conventional therapy or TNF-alpha inhibitor treatment. Patients who receive conventional therapy initially (i.e. equivalent to the placebo arm in the GO-RAISE trial for golimumab) continue on conventional therapy for the remainder of the time horizon. The model assumes that no patient would discontinue while on conventional therapy and that no switching between different types of conventional therapy occurs (as this would add considerable complexity to the model with limited evaluative benefit).

The proportion of patients that continue treatment on each TNF-alpha inhibitor after 12 weeks (i.e. percentage of responders) is determined by the relative risk (RR) of response to treatment, calculated from the results (OR) of the NMA for response (Section 5.9). Patients who respond to treatment with a TNF-alpha inhibitor continue on the same drug. Otherwise patients discontinue treatment with TNF-alpha inhibitors and switch to conventional therapy.

Figure 12: Short-term decision tree component of model



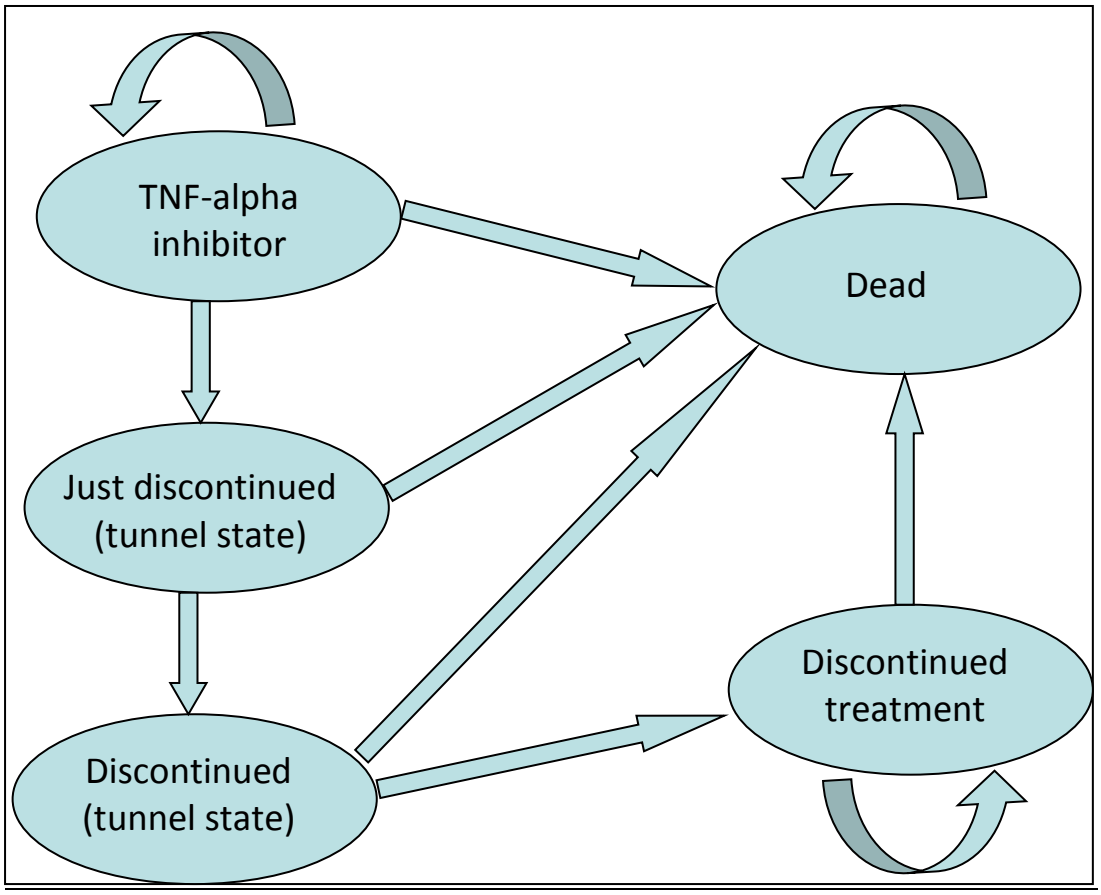
Based on the relative risk of response to treatment at 12 weeks, if a patient achieves a response with a TNF-alpha inhibitor, they remain on treatment. If a patient fails to achieve a response, they switch to conventional therapy. The first cycle of the Markov model starts at week 12 with the first transitions being applied at 24 weeks. Patients who start on conventional therapy remain on conventional therapy throughout the model. After 12 weeks, the rate that patients switch treatment from TNF-alpha inhibitors to conventional therapy is determined by the discontinuation rate from golimumab from the GO-RAISE trial. AS, ankylosing spondylitis; TNF, tumour necrosis factor.

Markov Model

Patients enter the Markov model (shown in Figure 13) at week 12. It is assumed that patients stay on treatment with one TNF-alpha inhibitor and do not switch to a second TNF-alpha inhibitor, in line with the absence of available clinical evidence for sequential use and due to a lack of NICE guidance recommending sequential use of TNF-alpha inhibitors for AS.

The cycle length is 12 weeks with a half-cycle correction (as used for NICE TA233). During each cycle, patients on TNF-alpha inhibitors either stay on treatment or discontinue due to lack of efficacy or AEs. The discontinuation rates for each TNF-alpha inhibitor are based on the all-cause discontinuation rate from the GO-RAISE study and are applied for the remainder of the time horizon (explained in Section 6.3.3). To model the lower disease activity just after discontinuation of TNF-alpha inhibitors, two 12-week tunnel health states are included in the model: 'Just discontinued' and 'Discontinued'.

Figure 13: Long-term Markov model component of model

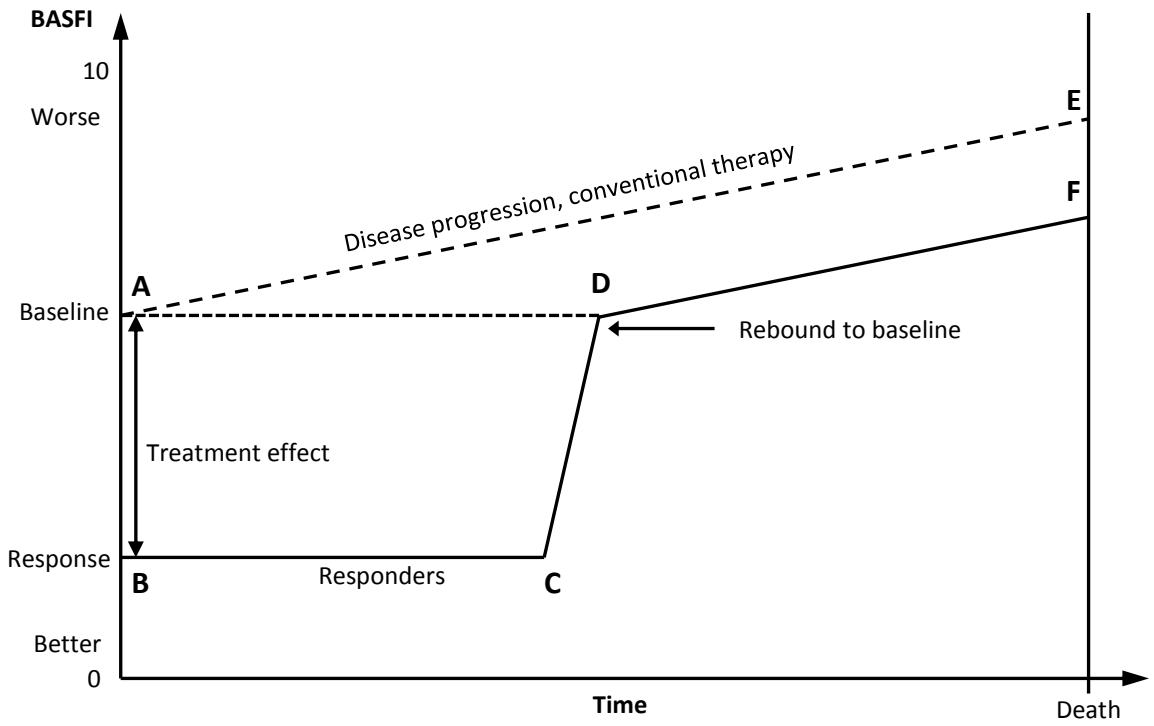


Patients may die whilst in any of the health states. Whilst on treatment with a TNF-alpha inhibitor, a patient will either stay on treatment or discontinue treatment and move to the tunnel state "Just discontinued". Since the transition from treatment with TNF-alpha inhibitor to the discontinued treatment state is assumed to take 24 weeks or two cycles, for the cycle following discontinuation, patients move to the second discontinued tunnel state "Discontinued" and then onto the "Discontinued treatment" state in the subsequent cycle. The discontinued state is assumed to be the same as conventional therapy. TNF, tumour necrosis factor.

Following discontinuation from TNF-alpha inhibitors, the health status of patients (according to the BASFI and BASDAI scores) is assumed to deteriorate/rebound to the baseline BASFI and BASDAI scores (Figure 14). Therefore, patients are assumed to achieve a lifetime benefit from treatment with TNF-alpha inhibitors following discontinuation, although the rate of disease progression thereafter is assumed to be equal to that of patients on conventional therapy[81]. Patients are expected to reach the baseline BASFI/BASDAI score within 24 weeks which is modelled using two tunnel states ('Just discontinued' and 'Discontinued') (the 24 week timeframe for rebound was informed by Baraliakos *et al*. 2005[82]). BASFI and BASDAI scores for the 'Just discontinued' tunnel state are assumed to be halfway between the respective cycle

scores of patients treated with TNF-alpha inhibitors and the BASFI and BASDAI scores at baseline.

Figure 14: Scenarios for rebound assumptions following discontinuation of TNF-alpha inhibitors



Disease progression of patients on conventional therapy (A to E) is assumed to be linear from baseline. With TNF-alpha inhibitors, patients achieve a response (treatment effect, A to B) and are then assumed to achieve a stable response (B to C) until they discontinue treatment (C). Upon discontinuation of TNF-alpha inhibitors, the BASFI score is assumed to rebound (C to D) to the baseline BASFI score after which their disease progresses at the same rate as for conventional therapy (D to F). BASFI, Bath Ankylosing Spondylitis Functional Index.

In order to model the return to baseline following discontinuation of TNF-alpha inhibitors, the BASFI/BASDAI scores of the 'Discontinued treatment' health state for each cycle are a weighted mean of the BASFI/BASDAI scores of patients in the 'Discontinued treatment' state from the previous cycle and patients who have just entered the 'Discontinued treatment' state within the cycle. The calculation also accounts for mortality associated with the respective health states. For the BASFI score for the discontinued state the equation is as follows:

% patients alive who were in discontinued state in previous cycle × (BASFI score from previous cycle + progression per cycle)	+	% patients alive who enter present discontinued cycle × baseline BASFI

The above equation was replicated for the BASDAI score.

The conventional therapy health state includes a fixed rate for disease progression (Section 6.3.2), with a rate of transition to the 'Dead' state that is based on the SMR for AS patients (Section 6.3.5).

For the base case analysis, a lifetime time horizon is employed which is consistent with the scope for this appraisal. Patients are followed up until 99 years of age, at which point 0.2% of patients remain alive. An annual discount rate of 3.5% is applied to both costs and benefits in line with the NICE reference case.

6.2.3. Technologies

In-line with the scope for this appraisal, other comparators for infliximab are biologic treatments that are licensed for use in the treatment of AS and have robust evidence of efficacy at the appropriate stage of the treatment pathway. In the model, the following TNF-alpha inhibitors are considered:

- Adalimumab: 40mg once every two weeks
- Certolizumab pegol: 400mg at weeks 0, 2, and 4, then 400mg every 4 weeks
- Etanercept: 50mg once a week
- Golimumab: 50mg once monthly
- Infliximab: 5mg/kg at weeks 0, 2, and 6, then every 6 to 8 weeks (the mid-point of 7 weeks is assumed in the model)

Although TNF-alpha inhibitors are often used in combination with NSAIDs in clinical practice, due to their negligible costs, NSAIDs were not included in the TNF-alpha inhibitor arms in this analysis.

Conventional therapy includes a fixed combination of NSAIDs, COX-2 inhibitors, steroids, gastro-protectants, bisphosphonates, and physiotherapy. The treatments included in the conventional therapy arm were informed through consultation with UK clinical experts (conducted as part of NICE TA233) and are aligned with the therapies received by patients in the placebo arm of the GO-RAISE trial. Although this trial was conducted in 57 centres in the US, Canada, Europe, and Asia, the treatments comprising conventional therapy are consistent with the AS treatment

pathway recommended by the Assessment of Spondyloarthritis International Society and the European League Against Rheumatism (in 2010)[13].

6.3. Clinical Parameters and Variables

Baseline data for the model are based on the GO-RAISE trial, considering an average patient, and are mean values across all treatment arms (i.e. for patients before allocation). The proportion of males is 71.6%. The mean age of subjects is 39.3 years (SE 0.82). For the BASDAI and BASFI scores at baseline, the scores are an average of patients randomised to the placebo arm and to the golimumab 50mg arm, and are 6.538 (SE 0.11) and 5.036 (SE 0.16), respectively.

6.3.1. Efficacy

The ASAS score is a composite measure comprising a VAS for pain, inflammation, well-being, and function. Improvement in three modalities by 20% or more, without deterioration in the fourth modality constitutes an ASAS20 response. The BASDAI score is an alternative measure which has been recommended by the ASAS Working Group (Keat *et al*. 2005[83]). Specifically, response is based on a patient achieving a 50% decrease in the BASDAI score, termed BASDAI50.

The proportion of patients achieving ASAS20 or BASDAI50 at week 12 (+/-2 weeks) for each TNF-alpha inhibitor was obtained from each of the studies included in the systematic review and incorporated into a network meta-analysis in order to compare response rates with each of the TNF-alpha inhibitors. For conventional therapy, the absolute effect of treatment is estimated from the placebo arms of the studies included in the NMA and is based on the predictive distribution of the baseline probability used in a random effects model, as recommended by the NICE DSU[64].

The output of the NMA is the OR of response. The efficacy input needed for the model is the proportion of responders which can be calculated from the following equation:

$$Responders = RR \times AET_{Pl} = \left[\frac{OR_{TNF}}{1 - AET_{Pl} + (AET_{Pl} \times OR_{TNF})}\right] \times AET_{Pl}$$

Where:

RR is the relative risk of response;
AET_{Pl} is the absolute treatment effect of placebo;
OR_{TNF} is the odds ratio of TNF-alpha treatment versus placebo

Estimates for the ORs for responders and proportions of patients that responded to the different treatments according to ASAS20 and BASDAI50 are presented in Table 21.

Table 21: ORs and probability of ASAS20 and BASDAI50 response to TNF-alpha inhibitors and conventional therapy

Treatment	ASAS20		BASDAI50	
	OR (95% CrI)	Probability	OR (95% CrI)	Probability
Golimumab	3.48 (2.04-5.59)	0.56	5.54 (2.12-12.13)	0.49
Infliximab	7.30 (4.19-12.0)	0.73	22.44 (2.78-89.05)	0.79
Adalimumab	4.92 (3.18-7.27)	0.65	5.20 (2.14-10.62)	0.47
Etanercept*	4.43 (2.57-7.06)	0.62	5.46 (2.03-11.74)	0.60
Certolizumab pegol†	3.48 (1.34-7.60)	0.56	6.62 (1.66-17.59)	0.53
Conventional therapy	-	0.27	-	0.15

* etanercept based on 50mg dose once weekly; † certolizumab pegol based on 400mg dose every 4 weeks. ASAS, Assessment in Ankylosing Spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CrI, credible interval; OR, odds ratio.

6.3.2. Disease Progression

TNF-Alpha Inhibitors

The BASDAI score (described previously) is also used to assess disease progression along with the BASFI score, which is a measure of patient function. Baseline BASFI and BASDAI scores are assumed to be identical for all TNF-alpha inhibitors and are based on the baseline scores from the GO-RAISE trial. The rate of disease progression on treatment with TNF-alpha inhibitors is based on two sets of equations for BASFI and BASDAI as described in NICE TA233 and McLeod *et al*. 2007, and BASFI and BASDAI data from the GO-RAISE trial to 5 years.

The first set of equations is used to estimate BASFI and BASDAI scores to week 24. The second set of equations is used to estimate the BASFI and BASDAI scores to week 108. Consistent with the long-term data from the GO-RAISE trial, patients on treatment with TNF-alpha inhibitors are assumed to continue in a stable state for BASFI and BASDAI for the remainder of the time on treatment with TNF-alpha inhibitors; this assumption is supported by the 5-year GO-RAISE data (Figure 15).

Short-term estimation of BASFI and BASDAI

For the first 24 weeks, two equations are used to estimate the change from baseline in BASFI and BASDAI for patients on either TNF-alpha treatment or conventional therapy. Both equations are based on all patients who were randomised to receive either placebo or golimumab 50mg.

The equations incorporated coefficients for the marginal effects of differences in baseline BASFI and BASDAI scores, baseline age, and the proportion of males. For up to 24 weeks, treatments with TNF-alpha inhibitors or conventional therapy are accounted for using a dummy variable, which took the value of one for TNF-alpha inhibitors and zero for conventional care.

Equations for the first 24 weeks are shown below:

$$\text{BASFI} = \text{baseline BASFI} - (0.1008 - 0.0284 \times \text{age} + 0.1780 \times \text{baseline BASFI} + 1.8096 \times \text{treatment} + 0.04156 \times \text{male} + 5.2226 \times \text{week}^{(-2)} - 14.6396 \times \text{treatment} \times \text{week}^{(-2)})$$

Where:

Baseline BASFI is the BASFI score at baseline;
Age is the current age;
Treatment takes the value of 1 for TNF-alpha treatment and 0 for conventional therapy;
Male takes the value of 1 for males and 0 for females;
Week is the number of weeks

$$\text{BASDAI score} = \text{baseline BASDAI} - (0.4685 - 0.03399 \times \text{age} + 0.2212 \times \text{baseline BASDAI} + 2.0620 \times \text{treatment} + 0.2652 \times \text{male} - 3.4664 \times \text{week}^{(-2)} - 7.1029 \times \text{treatment} * \text{week}^{(-2)})$$

Where:

Baseline BASDAI is the BASDAI score at baseline;
Age is the current age;
Treatment takes the value of 1 for TNF-alpha treatment and 0 for conventional therapy;
Male takes the value of 1 for males and 0 for females;
Week is the number of weeks

Variable parameters and SEs are summarised in Table 22.

Table 22: Variable parameters and SEs for equations for estimation of disease progression (short-term)

Variable	Parameter	Standard error
BASFI		
Intercept	0.1008	0.557
Age	-0.0284	0.009874
Baseline BASFI	0.1780	0.05429
Treatment	1.8096	0.2551
Male	0.04156	0.2767
Week^(-2)	5.226	0.2767
Treatment × week^(-2)	-14.6396	2.2699
BASDAI		
Intercept	0.4685	0.8126
Age	-0.03399	0.0105
Baseline BASDAI	0.2212	0.08436
Treatment	2.0620	0.2742
Male	0.2652	0.2953
Week^(-2)	-3.4664	2.1365
Treatment × week^(-2)	-7.1029	2.6887

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index.

Long-term estimation of BASFI and BASDAI

For the base case model, estimation of long-term disease progression from week 24 to week 108 for patients who remained on treatment with TNF-alpha inhibitors is based on a second set of equations for the estimation of the BASFI and BASDAI scores:

BASFI score = baseline BASFI - (0.4933 - 0.03915 × age + 0.5706 × baseline BASFI + 0.6523 × male + 0.09524 × log (week))

Where:

Baseline BASFI is the BASFI score at baseline;
Age is the current age;
Treatment takes the value of 1 for TNF-alpha treatment and 0 for conventional therapy;
Male takes the value of 1 for males and 0 for females;
Week is the number of weeks

At week 108, the estimated BASFI score is 2.559 for all patients who did not discontinue treatment with TNF-alpha inhibitors and is equivalent to a change from baseline of -2.477. For the GO-RAISE trial, the mean change from baseline for BASFI at week 104 is -2.7 (SD 2.07). Therefore, the above equation for estimation of the BASFI score over the long-term produced an under-estimate of the BASFI at week 104, which represents a conservative approach.

BASDAI score (from 24 weeks) = baseline BASDAI - (0.6277 - 0.03531 × age + 0.5762 × baseline BASDAI + 0.2196 × male + 0.2196 × log (week)

Where:

Baseline BASDAI is the BASFI score at baseline;
Age is the current age;
Treatment takes the value of 1 for TNF-alpha treatment and 0 for conventional therapy;
Male takes the value of 1 for males and 0 for females;
Week is the number of weeks

At week 108, the estimated BASDAI score is constant at 2.938 for all patients who did not discontinue treatment with TNF-alpha inhibitors and is equivalent to a change from baseline of -3.6. For the GO-RAISE trial, the mean change from baseline for BASDAI at week 104 is -4.2 (SD 2.19). Therefore, the equation for estimation of the BASDAI score over the long-term produced an under-estimate of the BASDAI at week 104, which also represents a conservative approach.

Variable parameters and SEs are summarised in Table 23.

Table 23: Variable parameters/SEs for equations to estimate disease progression (long-term)

Variable	Parameter	Standard error
BASFI		
Intercept	0.4933	0.7364
Age	-0.03915	0.01321
Baseline BASFI	0.5706	0.07292
Male	0.6523	0.4001
Log (week)	0.09524	0.04938
BASDAI		
Intercept	0.6277	1.0303
Age	-0.03531	0.01367
Baseline BASDAI	0.5762	0.1055
Male	0.2196	0.4094
Log (week)	0.2196	0.06908

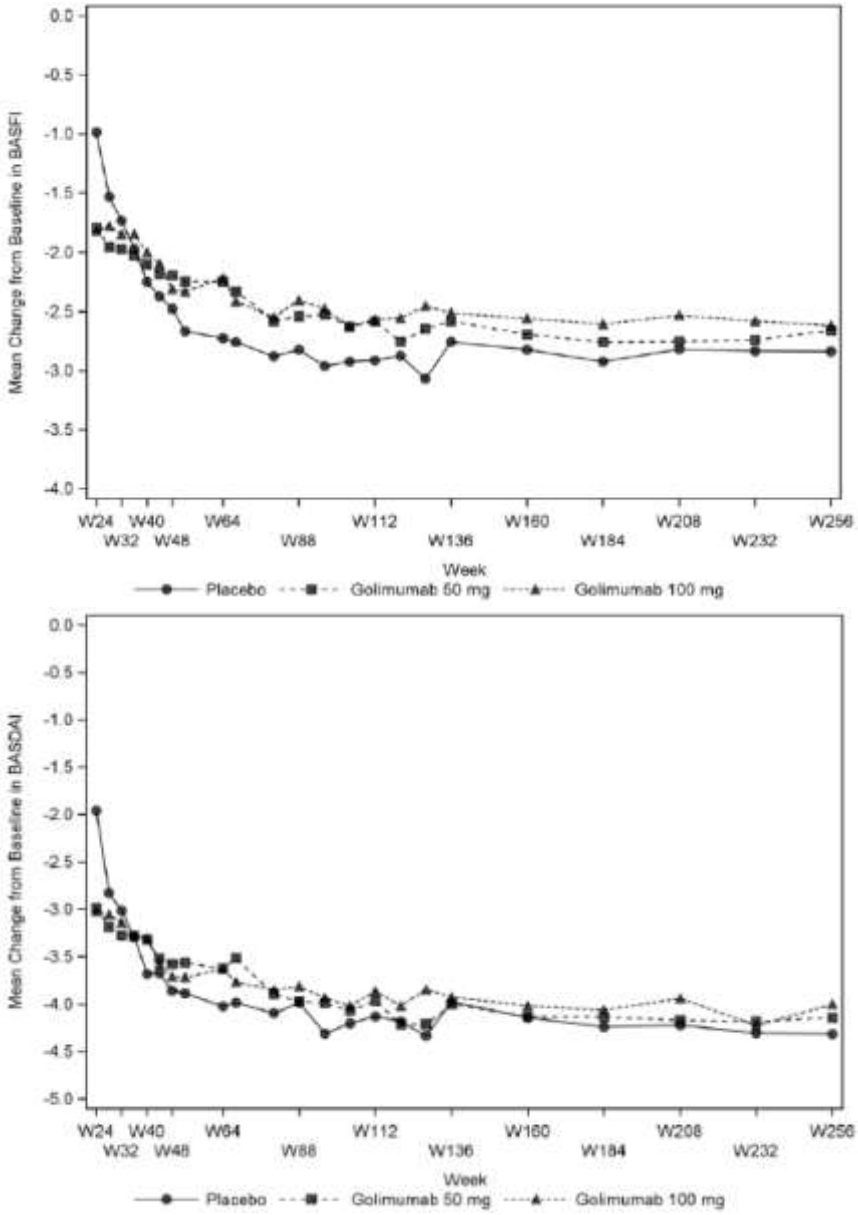
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index.

From week 24 (for remainder of the time on treatment), the BASFI regression equation for long-term disease progression produces a minimal increase in the BASFI score when on treatment with TNF-alpha inhibitors, as evidenced by the positive coefficient for age and log (week) (Table 23). This minimal increase is consistent with the data in the GO-RAISE trial in which the BASFI and BASDAI scores remained constant and improvement was sustained for 2-3 years (Figure 15). Further, in a separate study of 842 patients who received treatment with TNF-alpha inhibitors and were registered in the DANBIO registry (a Danish nationwide rheumatological

database), analysis of the BASFI and BASDAI scores whilst on treatment with TNF-alpha inhibitors showed that scores of both levelled off one year after initiation of treatment (referenced by McLeod *et al*.). BASFI scores were maintained to year 4 and increased at year 5; however, there is no evidence that this increase is maintained after year 5. BASDAI scores were also maintained to year 5.

The annual progression rate of BASFI for the post-week 256 time horizon is set to half the rate of conventional therapy in the base case analysis (described for conventional therapy in following section, consistent with Kobelt *et al*. 2004), or equal to the rate of conventional therapy in a sensitivity analysis.

Figure 15: Mean change from baseline in BASDAI and BASFI from week 104 to week 256



"Placebo" consisted of patients who were assigned to conventional therapy at baseline and either entered early escape at week 16 to receive golimumab 50mg through to week 256 or crossed-over at week 24 to receive golimumab 50mg through to week 256. "Golimumab 50mg" consisted of patients who were assigned to golimumab 50mg at baseline and who either entered early escape at week 16 to receive golimumab 100mg through week 256 or continued golimumab 50mg through to week 256. "Golimumab 100mg" consisted of patients who were assigned to golimumab 100mg at baseline and did not receive adjustments to their study medication.

Conventional Therapy

The rate of disease progression over the short-term (to week 24) for conventional therapy is calculated using the respective equations for estimation of the BASFI and BASDAI scores described above.

The rate of disease progression for conventional therapy from week 24 for the remainder of the time horizon is based on the approach taken in NICE TA233 in which a value reported by Kobelt *et al*. (2004) is used[74]. Kobelt and colleagues described a simple linear regression for annual disease progression in which the BASFI score increased by a range of 0.03 to 0.09 units per year. For the base case model, patients on conventional therapy are assumed to progress at a rate of 0.07 units per year after week 24 and by a range of 0.03 to 0.09 units per year for the sensitivity analyses.

6.3.3. Discontinuation of Treatment

Short-Term Discontinuation (to week 12)

It is assumed that patients discontinued treatment due to either a lack of efficacy or due to SAEs. According to expert opinion, patients who discontinue treatment with TNF-alpha inhibitors due to SAEs would be unlikely to benefit from continued treatment and trying to separate discontinuation due to a lack of response to treatment from discontinuation due to SAEs would likely lead to double counting. Thus, in the short-term, the proportion of patients who discontinued treatment with TNF-alpha inhibitors due to lack of response is assumed to also include those who discontinued due to SAEs. To week 12, the response rate for each TNF-alpha inhibitor (assessed through ASAS20 or BASDAI50) is therefore the key driver of the difference in the rate of discontinuation between TNF-alpha inhibitors (i.e. if patients do not respond, they discontinue).

Long-Term Discontinuation (post-week 12)

It is not appropriate to extrapolate responder (discontinuation) data at week 12 over the long-term. In the absence of long-term discontinuation data for TNF-alpha inhibitors, the all-cause, annual rate of discontinuation for patients on golimumab was retrieved from the 5-year follow-up to the GO-RAISE study and applied to all TNF-alpha inhibitors in the model. In the GO-RAISE study, the proportion of patients who discontinued treatment in the golimumab 50mg arm from week 24 to week 256 was 27.3%, i.e. the number of patients on treatment with golimumab

50mg at week 24 was 128 and at week 256 was 93, equivalent to a decrease of 27.3% over 4.46 years. This is equivalent to an annual discontinuation rate of 6.1% (lower than the long-term, annual discontinuation rate of 15.0% stated in the NICE Assessment report by McLeod *et al.*[76]). The annual discontinuation rate of 6.1% is applied for the entire time horizon after week 12 in the base case analysis. A rate of 15.0% is used in a sensitivity analysis. The highest rate of discontinuation reported in the literature is 22.3% (referenced by McLeod *et al.*), which is also used in a sensitivity analysis. Patients who discontinued treatment are assumed not to switch to another TNF-alpha inhibitor. Patients on conventional therapy are assumed not to discontinue treatment.

6.3.4. Adverse Events

AEs are included in the model to reflect the tolerability profiles of the comparator treatments. AEs are not considered as a separate health state, but their associated costs and disutilities are incorporated into the calculation for estimating the ICERs. Only disutilities associated with SAEs are applied (for one cycle), no disutility is applied for the remaining AEs and ISRs.

The types and numbers of AEs from GO-RAISE are shown in Table 24. Cycle rates for conventional therapy are calculated by dividing the number of events observed by the number of 12 week cycles in the observational period (24 weeks). The OR of AEs, ISRs, and SAEs (for each TNF-alpha inhibitor, obtained from the NMA [Table 25]) are then applied to the per cycle rate of 0.33 (SD 0.04) for placebo (conventional therapy) to produce the per cycle rate of AEs, ISRs, and SAEs for each TNF-alpha inhibitor. From this per cycle rate of AEs for each TNF-alpha inhibitor the per cycle rate of ISRs and SAEs were subtracted from the total rate of AEs to produce a per cycle rate for AEs excluding ISRs and SAEs.

Table 24: Adverse events in GO-RAISE at 24 weeks

	Placebo
Number of patients	78
Average duration of follow-up (weeks)	19.5
Sample size in trial	77
Number of events observed	41
Total number of cycles administered	125.1
Infections (not requiring hospitalisation +/or intravenous antibiotics)	21
Infections (requiring hospitalisation +/or intravenous antibiotics)	3
Tuberculosis	0
Nausea	4
Abdominal pain	3
Heart failure	0

	Placebo
Hypersensitivity reaction	0
Fever	0
Headache	2
Depression	1
Lupus erythematosus-like syndrome	0
Pruritus	1
Injection-site reaction	2
Blood disorder	2
Skin cancer	2
Lymphoma	0

Table 25: ORs for ISRs, AEs, and SAEs with TNF-alpha inhibitors and conventional therapy

	ISR, OR (95% CrI)	AE (≥1), OR (95% CrI)	SAE, OR (95% CrI)
Golimumab	3.03 (0.43-32.54)	1.31 (0.18-9.53)	0.70 (0.05-9.76)
Infliximab	1.23 (0.25-6.31)	1.79 (0.25-12.97)	2.99 (0.41-35.35)
Adalimumab	N/A	1.89 (0.27-13.38)	0.88 (0.10-7.59)
Etanercept*	3.16 (1.06-12.74)	1.03 (0.27-4.36)	2.85 (0.10-158.50)
Certolizumab pegol†	N/A	N/A	N/A
Conventional therapy‡	0.10	0.56	0.04

* etanercept based on 50mg dose once weekly; † certolizumab pegol based on 400mg dose every 4 weeks; ‡ baseline probabilities are reported for conventional therapy. AE, adverse event; CrI, credible interval; ISR, injection (infusion)-site reaction; N/A, not applicable; OR, odds ratio; SAE, serious adverse event.

For adalimumab, data are unavailable for ISRs, therefore, the mid-point of the range of OR data for ISRs is used for adalimumab and the SD of the cohort is applied. For certolizumab pegol, data for AEs, SAEs, and ISRs are unavailable, therefore, the mid-range and SD for each variable is used from the other TNF-alpha inhibitors.

6.3.5. Mortality

Patients are at risk of death in all stages of the model. The mortality rate is assumed to be constant for all interventions. Due to the short-term nature of the trials, data on mortality are not available. Published evidence has demonstrated that patients with AS have a higher mortality rate[84,85,86,87]. National life tables for the UK were used to obtain age- and gender-dependent rates of mortality (Table 26)[88].

Table 26: National mortality rates for the UK population and SMR for patients with AS

Age (years)	Mortality of general population		SMR of people with AS	
	Male	Female	Male	Female
18	0.00049	0.00019	0.000791	0.000261
19	0.00047	0.00022	0.000769	0.000308
20	0.00052	0.00021	0.000846	0.000293
21	0.00056	0.00021	0.000906	0.000286
22	0.00056	0.00021	0.00091	0.000286

Age (years)	Mortality of general population		SMR of people with AS	
	Male	Female	Male	Female
23	0.00059	0.00025	0.000962	0.000342
24	0.00055	0.00025	0.000893	0.000339
25	0.00061	0.00026	0.000998	0.00036
26	0.00061	0.00027	0.000994	0.000371
27	0.00063	0.00033	0.001022	0.00045
28	0.00070	0.00034	0.001136	0.000472
29	0.00075	0.00032	0.001227	0.000443
30	0.00081	0.00038	0.001322	0.000523
31	0.00082	0.00041	0.001338	0.00056
32	0.00084	0.00045	0.001369	0.000617
33	0.00091	0.00049	0.001482	0.000672
34	0.00100	0.00053	0.001622	0.000726
35	0.00104	0.00059	0.001687	0.00081
36	0.00112	0.00061	0.001824	0.000842
37	0.00123	0.00069	0.002005	0.000954
38	0.00133	0.00077	0.002166	0.001056
39	0.00145	0.00079	0.002355	0.001094
40	0.00158	0.00089	0.002575	0.00123
41	0.00162	0.00101	0.002641	0.001394
42	0.00176	0.00108	0.002872	0.001484
43	0.00189	0.00116	0.003077	0.001597
44	0.00216	0.00127	0.003519	0.001758
45	0.00227	0.00140	0.003695	0.001933
46	0.00235	0.00154	0.003829	0.002124
47	0.00249	0.00162	0.004054	0.002237
48	0.00273	0.00178	0.004456	0.002462
49	0.00293	0.00201	0.004768	0.002778
50	0.00319	0.00218	0.005195	0.003004
51	0.00352	0.00247	0.005733	0.003406
52	0.00395	0.00271	0.006437	0.003745
53	0.00430	0.00293	0.007002	0.004042
54	0.00465	0.00320	0.007584	0.004422
55	0.00524	0.00344	0.008546	0.004746
56	0.00586	0.00381	0.009558	0.005258
57	0.00624	0.00417	0.010176	0.005748
58	0.00688	0.00450	0.011218	0.006203
59	0.00741	0.00503	0.012082	0.006943
60	0.00824	0.00545	0.013434	0.007518
61	0.00897	0.00593	0.014615	0.008177
62	0.00981	0.00637	0.015985	0.008784
63	0.01047	0.00680	0.017068	0.009384
64	0.01147	0.00747	0.018696	0.010302
65	0.01244	0.00813	0.020276	0.011225
66	0.01419	0.00920	0.023133	0.012699
67	0.01545	0.01008	0.025184	0.013913
68	0.01671	0.01091	0.027241	0.01505
69	0.01897	0.01228	0.030916	0.016952
70	0.02131	0.01390	0.034727	0.019188
71	0.02352	0.01497	0.038341	0.020659
72	0.02569	0.01690	0.041878	0.023326
73	0.02786	0.01834	0.045413	0.025308

Age (years)	Mortality of general population		SMR of people with AS	
	Male	Female	Male	Female
74	0.03115	0.02058	0.050768	0.028406
75	0.03403	0.02280	0.055475	0.031458
76	0.03797	0.02573	0.061896	0.035509
77	0.04201	0.02902	0.068478	0.040041
78	0.04699	0.03274	0.076599	0.045174
79	0.05165	0.03680	0.084186	0.050781
80	0.05807	0.04162	0.094652	0.057429
81	0.06566	0.04705	0.107023	0.064933
82	0.07353	0.05310	0.119847	0.073272
83	0.08173	0.06079	0.133218	0.083886
84	0.09151	0.06850	0.149155	0.094524
85	0.10190	0.07659	0.166089	0.10569
86	0.11302	0.08656	0.184216	0.119453
87	0.12635	0.09593	0.205944	0.132382
88	0.13863	0.10818	0.225965	0.149286
89	0.15701	0.12166	0.255928	0.167884
90	0.16942	0.13922	0.276156	0.192124
91	0.18398	0.15066	0.299892	0.207914
92	0.19736	0.16721	0.32169	0.230746
93	0.21474	0.17920	0.350026	0.247292
94	0.23816	0.20282	0.388199	0.279889
95	0.25943	0.22400	0.422863	0.309119
96	0.28296	0.24550	0.461218	0.338789
97	0.30413	0.26307	0.49573	0.363037
98	0.32402	0.28276	0.528159	0.39021
99	0.34238	0.30558	0.558076	0.421695
100	0.36544	0.32522	0.595667	0.448802

AS, ankylosing spondylitis; SMR, standardised mortality rate.

The proportion of males and females recruited in the GO-RAISE trial is used to estimate a weighted average mortality risk by gender. A study by Bakland *et al*. (2011) reported that the SMR of people with AS is 1.63 (95% CI: 1.29-1.97) for males, 1.38 (95% CI: 0.48-2.28) females, and 1.61 (95% CI: 1.29-1.93) for the combined cohort[89]. The gender-specific SMR for AS from is applied to the mortality rates from the general population to calculate adjusted mortality rates for AS patients in the model.

A systematic literature review performed as part of a previous NICE review reported that there is no published evidence on the impact of treatment with TNF-alpha inhibitors on the mortality of AS patients. Therefore, in the absence of evidence that treatment with TNF-alpha inhibitors has a positive effect on the mortality of patients with AS compared with conventional therapy, we applied the conservative approach that patients treated with TNF-alpha inhibitors had the same SMR as patients with AS who did not receive TNF-alpha inhibitors.

Since the mortality rates of the national life tables were annual rates, the rates were adjusted for the 12 week cycle length of the model using the following equation:

$$r = \frac{\ln(1 - P)]}{t}$$

The cycle rate was transformed to transition probabilities using the following equation:

$$p = 1 - exp(-rt)$$

6.4. Measurement and Valuation of Health-Related Quality of Life

As previously reported in NICE TA233, patients with AS typically suffer the greatest loss of function in the first 10 years (Robertson *et al*. 2004)[90]. Consequently, patients may have substantial limitations in activity at a relatively young age. Due to the nature of the disease, patients continue to have a gradual decline in physical function over time, typically measured by the BASFI score[90]. In NICE TA233 a systematic review did not obtain any relevant studies reporting quality of life, and therefore an alternative approach was taken, as outlined below.

Although data were collected for SF-36 in the 5-year GO-RAISE trial, use of these data to measure health-related quality of life from the Short Form-6 Domain (SF-6D) index was considered inappropriate because it was not consistent with the NICE reference case. In addition, Boonen *et al*. 2007[91] demonstrated that SF-6D over-estimates health-related quality of life for people with AS who have BASFI and BASDAI scores ≥4 (as was the case for the GO-RAISE trial) compared to EQ-5D, which is consistent with other conditions, such as arthritis and lower back pain (Cunillera *et al*. 2010)[92]. We also chose not to use the mapping function detailed by Rowen *et al*. 2009[93] to generate the EQ-5D index from SF-36 because the authors reported that this would most likely over-estimate the EQ-5D index for severe forms of the disease (i.e. EQ-5D index of 0.5-0.6). In summary, use of either the SF-6D index or mapping of SF-36 to EQ-5D index would most likely produce an under-estimate of the treatment effect.

Long-term BASDAI and BASFI scores were calculated as described in Section 6.3.2. Data for EQ-5D utility weights are then calculated for the UK tariff from the BASFI and BASDAI scores using the mapping algorithm used in NICE TA233. This equation is shown below and parameters and SEs are shown in Table 27.

$$\text{EQ-5D index} = 0.877121 - 0.03841 \times \text{BASDAI} - 0.03225 \times \text{BASFI} - 0.02789 \times \text{male} + 0.00168 \times \text{age}$$

Where:

EQ-5D index is the utility weight based on the UK tariff;
BASDAI is the BASDAI score at each cycle;
BASFI is the BASFI score at each cycle;
Male takes the value of 1 for males and 0 for females;
Age is the current age

Table 27: Variable parameters/SEs for equation to estimate EQ-5D index

Variable	Parameter	Standard error
Intercept	0.87721	0.02637
BASDAI	-0.03841	0.00286
BASFI	-0.03225	0.00244
Male	-0.02789	0.01036
Age	0.00168	0.00044

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index.

The mean estimate of the EQ-5D index at baseline from the GO-RAISE trial was calculated to be 0.510 and at week 104 was estimated to be 0.748, equivalent to a change from baseline of 0.238. Braun *et al*. 2007 reported that the change from baseline for EQ-5D index at week 12 was approximately 0.3 following weekly treatment with 50mg etanercept[94]. Boonen *et al*. 2008 reported the EQ-5D index of patients with AS prior to treatment with etanercept to be 0.49 (SD 0.3) with a change from baseline of 0.24 at week 72[95]. Therefore, the estimated EQ-5D index and change from baseline produced by the above equation is consistent with the EQ-5D index calculated directly from EQ-5D questionnaires completed by AS patients reported in the literature. Key advantages to using this equation to map the BASDAI and BASFI scores to EQ-5D include the incorporation of the impact of disease progression over the long-term (lifetime time horizon) into the calculation of the EQ-5D index, comparability with previous submissions, and consistency of the estimated EQ-5D index at baseline and quality-adjusted life year (QALY) gain with published data.

For disutility due to SAEs, a utility weight decrement of 0.01 was applied, based on the assumption used in NICE TA233.

6.5. Resource Identification and Measurement

First-line treatment of AS in the UK involves a combination of physiotherapy and medication (conventional therapy). TNF-alpha inhibitors can then be administered for disease which is

uncontrolled with conventional therapy. Disease management i.e. the observation of disease progression through laboratory and imaging tests and the management of drug-related AEs is also part of the clinical management of the condition. The current clinical management of this condition requires patients to have regular contact with specialist rheumatology centres in the UK. This involves regular attendance at an outpatient clinic and face-to-face consultation with a consultant or non-consultant in a rheumatology department. Patients with severe active AS may also be hospitalised occasionally. Therefore, the resource use and costs considered in the model include: 1) drugs, 2) disease management (including medical staff visits, hospitalisations, personal and social care, and laboratory and imaging tests), and 3) AEs.

As part of NICE TA233 a systematic review was performed to identify studies reporting cost and resource utilisation; however, only one relevant study was identified (Kobelt *et al*. 2004). This study informed the extrapolation of short-term costs to the long-term (see below).

All costs are based on 2012/2013 prices. Costs are predominantly obtained from NHS reference costs 2012-2013[96], the British National Formulary (BNF) 2013[97], and Personal Social Services Resource Unit (PSSRU) 2013[98]. Expert opinion was used in the absence of published resource use data. For resource use associated with disease management and the management of AEs, opinion was elicited via a survey with clinician experts selected based on their experience in AS. In total, seven specialists with experience and expertise in treating AS were interviewed and two physiotherapists were also approached to validate the relevant answers of the clinicians. Resource use was estimated separately for conventional therapy and TNF-alpha inhibitors. Answers were collated and synthesised using descriptive statistics i.e. mean, SD.

Per cycle resource use and costs for drugs, disease management, and AEs were informed as above. For drugs and AEs, the estimated costs were applied to all cycles of the model. For disease management, these per cycle costs were adjusted post-week 24 using the equation detailed below. This adjustment is to reflect the increase in disease severity over time, as described by the BASFI component of the equation, which may necessitate increased resource use and costs for disease management.

$$\text{Annual mean AS-related NHS cost} = 1585.30 * \exp(0.1832 * \text{BASFI})$$

The monetary component of the equation above (£1585.30) was inflated from the year 2005/2006 to 2013 to £1,902.49 using the Pay and Prices index published by the PSSRU.

6.5.1. Drug Resource Use and Costs

TNF-Alpha Inhibitors

The costs for each TNF-alpha inhibitor per cycle are shown in Table 28 and are based on the recommended dose for each of the comparator treatments according to the summary of product characteristics, with cost information obtained from the BNF.

Table 28: Per 12-week cycle drug costs for TNF-alpha inhibitors

Drug		Cost*	Dose	Source
Golimumab[a]		£2112.82	50mg, once monthly	BNF 65 2013
Infliximab[b]	First cycle	£5362.44	Repeated 2 weeks and 6 weeks after initial infusion, then every 6-8 weeks	BNF 65 2013
	Second cycle	£2681.22		
Adalimumab		£2112.84	40mg, once every two weeks	BNF 65 2013
Etanercept		£2145.00	50mg, once weekly	BNF 65 2013
Certolizumab pegol[c]	First cycle	£0.00	400mg at weeks 0, 2, and 4, then 400mg once every 4 weeks	BNF 65 2013
	Second cycle	£2145.00		

[a] price of 50mg golimumab, based on the PAS (in which the 100mg dose is the same cost as the 50mg dose); [b] including costs of infusion and drug based on a 7-weekly dosing interval; [c] cost based on PAS in which the drug is provided at £0 for the first cycle (12 weeks).

The cost of golimumab was based on an accepted Patient Access Scheme (PAS) in which the cost of the 100mg dose (administered for patients with a weight >100kg) is the same price as the 50mg dose. Because of the inclusion of the PAS for golimumab, patient weight is not taken into account in the economic model. The cost of certolizumab pegol was based on an approved PAS in which certolizumab pegol is provided at zero cost for the first 3 months. Infusion costs were included for infliximab.

Conventional Therapy

The drugs/therapies considered to represent conventional therapy in the UK were based on the therapies received in the placebo arm of GO-RAISE and on the results of the clinician survey, as described above and in NICE TA233. Conventional therapy was assumed to include NSAIDs, COX-2 inhibitors, steroids, gastro-protectants, bisphosphonates, and other medications. The disaggregated resource use estimates and associated costs for the drugs and non-drug therapies that comprise conventional therapy are shown in Table 29.

Table 29: Per 12-week cycle drug/therapy use cost for conventional therapy

Drug/therapy	Resource use, mean (SD)				Pack cost, £ 2013	Source	Cost per cycle, £ 2013
	% receiving	Average dose, mg	Treatment duration	HCP admin. time			
NSAIDS							
Diclofenac	0.27 (0.08)	150 (0.00)*	Ongoing	0.00 (0.00)	6.18 (28x50mg)	BNF 65 2013	15.10
Naproxen	0.11 (0.12)	1000 (0.00)*	Ongoing	0.00 (0.00)	1.65 (28x500mg)	BNF 65 2013	1.31
Indomethacin	0.04 (0.08)	125 (0.00)*	Ongoing	0.00 (0.00)	1.70 (28x50mg)	BNF 65 2013	0.46
Ibuprofen	0.14 (0.08)	1600 (438.18)	Ongoing	0.00 (0.00)	3.96 (84x600mg)	BNF 65 2013	1.51
COX-2 inhibitors							
Arcoxia	0.25 (0.14)	90 (17.32)	Ongoing	0.00 (0.00)	22.96 (28x90mg)	BNF 65 2013	17.22
Celecoxib	0.10 (0.06)	285.71 (106.90)	Ongoing	0.00 (0.00)	21.55 (30x200mg)	BNF 65 2013	8.67
Steroids							
Prednisolone	0.03 (0.03)	10.83 (5.85)	5.96 weeks (0.00)	0.33 min (0.82)	1.21 (28x5mg)	BNF 65 2013	0.23
Methylprednisolone	0.02 (0.06)	270 (325.27)	-	5 min (7.07)	6.19 (30x4mg)	BNF 65 2013	26.74
Intramuscular depomedrone	0.03 (0.04)	113.33 (16.33)	-	13.08 min (23.15)	7.47 (1x120mg)	BNF 65 2013	19.47
Gastro-protectants							
Omeprazole	0.36 (0.31)	20 (0.00)*	-	-	1.62 (28x20mg)	BNF 65 2013	1.77
Lansoprazole	0.28 (0.20)	24.29 (7.32)	-	-	1.20 (28x15mg)	BNF 65 2013	1.62
Other							
Sulphadiazine	0.09 (0.10)	2000 (0.00)*	-	15 min (17.32)	37.50 (56x500mg)	BNF 65 2013	19.61
Methotrexate	0.08 (0.08)	14.29 (8.43)	-	22.5 min (15.00)	3.27 (28x2.5mg)	BNF 65 2013	4.40
Bisphosphonates (Fosamax)	0.07 (0.10)	-	-	-	22.80 (4x70mg)	BNF 65 2013	0.49
Physiotherapy†	0.61 (0.42)	0.93/week (0.80)	47.57 min (45.18)	45.43 min (48.08)	35.00 (per hour)	PSSRU 2013	189.38
Patient education	0.93 (0.10)	0.08/week (0.09)	42.5 min (19.94)	70 min (84.14)	68.00 (one-off)	Clinical expert estimate (NICE TA233)	45.07
						Total cost	**382.28**

* patients receiving these medications received fixed doses; † physiotherapy calculated as the mean of hospital and community-based physiotherapy (PSSRU 13.1: Hospital physiotherapist [wages/salary, salary on-costs, qualifications, overheads, and capital overheads]; 9.1: Community physiotherapist [wages/salary, salary on-costs, qualifications, overheads, and capital overheads]). Admin., administration; BNF, British National Formulary; HCP, healthcare professional; NR, not reported; NSAID, non-steroidal anti-inflammatory steroid; PSSRU, Personal Social Service Research unit; SD, standard deviation.

6.5.2. Disease Management and Adverse Events Resource Use and Costs

The sources of unit costs are described in Table 30. Resource use estimates for disease management are presented in Table 31, separately for TNF-alpha inhibitors and conventional therapy. Per cycle resource use and costs for disease management are summarised in Table 32. Per cycle resource use and costs for AEs are shown in Table 33.

Weighted mean estimates of the 12-week costs of AEs for TNF-alpha inhibitors and conventional therapy were calculated from the total aggregated costs and frequency of AEs by treatment group from the GO-RAISE study. This weighted mean was calculated by summing the product of the number of events per AE and the 12-week costs per AE divided by the total number of AE events. Since AEs did not constitute a separate health state, the weighted mean costs multiplied by the cycle rate of experiencing an AE were added to the aggregated per cycle costs for TNF-alpha inhibitors and conventional therapy.

Table 30: Unit costs for disease management and adverse events

Category	Type	Unit cost, £ 2013	Source
Medical staff visits	Rheumatologist	139.00	PSSRU 2013 (15.5: Consultant: Medical. Cost per patient hour, including qualification costs)
	Physiotherapist - hospital	36.00	PSSRU 2013 (13.1: Hospital physiotherapy. Cost per hour in clinic, including qualification costs)
	Specialist nurse	90.00	PSSRU 2013 (10.7: Nurse advanced (lead specialist, clinical nurse specialist, senior specialist). Cost per hour of client contact, including qualifications)
	Physiotherapist - community	34.00	PSSRU 2013 (9.1: Community physiotherapist. Cost per hour of client contact, including qualification cost)
	General practitioner	45.00	PSSRU 2013 (10.8b: General practitioner-unit costs. Cost per patient consultation [11.7 minutes], including direct staff care & qualification costs)
	District nurse	48.00	PSSRU 2013 (10.1: Community nurse (district nursing sister, district nurse), including qualification costs)
	Orthopaedic surgeon	140.00	PSSRU 2013 (15.6: Consultant: surgical. Including qualification costs)
	Spinal surgeon	140.00	PSSRU 2013 (15.6: Consultant: surgical. Including qualification costs)
	Helpline	0.25	BT landline rate per 5 minute call
Hospitalisations	Intensive care unit	1344.24	NHS ref. costs 2012-2013 (Critical Care Services - Adult: Critical Care Unit. XC04Z mid-range, 4 organs)
	General ward	464.00	NHS ref. costs 2012-2013 (Non-Elective Inpatient (Short Stay) HRG Data HD23D)
	A&E admission	108.00	NHS ref. costs 2012-2013 (Accident and Emergency Services: Leading to Admitted VB09Z)
Personal and social care	Day care	38.00	PSSRU 2013 (1.4 Local authority day care for older people)
	Home care	98.70	PSSRU 2013 (8.1.3 Community care package for older people: median cost based on all costs - £691)
	Walking stick	15.95	Medisave.co.uk (Folding Adjustable Walking Stick 31-35 Inches Standard)
	Orthotics	27.99	PhysioRoom.com
	Wheelchair	89.00	PSSRU 2013 (7.2 NHS wheelchair. Per self or attendant propelled chair per year)
Laboratory tests	Urea/electrolyte test	1.25	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS04)
	Full blood count	3.01	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS02)
	Liver function test	1.25	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS04)
	Calcium	1.25	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS04)
	C-reactive protein	1.25	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS04)
	ESR	1.25	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS04)
	Urine culture	6.78	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS04)
	Blood culture	6.78	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS04)
	Sputum testing	6.78	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS04)
	Amylase	1.25	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS04)

Category	Type	Unit cost, £ 2013	Source
	Skin test	125.18	NHS ref. costs 2012-2013 (Outpatient Procedures, minor skin procedures, 13 years and older, JC43A)
	Chest x-ray	28.28	NHS ref. costs 2012-2013 (NHS Direct Access: Diagnostic Services DADS, Direct Access Plain Film, DAPF)
	Tuberculin (x-ray abnormal)	125.18	NHS ref. costs 2012-2013 (Outpatient Procedures, minor skin procedures, 13 years and older, JC43A)
	Urine test	6.78	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS04)
	Montoux	125.18	NHS ref. costs 2012-2013 (Outpatient Procedures, minor skin procedures, 13 years and older, JC43A)
	Varicella zoster serology	3.01	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS02)
	T spot test	3.01	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS02)
	CSF test	6.78	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS04)
	Autoimmune profile	3.01	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS02)
	ANF	3.01	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS02)
	DNA	3.01	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS02)
	Complements	3.01	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS02)
	Urine dipstick	1.25	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS04)
	Ferritin	3.01	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS02)
	Vitamin B12	3.01	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS02)
	Folate tests	3.01	NHS ref. costs 2012-2013 (NHS Trusts Direct Access: Pathology Services DAPS02)
	Skin biopsy	125.18	NHS ref. costs 2012-2013 (Outpatient Procedures, minor skin procedures, 13 years and older, JC43A)
	Lymph node biopsy	190.30	NHS ref. costs 2012-2013 (Outpatient Procedures, Procedures on the lymphatic system, with CC score 0, WA24B)
Imaging tests	Bone density scan	54.69	NHS ref. costs 2012-2013 (Diagnostic Imaging: Outpatients DIAGIMOP, Service code 410 Rheumatology, RA15Z)
	Spinal x-ray	28.28	NHS ref. costs 2012-2013 (NHS Direct Access: Diagnostic Services DADS, Direct Access Plain Film, DAPF)
	Pelvic x-ray	28.28	NHS ref. costs 2012-2013 (NHS Direct Access: Diagnostic Services DADS, Direct Access Plain Film, DAPF)
	Magnetic resonance imaging	144.71	NHS ref. costs 2012-2013 (Diagnostic Imaging: Outpatients DIAGIMOP, Service code 410 Rheumatology,RA02A)
	Ultrasound	43.70	NHS ref. costs 2012-2013 (Diagnostic Imaging: Outpatients DIAGIMOP, Service code 410 Rheumatology, RA23Z)
	Bone scan	67.14	NHS ref. costs 2012-2013 (Diagnostic Imaging: Outpatients DIAGIMOP, Service code 410 Rheumatology, RA15Z)
	Abdominal CT scan	104.20	NHS ref. costs 2012-2013 (Diagnostic Imaging: Outpatients DIAGIMOP, Service code 410 Rheumatology, RA09A)
	Echocardiogram	61.60	NHS ref. costs 2012-2013 (NHS Direct Access: Outpatients DIAGIMOP Diagnostic imaging, Service code 410 Rheumatology, Direct Access RA60A)
	ECG	53.26	NHS ref. costs 2012-2013 (Direct Access: Diagnostic Services EA4Z7)
	Endoscopy	414.52	NHS ref. costs 2012-2013 (Day Cases HRG Data, mean of total FZ63Z)
	Upper GI endoscopy	594.08	NHS ref. costs 2012-2013 (Day Cases HRG Data, mean of total, FZ60Z)
AE	Amoxicillin	0.0001	BNF 65 2013

Category	Type	Unit cost, £ 2013	Source
medications*	Co-amoxiclav 250mg	0.0004	BNF 65 2013
	Co-amoxiclav 500mg	0.0003	BNF 65 2013
	Tazocin	0.0034	BNF 65 2013
	Gentamicin	0.1480	BNF 65 2013
	Cefuroxime	0.0038	BNF 65 2013
	Rifater	0.2195	BNF 65 2013
	Ethambutol	0.0021	BNF 65 2013
	Rifinah 300	0.3754	BNF 65 2013
	Maxolon	0.0062	BNF 65 2013
	Omeprazole	0.0029	BNF 65 2013
	Lansoprazole	0.0029	BNF 65 2013
	Paracetamol	0.0000	BNF 65 2013
	Furosemide	0.0007	BNF 65 2013
	Piriton	0.0145	BNF 65 2013
	Cetirizine	0.0028	BNF 65 2013
	Fluoxetine	0.0024	BNF 65 2013
	Prednisolone	0.0084	BNF 65 2013
	Ferrous sulphate	0.0002	BNF 65 2013
Additional AE treatments	Blood transfusion	151.04	National Blood Service: National Prices 2007/2008
	Surgery (for skin cancer)	1670.44	NHS ref. costs 2012-2013 (Elective Inpatient HRG Data Intermediate Skin Procedures JC42A)
	Chemo/radiotherapy/surgery	147.04	NHS ref. costs 2012-2013 (Consultant Led: First Attendance, outpatient, Multiprofessional Non-Admitted Rheumatology, service code 410)

* drug costs are per mg. A&E, Accident & Emergency; AE, adverse event; ANF, antinuclear factor; BNF, British National Formulary; CSF, cerebral spinal fluid; CT, computed tomography; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; ref., reference; SD, standard deviation; TNF, tumour necrosis factor.

Table 31: Resource use for disease management

Category	Item	Conventional therapy, mean (SD)				TNF-alpha inhibitor, mean (SD)			
		Per 4 weeks	One-off	% utilising	Other	Per 4 weeks	One-off	% utilising	Other
Medical staff visits	Rheumatologist	0.14 (0.07)				0.13 (0.12)			
	Physiotherapist - hospital	1.31 (1.92)				1.19 (1.87)			
	Specialist nurse	0.02 (0.04)	0.25 (0.50)			0.21 (0.21)	-		
	Helpline		-				0.04 (0.08)		
	Orthopaedic surgeon		0.25 (0.50)				0.25 (0.50)		
	Spinal surgeon		0.25 (0.50)				0.25 (0.50)		
	Physiotherapist - community	1.00 (2.00)				1.00 (2.00)			
	General practitioner	0.22 (0.20)				0.10 (0.15)			
	District nurse	-				1.00 (2.00)			
Laboratory tests	Urea and electrolyte	0.11 (0.04)		0.84 (0.29)		0.26 (0.09)		0.75 (0.50)	
	Full blood count	0.11 (0.04)		0.86 (0.25)		0.23 (0.09)		1.00 (0.00)	
	Liver function test	0.32 (0.40)		0.75 (0.47)		0.26 (0.09)		0.75 (0.50)	
	Calcium	0.12 (0.04)		0.74 (0.49)		0.26 (0.09)		0.75 (0.50)	
	C-reactive protein	0.11 (0.04)		0.89 (0.19)		0.21 (0.12)		0.88 (0.25)	
Monitoring test for TB	Chest x-ray	0.08 (0.02)		0.03 (0.05)		0.03 (0.04)		0.75 (0.50)	
	Skin test	-		-		1.00 (0.30)		0.25 (0.50)	
	Urine test	0.23 (0.07)		0.25 (0.50)		0.31 (0.09)		1.00 (0.30)	
	Montoux	-		-		1.00 (0.30)		0.20 (0.40)	
	Varicella zoster serology	-		-		1.00 (0.30)		0.25 (0.50)	
	T spot test	-		-		1.00 (0.30)		0.03 (0.05)	
Imaging investigations	Bone density scan	0.02 (0.01)		0.68 (0.39)		0.02 (0.01)		0.68 (0.39)	
	Spinal x-ray	0.02 (0.01)	-	1.00 (0.00)		0.02 (0.02)	0.25 (0.50)	0.90 (0.20)	
	Pelvic x-ray	0.01 (0.02)	0.50 (0.58)	1.00 (0.00)		0.02 (0.02)	0.33 (0.58)	0.75 (0.5)	
	MRI	1.00 (0.00)		0.39 (0.42)		1.00 (0.00)		0.39 (0.42)	
	Ultrasound		1.00 (0.00)	0.03 (0.03)			1.00 (0.00)	0.02 (0.02)	
Hospitalisation	Hospitalisation			0.03 (0.03)				0.02 (0.02)	
	# of hospitalisations	0.08 (0.00)				0.08 (0.00)			
	ICU stay				2.00 (2.83)*				1.00 (1.41)*
	General ward stay				10.50 (4.95)*				8.50 (2.12)*

Category	Item	Conventional therapy, mean (SD)				TNF-alpha inhibitor, mean (SD)			
		Per 4 weeks	One-off	% utilising	Other	Per 4 weeks	One-off	% utilising	Other
	A&E admission			0.13 (0.11)				0.00 (0.00)	
	Rheumatologist follow-up				0.50 (0.58)†				0.25 (0.50)†
	Physio follow-up				1.75 (2.87)†				1.75 (2.87)†
	GP follow-up				1.50 (1.91)†				0.75 (0.96)†
	Nurse follow-up				0.50 (1.00)†				0.00 (0.00)†
	Helpline follow-up				1.25 (1.50)†				1.25 (1.89)†
	Orthopaedic surgeon follow-up				0.50 (1.00)†				0.50 (1.00)†
Social care	Day care	4.00 (1.20)		0.25 (0.50)	1.00 (0.30)‡	0.48 (0.03)		-	1.00 (0.00)‡
	Home care	4.00 (0.00)	-	0.33 (0.58)	1.00 (0.00)‡	-	1.00 (0.30)	0.01 (0.02)	-
	Physiotherapy	0.12 (0.16)		0.25 (0.50)	1.00 (0.00)‡	4.15 (5.44)		0.25 (0.50)	1.00 (0.00)‡
Assistive devices	Walking stick	0.01 (0.01)	0.08 (0.02)		1.00 (0.30)‡	0.003 (0.01)	1.00 (0.03)		1.00 (0.30)‡
	Orthotics		0.12 (0.05)	0.10 (0.12)	1.00 (0.00)‡		1.00 (0.00)	0.80 (0.10)	1.00 (0.00)‡
	Wheelchair		1.00 (0.30)	0.13 (0.25)	1.00 (0.30)‡		-	-	-

* number of days; † per hospitalisation; ‡ proportion that is NHS-funded. A&E, Accident & Emergency; GP, general practitioner; ICU, intensive care unit; MRI, magnetic resonance imaging; SD, standard deviation; TNF, tumour necrosis factor.

Table 32: Per 12-week cycle resource use and costs for disease management

Category	Type	TNF-alpha inhibitors		Conventional therapy	
		Units per cycle	Per cycle cost, £ 2013 (SD)	Units per cycle	Per cycle cost, £ 2013 (SD)
Medical staff visits	Rheumatologist	0.389	54.12	0.420	58.42
	Hospital physiotherapist	3.582	128.97	3.93	141.54
	Specialist nurse	0.633	56.96	0.311	27.96
	Community physiotherapist	6.146	208.97	11.09	376.93
	General practitioner	0.291	13.08	0.671	30.20
	District nurse	3	144.00	0	0.00
	Orthopaedic surgeon	0.252	35.28	0.253	35.44
	Spinal surgeon	0.25	35.00	1	140.00
	Helpline	0.120	0.03	0.00791	0.002
		Total cost	**676.41 (203.00)**	**Total cost**	**810.50 (243.15)**
Hospitalisations	Intensive care unit	0.004027	5.41	0.0127	17.01
	General ward	0.03423	15.88	0.06645	30.83
	A&E admission	0	0.00	0.0007911	0.09
		Total cost	**21.30 (6.39)**	**Total cost**	**47.93 (14.38)**
Personal and social care	Day care	0	0.00	3	114.00
	Home care	0	0.00	4	394.80
	Walking stick	0.0025	0.04	0.000384	0.006
	Orthotics	0.075	2.10	0.0115	0.32
	Wheelchair	0	0.00	0.125	11.13
		Total cost	**2.14 (0.64)**	**Total cost**	**520.25 (156.08)**
Laboratory tests	Urea/electrolyte test	0.575	0.72	0.265	0.33
	Full blood count	0.69	2.08	0.273	0.82
	Liver function test	0.575	0.72	0.712	0.89
	Calcium	0.575	0.72	0.256	0.32
	C-reactive protein	0.554	0.69	0.281	0.35
	Skin test	0.25	1.70	0	0.00
	Chest x-ray	1.558	44.05	0.00575	0.16
	Tuberculin (if x-ray abnormal)	0	0.00	0	0.00
	Urine test	0.921	6.24	0.173	1.17

Category	Type	TNF-alpha inhibitors		Conventional therapy	
		Units per cycle	**Per cycle cost, £ 2013 (SD)**	**Units per cycle**	**Per cycle cost, £ 2013 (SD)**
	Montoux	0.2	25.04	0	0.00
	Varicella zoster serology	0.25	0.75	0	0.00
	T spot test	0.025	0.08	0	0.00
		Total cost	**82.77 (24.83)**	**Total cost**	**4.04 (1.21)**
Imaging tests	Bone density scanning	0.0434	2.37	0.0375	2.05
	Spinal x-ray	0.727	20.56	0.0729	2.06
	Pelvic x-ray	0.376	10.65	0.543	15.36
	Magnetic resonance imaging	0.3875	56.07	0.3875	56.07
	Ultrasound	0.02	0.87	0.0275	1.20
		Total cost	**90.53 (27.16)**	**Total cost**	**76.75 (23.03)**

A&E, Accident & Emergency; SD, standard deviation; TNF, tumour necrosis factor.

Table 33: Per 12-week cycle resource use and costs for adverse events

Category	Resource	Unit	Mean (SD)	Total cost, £ 2013
Infections not requiring hospitalisation and/or IV antibiotics	-	% treated as outpatients	0.27 (0.49)	-
		# of specialist visits	1.33 (0.58)	49.11
		# of GP visits	4.50 (3.70)	53.66
	Blood tests	% undergoing test; # of times tested	0.66 (0.45); 1.25 (0.50)	2.49
	Chest x-ray	% undergoing test; # of times tested	0.06 (0.05); 1.00 (0.00)	1.77
	Urine culture	% undergoing test; # of times tested	0.06 (0.09); 1.00 (0.00)	0.42
	Liver function test	% undergoing test; # of times tested	0.03 (0.04); 0.33 (0.58)	0.010
	ESR	% undergoing test; # of times tested	0.22 (0.33); 0.67 (0.58)	0.18
	CRP	% undergoing test; # of times tested	0.16 (0.29); 1.00 (0.00)	0.20
	Amoxicillin	% receiving; average dose (mg/day); average duration (days)	0.45 (0.42); 1375.00 (216.51); 7.00 (0.00)	0.50
	Co-amoxiclav	% receiving; average dose (mg/day); average duration (days)	0.63 (1.25); 1125.00 (337.50); 5.00 (1.50)	8.51
			Total cost	**116.85**
Infections requiring hospitalisation and/or IV antibiotics	-	% hospitalised; % treated as outpatients	0.35 (0.46); 0.34 (0.47)	-
		Average hospital stay (days)	9.33 (4.04)	1494.08
		Average ICU stay (days)	0.33 (0.58)	154.59
		# of specialist visits	2.67 (1.15)	124.17
		# of GP visits	2.33 (2.52)	35.18
	Blood tests	% undergoing test; # of times tested	0.50 (0.58); 4.50 (2.12)	6.77
	Blood cultures	% undergoing test; # of times tested	0.50 (0.58); 3.50 (3.54)	11.87
	ESR	% undergoing test; # of times tested	0.33 (0.58); 1.00 (0.30)	0.42
	CRP	% undergoing test; # of times tested	0.33 (0.58); 1.00(0.30)	0.42
	Chest x-ray	% undergoing test; # of times tested	0.33 (0.58); 1.00 (0.30)	9.43
	Co-amoxiclav	% receiving; average dose (mg/day); average duration (days)	0.13 (0.25); 1125.00 (337.50); 7.00 (2.10)	2.38
	Tazocin	% receiving; average dose (mg/day); average duration (days)	0.25 (0.50); 13500.00 (0.00); 7.00 (0.00)	79.64
	Plus gentamicin	% receiving; average dose (mg/day); average duration (days)	0.25 (0.50); 350.00 (0.00); 5.00 (0.00)	64.75
	Plus co-amoxiclav	% receiving; average dose (mg/day); average duration (days)	0.25 (0.50); 1875.00 (0.00); 7.00 (2.10)	7.94
	Cefuroxime	% receiving; average dose (mg/day); average duration (days)	0.23 (0.45); 2250.00 (675.00); 10.00 (3.00)	19.06
			Total cost	**2010.69**
Tuberculosis	-	% hospitalised; % treated as outpatients	0.08 (0.17); 0.58 (0.50)	-

Category	Resource	Unit	Mean (SD)	Total cost, £ 2013
		Average hospital stay (days)	7.00 (2.10)	267.96
		Average ICU stay (days)	0.00 (0.00)	0.00
		# of specialist visits	5.33 (1.15)	431.83
		# of GP visits	2.67 (1.15)	69.90
	Chest x-ray	% undergoing test; # of times tested	0.75 (0.50); 3.67 (2.31)	77.78
	Sputum testing	% undergoing test; # of times tested	0.50 (0.58); 4.00 (1.41)	250.37
	Rifater	% receiving; average dose (tablets/day); average duration (days)	0.75 (0.50); 6.00 (0.00); 60.00 (0.00)	59.27
	Plus ethambutol	% receiving; average dose (mg/day); average duration (days)	0.75 (0.50); 1050.00 (0.00); 60.00 (0.00)	101.33
	Rifinah 300	% receiving; average dose (tablets/day); average duration (days)	0.75 (0.50); 2.00 (0.00); 120.00 (0.00)	67.56
			Total cost	**1326.00**
Nausea	-	% hospitalised; % treated as outpatients	0.00 (0.00); 0.55 (0.53)	-
		# of specialist visits	0.50 (0.58)	37.88
		# of GP visits	1.75 (0.50)	42.92
	Blood tests	% undergoing test; # of times tested	0.02 (0.03); 1.00 (0.00)	0.060
	Endoscopy	% undergoing test; # of times tested	0.13 (0.25); 1.00 (0.30)	51.82
	Abdominal CT scan	% undergoing test; # of times tested	0.13 (0.25); 1.00 (0.30)	13.03
	Urea/electrolyte test	% undergoing test; # of times tested	0.03 (0.05); 1.00 (0.30)	0.031
	Liver function test	% undergoing test; # of times tested	0.03 (0.05); 1.00 (0.30)	0.031
	Maxolon	% receiving; average dose (mg/day); average duration (days)	0.18 (0.35); 30.00 (9.00); 7.00 (2.10)	0.23
	Omeprazole	% receiving; average dose (mg/day); average duration (days)	0.0025 (0.01); 20.00 (6.00); 42.00 (12.60)	0.0060
	Lansoprazole	% receiving; average dose (mg/day); average duration (days)	0.25 (0.50); 15.00 (4.50); 30.00 (9.00)	0.32
			Total cost	**146.32**
Abdominal pain	-	% hospitalised; % treated as outpatients	0.00 (0.00); 0.53 (0.55)	-
		# of specialist visits	0.50 (1.00)	36.49
		# of GP visits	2.00 (0.00)	47.25
	Blood tests	% undergoing test; # of times tested	0.44 (0.49); 1.33 (0.58)	1.75
	Amylase	% undergoing test; # of times tested	0.18 (0.35); 2.00 (0.60)	0.44
	Endoscopy	% undergoing test; # of times tested	0.01 (0.02); 1.00 (0.30)	3.11
	Urea/electrolyte test	% undergoing test; # of times tested	0.03 (0.05); 1.00 (0.30)	0.031
	Liver function test	% undergoing test; # of times tested	0.03 (0.05); 1.00 (0.30)	0.031
	Paracetamol	% receiving; average dose (mg/day); average duration (days)	0.20 (0.40); 4000 (1200); 7.00 (2.10)	0.11

Category	Resource	Unit	Mean (SD)	Total cost, £ 2013
	Omeprazole	% receiving; average dose (mg/day); average duration (days)	0.01 (0.02); 20.00 (6.00); 42.00 (12.60)	0.024
			Total cost	**89.23**
Heart failure	-	% hospitalised; % treated as outpatients	0.0025 (0.01); 0.25 (0.50)	-
		Average hospital stay (days)	10.00 (3.00)	11.60
		Average ICU stay (days)	1.00 (0.30)	3.36
		# of specialist visits	2.00 (0.60)	69.50
		# of GP visits	2.00 (0.60)	22.50
	Blood tests	% undergoing test; # of times tested	0.25 (0.50); 1.00 (0.30)	0.75
	Chest x-ray	% undergoing test; # of times tested	0.50 (0.58); 1.00 (0.00)	14.14
	Echocardiogram	% undergoing test; # of times tested	0.38 (0.48); 1.00 (0.00)	23.10
	ECG	% undergoing test; # of times tested	0.25 (0.50); 1.00 (0.30)	13.31
	Urea/electrolyte test	% undergoing test; # of times tested	0.25 (0.50); 1.00 (0.30)	0.31
	Furosemide	% receiving; average dose (mg/day); average duration (days)	0.71 (0.48); 53.33 (23.09); 84.00 (0.00)	2.08
			Total cost	**160.66**
Hypersensitivity reaction	-	% hospitalised; % treated as outpatients	0.0025 (0.01); 0.27 (0.49)	-
		Average hospital stay (days)	0.00 (0.00)	0.00
		Average ICU stay (days)	2.00 (0.60)	6.72
		# of specialist visits	0.75 (0.96)	27.63
		# of GP visits	1.00 (1.15)	11.93
	Blood tests	% undergoing test; # of times tested	0.25 (0.50); 1.00 (0.30)	0.75
	Piriton	% receiving; average dose (mg/day); average duration (days)	0.50 (0.44); 13.33 (8.33); 9.67 (7.51)	0.93
	Cetirizine	% receiving; average dose (mg/day); average duration (days)	0.01 (0.01); 10.00 (3.00); 1.00 (0.00)	0.00014
	Paracetamol	% receiving; average dose (mg/day); average duration (days)	0.20 (0.40); 4000.00 (1200.00); 2.00 (0.60)	0.032
			Total cost	**47.99**
Fever	-	% hospitalised; % treated as outpatients	0.00 (0.00); 0.50 (0.58)	-
		# of specialist visits	2.00 (0.00)	139.00
		# of GP visits	1.00 (1.41)	22.50
	Blood tests	% undergoing test; # of times tested	0.50 (0.58); 2.50 (0.71)	3.76
	Chest x-ray	% undergoing test; # of times tested	0.50 (0.58); 1.50 (0.71)	21.21
	Urine test	% undergoing test; # of times tested	0.25 (0.50); 2.00 (0.60)	3.39
	ESR	% undergoing test; # of times tested	0.25 (0.50); 1.00 (0.30)	0.31

Category	Resource	Unit	Mean (SD)	Total cost, £ 2013
	CRP	% undergoing test; # of times tested	0.25 (0.50); 1.00 (0.30)	0.31
	Urea/electrolyte test	% undergoing test; # of times tested	0.25 (0.50); 1.00 (0.30)	0.31
	Liver function test	% undergoing test; # of times tested	0.25 (0.50); 1.00 (0.30)	0.31
	Paracetamol	% receiving; average dose (mg/day); average duration (days)	0.46 (0.53); 4000.00 (0.00); 7.00 (0.00)	0.26
			Total cost	**191.37**
Headache	-	% hospitalised; % treated as outpatients	0.00 (0.00); 0.26 (0.49)	-
		# of specialist visits	1.00 (1.41)	36.49
		# of GP visits	1.50 (0.71)	17.72
	Blood tests	% undergoing test; # of times tested	0.05 (0.10); 1.00 (0.30)	0.15
	CT scan	% undergoing test; # of times tested	0.05 (0.10); 1.00 (0.30)	5.21
	CSF test	% undergoing test; # of times tested	0.05 (0.10); 1.00 (0.30)	0.34
	Paracetamol	% receiving; average dose (mg/day); average duration (days)	0.34 (0.39); 4000.00 (0.00); 14.00 (0.00)	0.38
			Total cost	**60.28**
Depression	-	% hospitalised; % treated as outpatients	0.00 (0.00); 0.25 (0.50)	-
		# of specialist visits	2.00 (0.60)	69.50
		# of GP visits	2.00 (0.60)	22.50
	Fluoxetine	% receiving; average dose (mg/day); average duration (days)	0.03 (0.05); 20.00 (6.00); 84.00 (0.00)	0.099
			Total cost	**92.10**
Lupus erythematosus-like syndrome	-	% hospitalised; % treated as outpatients	0.00 (0.00); 0.25 (0.50)	-
		# of specialist visits	3.50 (2.12)	122.84
		# of GP visits	1.50 (0.71)	17.04
	Blood tests	% undergoing test; # of times tested	0.50 (0.58); 2.00 (1.41)	3.01
	Autoimmune profile	% undergoing test; # of times tested	0.25 (0.50); 1.00 (0.30)	0.75
	ESR	% undergoing test; # of times tested	0.25 (0.50); 3.00 (0.90)	0.93
	CRP	% undergoing test; # of times tested	0.25 (0.50); 3.00 (0.90)	0.93
	Urea/electrolyte test	% undergoing test; # of times tested	0.25 (0.50); 3.00 (0.90)	0.93
	Liver function test	% undergoing test; # of times tested	0.25 (0.50); 3.00 (0.90)	0.93
	ANF	% undergoing test; # of times tested	0.25 (0.50); 3.00 (0.90)	2.26
	DNA	% undergoing test; # of times tested	0.25 (0.50); 3.00 (0.90)	2.26
	Complements	% undergoing test; # of times tested	0.25 (0.50); 3.00 (0.90)	2.26
	Urine dipstick	% undergoing test; # of times tested	0.25 (0.50); 3.00 (0.90)	0.93

Category	Resource	Unit	Mean (SD)	Total cost, £ 2013
	Prednisolone	% receiving; average dose (mg/day); average duration (days)	0.05 (0.10); 20.00 (6.00); 28.00 (8.40)	0.24
			Total cost	**155.32**
Pruritis	-	% hospitalised; % treated as outpatients	0.0025 (0.01); 0.51 (0.57)	-
		Average hospital stay (days)	0.00 (0.00)	0.00
		Average ICU stay (days)	2.00 (0.60)	6.72
		# of specialist visits	0.50 (1.00)	35.10
		# of GP visits	1.75 (0.50)	39.77
	Blood tests	% undergoing test; # of times tested	0.25 (0.50); 1.00 (0.30)	0.75
	Piriton	% receiving; average dose (mg/day); average duration (days)	0.18 (0.35); 20.00 (6.00); 14.00 (4.20)	0.71
	Cetirizine	% receiving; average dose (mg/day); average duration (days)	0.13 (0.25); 10.00 (3.00); 1.00 (0.00)	0.0035
			Total cost	**83.05**
Injection-site reaction	-	% hospitalised; % treated as outpatients	0.00 (0.00); 0.34 (0.46)	-
		# of specialist visits	1.75 (0.50)	82.71
		# of GP visits	0.75 (0.96)	11.48
	Cetirizine	% receiving; average dose (mg/day); average duration (days)	0.02 (0.04); 10.00 (3.00); 1.00 (0.00)	0.00053
			Total cost	**94.18**
Blood disorder	-	% hospitalised; % treated as outpatients	0.0025 (0.01); 0.34 (0.46)	-
		Average hospital stay (days)	0.03 (0.01)	0.035
		Average ICU stay (days)	0.00 (0.00)	0.00
		# of specialist visits	1.17 (0.76)	54.73
		# of GP visits	2.00 (0.00)	30.38
	Blood tests	% undergoing test; # of times tested	0.51 (0.57); 2.00 (1.00)	3.04
	Ferritin	% undergoing test; # of times tested	0.51 (0.57); 2.00 (1.00)	3.04
	Vitamin B12	% undergoing test; # of times tested	0.51 (0.57); 2.00 (1.00)	3.04
	Folate tests	% undergoing test; # of times tested	0.51 (0.57); 2.00 (1.00)	3.04
	Upper GI endoscopy	% undergoing test; # of times tested	0.11 (0.20); 1.00 (0.00)	62.38
	Blood transfusion	% receiving; average duration (days)	0.03 (0.05); 7.00 (2.10)	26.43
	Omeprazole	% receiving; average dose (mg/day); average duration (days)	0.01 (0.01); 20.00 (6.00); 42.00 (12.60)	0.012
	Ferrous sulphate	% receiving; average dose (mg/day); average duration (days)	0.08 (0.15); 600.00 (0.00); 135.00 (63.64)	1.17
	Lansoprozole	% receiving; average dose (mg/day); average duration (days)	0.18 (0.35); 15.00 (4.50); 84.00 (0.00)	0.63
			Total cost	**187.92**

Category	Resource	Unit	Mean (SD)	Total cost, £ 2013
Skin cancer	-	% hospitalised; % treated as outpatients	0.00 (0.00); 0.25 (0.50)	-
		# of specialist visits	6.00 (1.80)	208.50
		# of GP visits	6.00 (1.80)	67.50
	Skin biopsy	% undergoing test; # of times tested	0.25 (0.50); 1.00 (0.30)	31.30
	Surgery	% receiving; average duration (days)	0.25 (0.50); 7.00 (2.10)	2923.28
			Total cost	**3230.57**
Lymphoma	-	% hospitalised; % treated as outpatients	0.00 (0.00); 0.25 (0.50)	-
		# of specialist visits	10.00 (0.00)	347.50
		# of GP visits	10.00 (3.00)	112.50
	Chest x-ray	% undergoing test; # of times tested	0.25 (0.50); 3.00 (0.90)	21.21
	CT scan chest/abdomen	% undergoing test; # of times tested	0.25 (0.50); 3.00 (0.90)	78.15
	Lymph node biopsy	% undergoing test; # of times tested	0.25 (0.50); 1.00 (0.30)	47.58
	Blood tests	% undergoing test; # of times tested	0.25 (0.50); 3.00 (0.90)	2.26
	Chemo/radio/surgery	% receiving	0.25 (0.50)	36.76
			Total cost	**645.96**

ANF, antinuclear factor; CRP, C-reactive protein; CSF, cerebral spinal fluid; CT, computed tomography; DNA, deoxyribonucleic acid; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; GP, general practitioner; ICU, intensive care unit; IV, intravenous; SD, standard deviation.

6.6. Base Case Analysis

The values used in the base case analysis are outlined in Table 34.

Table 34: Summary of variables considered in base case analysis

Variable	Value	Range	Distribution
Time horizon	Lifetime	-	-
Cycle length	12 weeks	-	-
Discount rate	3.5%	-	-
Starting age in the model	39.3 years	SE 0.82	Normal, truncated
Gender (% males)	71.6%	+/-30%	-
Baseline BASDAI score	6.54	SE 0.11	Normal, truncated
Baseline BASFI score	5.04	SE 0.16	Normal, truncated
Standardised mortality ratio for AS	Male: 1.63 Female: 1.38	SE 0.106 SE 0.324	Lognormal
RR for response with ADA (BASDAI50)	3.23	SE 3.14	Lognormal
RR for response with CZP (BASDAI50)	3.64	SE 9.74	Lognormal
RR for response with ETN (BASDAI50)	3.31	SE 4.52	Lognormal
RR for response with GOL (BASDAI50)	3.34	SE 3.58	Lognormal
RR for response with IFX (BASDAI50)	5.45	SE 51.32	Lognormal
Response rate with conventional therapy (absolute treatment effect) (BASDAI50)	0.145	SE 0.053	Beta
RR for ≥1AE rate for ADA	1.260	SE 3.238	Lognormal
RR for ≥AE rate for CZP	1.137	SE 0.00	Lognormal
RR for ≥AE rate for ETN	1.014	SE 1.339	Lognormal
RR for ≥AE rate for GOL	1.117	SE 2.313	Lognormal
RR for ≥AE rate for IFX	1.239	SE 0.00	Lognormal
≥AE rate for conventional therapy (absolute treatment effect)	0.562	SE 0.264	Beta
RR for SAE rate for ADA	0.887	SE 1.641	Lognormal
RR for SAE rate for CZP	1.744	SE 0.00	Lognormal
RR for SAE rate for ETN	2.661	SE 41.87	Lognormal
RR for SAE rate for GOL	0.707	SE 1.904	Lognormal
RR for SAE rate for IFX	2.781	SE 6.879	Lognormal
RR for SAE rate for conventional therapy (absolute treatment effect)	0.038	SE 0.095	Beta
RR for ISR rate with ADA	1.902	SE 0.00	Lognormal
RR for ISR rate with CZP	1.902	SE 0.00	Lognormal
RR for ISR rate with ETN	2.603	SE 4.13	Lognormal
RR for ISR rate with GOL	2.522	SE 6.991	Lognormal
RR for ISR rate with IFX	1.200	SE 1.847	Lognormal
ISR rate with conventional therapy (absolute treatment effect)	0.099	SE 0.120	Beta
Annual discontinuation rate with TNF-alpha inhibitors	6.1%	SE 2.0%	Beta

Variable	Value	Range	Distribution
Annual discontinuation rate with conventional therapy (absolute treatment effect)	0.0%	-	-
Rebound assumption	Rebound to baseline	-	-
12 week cost of ADA	£2112.84	SE £634.00	Gamma
12 week cost of CZP, first cycle	£0.00	SE £0.00	Gamma
12 week cost of CZP, second and subsequent cycles	£2145.00	SE £644.00	Gamma
12 week cost of ETN	£2145.00	SE £644.00	Gamma
12 week cost of GOL	£2112.82	SE £634.00	Gamma
12 week cost of IFX, first cycle	£6256.18	SE £1877.00	Gamma
12 week cost of IFX, second and subsequent cycles	£3128.09	SE £938.00	Gamma
12 week cost of conventional therapy	£382.28	SE £115.00	Gamma
Short-term treatment cost (TNF-alpha inhibitors)	£1198.66	-	Gamma
Short-term treatment cost (conventional therapy)	£1646.45	-	Gamma
Weighted average AE cost (TNF-alpha inhibitors)	£218.42	SE £65.53	Gamma
Weighted average AE cost (conventional therapy)	£401.75	SE £120.52	Gamma
Cost of ISRs	£94.18	SE £28.25	Gamma
Coefficient for BASFI score (long-term cost regression)	0.1832	SE 0.05496	Normal
Intercept (long-term cost regression)	£1585.30	SE £476.00	Normal
Disutililities due to AEs	0.01	SE 0.003	Gamma
Annual disease progression according to BASFI (conventional therapy)	0.07	0.021	Normal, truncated

ADA, adalimumab; AE, adverse event; AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; IFX, infliximab; ISR, injection (infusion)-site reaction; SAE, serious adverse event; TNF, tumour necrosis factor.

6.7. Sensitivity Analysis

6.7.1. Deterministic Sensitivity Analysis

One-way deterministic sensitivity analyses (DSAs) were used to identify the key drivers of uncertainty in the estimation of the incremental cost-effectiveness of each intervention. For continuous variables, where available, the SD or SE of each parameter was used to define the upper and lower values for sensitivity analysis. Where the SD or SE was not available, the upper and lower limits of the range were defined as +/-30% of the parameter. In addition, one-way sensitivity analyses were performed to characterise the effect of changing key assumptions for the base case. Key variables changed are shown in Table 35.

Table 35: Summary of variables adjusted for scenario analysis

Variable	Value	Rationale
Time horizon	1 year, 5 year	Bansback *et al*. (2007)
Age at baseline	30 years, 60 years	Upper bound of lifespan
Gender (% males)	0%, 100%	Full possible range
RR for response with ADA (BASDAI50)	ASAS20 2.39	Alternative measure for response used in UK clinical practice
RR for response with CZP (BASDAI50)	ASAS20 1.79	
RR for response with ETN (BASDAI50)	ASAS20 2.30	
RR for response with GOL (BASDAI50)	ASAS20 2.08	
RR for response with IFX (BASDAI50)	ASAS20 2.70	
Response with conventional therapy (absolute treatment effect) (BASDAI50)	ASAS20 27%	
Annual discontinuation rate with TNF-alpha inhibitors	15.0%, 22.3%	15.0% recommended by McLeod et al. 22.3% is the largest alternative published cited by McLeod et al.
Rebound assumption	Rebound to conventional	Wailoo *et al*. 2008
Disutililities due to SAEs (TNF-alpha inhibitors)	0.1	Maximum likely disutility presented in NICE TA233
Annual disease progression according to BASFI (conventional therapy)	0.03, 0.09	Kobelt *et al*. 2004

ADA, adalimumab; ASAS, Assessment in Ankylosing Spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; IFX, infliximab; SAE, serious adverse event; TNF, tumour necrosis factor.

6.7.2. Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis (PSA) was performed to account for multivariate and stochastic uncertainty in the model from which the probabilistic ICER was calculated in accordance with the NICE reference case. The PSA was based on the base case, including the PAS prices for golimumab and certolizumab pegol, and considering BASDAI50 as the outcome measure of response to treatment. The PSA was undertaken with 10,000 simulations. Distributions for parameters were based on recommendations by Briggs *et al*.[99] and are detailed in Table 34. A lognormal distribution was applied to the ORs for outcomes, including BASDAI50, AEs, and the SMR for AS. A gamma distribution was applied to costs. A normal, truncated distribution was applied to the baseline age limited to avoid incorporation of patients aged less than 18 years. A normal, truncated distribution was applied to the baseline BASFI and BASDAI scores to ensure that the range was limited to between 0 and 10. A gamma distribution was applied to disutilities and a beta distribution was applied to the discontinuation rate. A normal, truncated distribution was applied to the annual rates of progression of the BASFI score for conventional therapy.

Since parameters estimated by regression analysis (e.g. for disease progression from the GO-RAISE trial) are not independent, a Cholesky decomposition of the covariance matrix was employed where variance-covariance matrices were available (e.g. progression of the BASFI and BASDAI scores)[99]. Since variance-covariance matrices were not available for the long-term cost and utility regression, their parameters were assumed to be distributed normally.

6.8. Results

The Markov traces and details of the QALYs accrued over time are available in the Microsoft Excel® model accompanying this submission.

6.8.1. Base Case Analysis

Incremental results for the base case when TNF-alpha inhibitors are compared with conventional therapy are shown in Table 36. Incremental results for the base case when TNF-alpha inhibitors are compared with each other are shown in Table 37. The cost-effective acceptability curves demonstrating the probability that a specific treatment will be the most cost-effective over a range of willingness-to-pay (WTP) thresholds are presented in Figure 16.

TNF-alpha inhibitors result in increased QALYs when compared to conventional therapy, ranging from 1.09 for adalimumab to 1.17 for infliximab. This is achieved at an increased cost (from £20,153 when adalimumab is administered to £50,607 for infliximab). The estimated ICERs for each TNF-alpha inhibitor when compared with conventional therapy ranged from £18,508 to £43,432 per additional QALY gained (for adalimumab and infliximab versus conventional therapy, respectively). The incremental analysis of each treatment versus each other and based on the incremental cost demonstrated that etanercept is dominated by certolizumab pegol.

None of the assessed TNF-alpha inhibitors has more than 30% likelihood of being cost-effective. At a WTP threshold of £20,000, there is a 20% probability that golimumab and adalimumab are likely to be the most cost-effective treatments for AS with and a 30% probability that certolizumab pegol is likely to be cost-effective. However, the cost-effectiveness curves and the cost-effectiveness frontier highlight the considerable uncertainty in differentiating the cost-effectiveness of golimumab, adalimumab, certolizumab pegol, and etanercept.

Table 36: Absolute and incremental costs and QALYs, ICERs, and incremental analysis for TNF-alpha inhibitors versus conventional therapy

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Conventional therapy (reference)	162,600	10.5390	-	-	-
Adalimumab	182,752	11.6279	20,153	1.0889	18,508 (21,291)
Golimumab	183,235	11.6336	20,636	1.0946	18,852 (21,311)
Certolizumab pegol	184,570	11.6598	21,970	1.1208	19,603 (19,153)
Etanercept	186,030	11.6456	23,430	1.1066	21,174 (22,177)
Infliximab	213,207	11.7042	50,607	1.1652	43,432 (44,872)

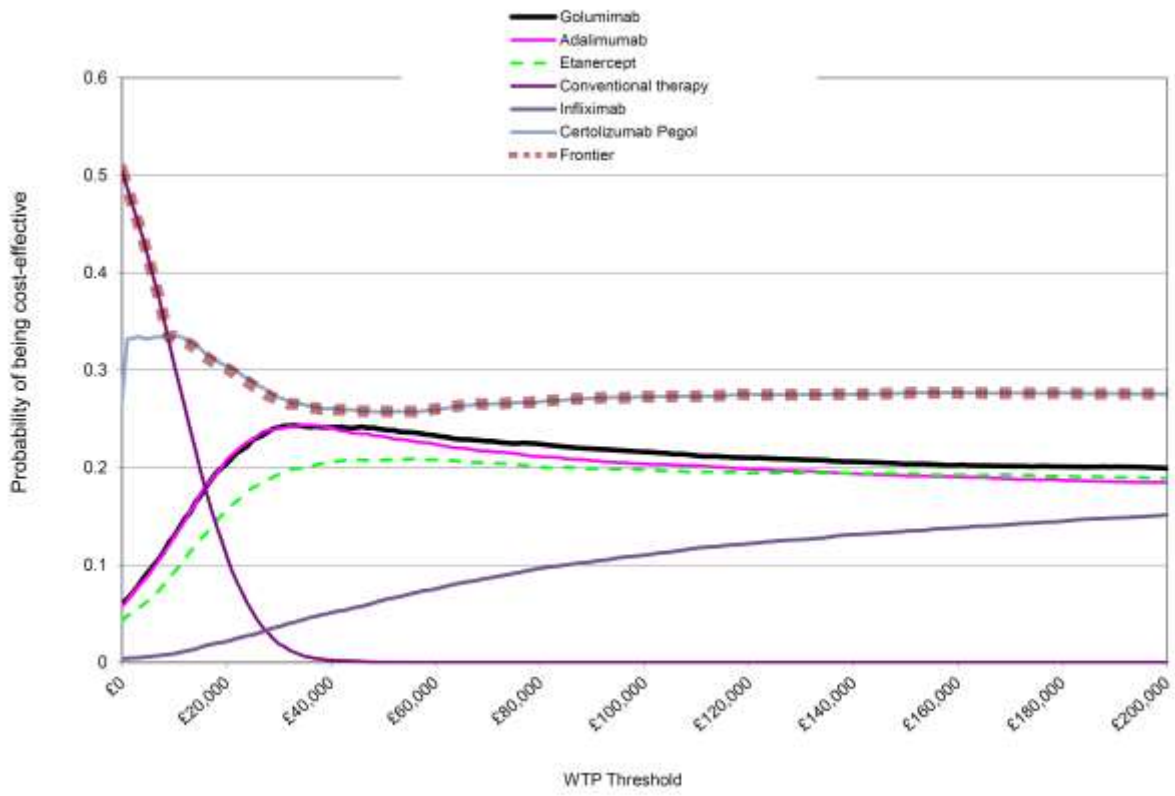
Results are based on the PSA and incremental analysis based on incremental cost. Results for the ICERs produced by the deterministic analyses are shown in brackets. QALY, quality-adjusted life year.

Table 37: Absolute and incremental costs and QALYs, and incremental analysis for TNF-alpha inhibitors versus each other

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost per QALY (£)
Conventional therapy (reference)	162,600	10.539	-	-	-
Adalimumab	182,752	11.628	20,153	1.0889	18,508
Golimumab	183,235	11.634	483	0.00578	83,572
Certolizumab pegol	184,570	11.660	1,335	0.0261	51,058
Etanercept	186,030	11.646	1,460	-0.0142	Dominated by CZP
Infliximab	213,207	11.704	28,637	0.0443	644,574

Results based on PSA and incremental analysis based on incremental cost. CZP, certolizumab pegol; QALY, quality-adjusted life year.

Figure 16: Cost-effective acceptability curves demonstrating the probability that a specific treatment will be the most cost-effective over a range of WTP thresholds



WTP, willingness-to-pay.

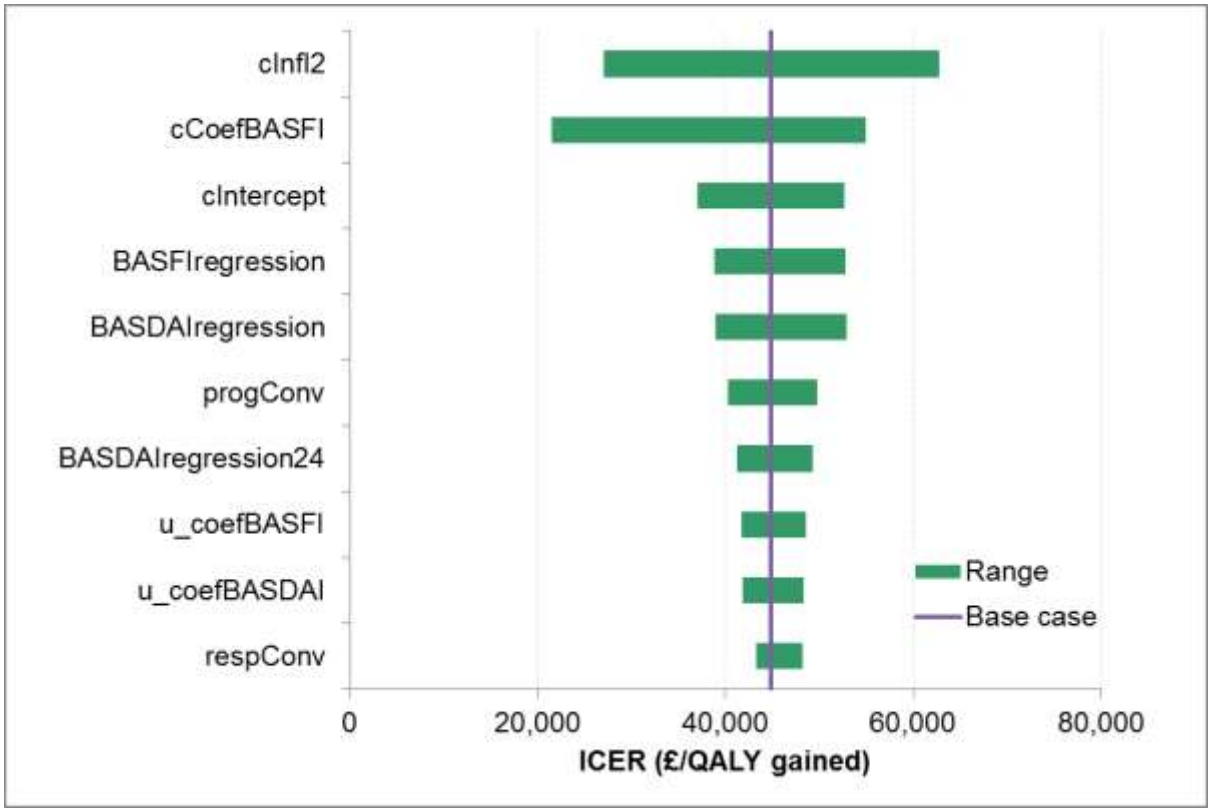
6.8.2. Deterministic Sensitivity Analysis

The deterministic sensitivity analysis indicates the ten key drivers which have the greatest impact upon the cost-effectiveness findings when varied (Figure 17). Full results for the top ten drivers are presented in Table 38. The results of the deterministic sensitivity analysis when all variables are considered are shown in Appendix C.

Based on the results of the deterministic sensitivity analyses, the ICERs of infliximab versus conventional therapy remained mostly robust. One-way sensitivity analysis of the ICER for infliximab versus conventional therapy demonstrates that the cost of infliximab (varied by +/- 30%) and the estimation of the long-term cost of treatment based on the BASFI (based on SE) are the two variables with the highest impact on the estimated ICER. When the lower bounds of these two variables were considered, the estimated ICERs for infliximab versus conventional therapy were below £30,000. An increase in the long-term treatment costs of AS associated with the BASFI score increased the long-term treatment costs for conventional therapy compared to

that of patients on TNF-alpha inhibitors, who have a lower BASFI score, resulting in an ICER lower than £30,000. Therefore, a relevant source of uncertainty seems to be related to the methodological approach used for the estimation of the long-term treatment costs. However, uncertainty surrounding all other variables seems to have a minimum impact on the estimated ICERs.

Figure 17: Tornado diagram of results of one-way sensitivity analysis



cInfl2, cost of infliximab for cycle 2 onwards; cCoefBASFI, coefficient for BASFI score in the long-term cost regression; cIntercept, intercept in the long-term cost regression; BASFIregression, BASFI scores in AS based on regression; BASDAIregression, BASDAI scores in AS based on regression; progCov, annual disease progression according to BASFI on conventional therapy; BASDAIregression24, BASDAI scores in AS based on regression in the first 24 weeks; u_coefBASFI, coefficient for BASFI score in the long-term utility regression; u_coefBASDAI, coefficient for BASDAI score in the long-term utility regression; respConv, percentage of patients responding according to BASDAI50 on conventional therapy. ICER, incremental cost-effectiveness analysis; QALY, quality-adjusted life year.

Table 38: Deterministic, one-way sensitivity analysis for infliximab (top ten drivers)

Variable	Parameter			ICER (£)	
	Mean	**Lower**	**Upper**	**Lower**	**Upper**
cInfl2	3128.09	2189.663	4066.517	26,975.37	62,767.77
cCoefBASFI	0.1832	0.075478	0.290922	54,966.24	21,477.74
cIntercept	1585.3	653.1436	2517.456	52,702.39	37,040.76
BASFIregression	Multiple	95% CI	95% CI	52,810.75	38,751.22
BASDAIregression	Multiple	95% CI	95% CI	52,853.23	38,984.34
progConv	0.07	0.049	0.091	49,791.05	40,218.15
BASDAIregression24	Multiple	95% CI	95% CI	41,181.36	49,288.23
u_coefBASFI	-0.032252	-0.037025	-0.027479	41,718.81	48,539.81
u_coefBASDAI	-0.038409	-0.044005	-0.032813	41,876.50	48,328.07
respConv	0.1455	0.06158	0.2699	48,195.69	43,296.00

The deterministic ICER for the base case was £44,872. Range for each variable was set to +/-30% or the SE where available. cInfl2, cost of infliximab for cycle 2 onwards; cCoefBASFI, coefficient for BASFI score in the long-term cost regression; cIntercept, intercept in the long-term cost regression; BASFIregression, BASFI scores in AS based on regression; BASDAIregression, BASDAI scores in AS based on regression; progCov, annual disease progression according to BASFI on conventional therapy; BASDAIregression24, BASDAI scores in AS based on regression in the first 24 weeks; u_coefBASFI, coefficient for BASFI score in the long-term utility regression; u_coefBASDAI, coefficient for BASDAI score in the long-term utility regression; respConv, percentage of patients responding according to BASDAI50 on conventional therapy. CI, confidence interval; ICER, incremental cost-effectiveness analysis.

Finally, Table 42 presents the results of the scenario analyses. Based on the key assumptions shown, TNF-alpha inhibitors:

- are more cost-effective as the time horizon increases;
- are a more cost-effective treatment for younger patients (e.g. 30 years);
- are cost-effective regardless of gender with the exception of infliximab;
- remain cost-effective regardless of whether the BASDAI50 or ASAS20 response criteria are used to define response with the exception of infliximab;
- are cost-effectiveness regardless of the discontinuation rate; and
- are cost-effective regardless of the disutility rate applied for SAEs

TNF-alpha inhibitors that are cost-effective for the key structural assumption of rebound to baseline following discontinuation of treatment, remain cost-effective when they are assumed to rebound to the BASFI score of conventional treatment at any point in the time horizon. In addition, when the annual rate of BASFI progression for conventional therapy is reduced from 0.07 to 0.03, TNF-alpha inhibitors that are cost-effective at the higher rate remain cost-effective at the lower rate.

Table 39: Effect of key variables and scenario analyses on the ICER for each TNF-alpha inhibitor versus conventional therapy

Variable		Parameter for base case	Alternative parameter	Infliximab	Golimumab	Adalimumab	Certolizumab pegol	Etanercept
Base case		-	-	£44,872	£21,311	£21,291	£19,153	£22,177
Time horizon		Lifetime	1 year	£113,279	£39,492	£39,669	£612	£40,907
			5 years	£63,281	£30,855	£30,868	£23,600	£31,911
Age at baseline		39.3 years	30 years	£39,884	£17,975	£17,954	£16,043	£18,775
			60 years	£61,684	£32,147	£32,131	£28,757	£33,237
Gender (% males)		71.6%	0%	£47,894	£23,190	£23,168	£20,983	£24,102
			100%	£43,706	£20,590	£20,570	£18,452	£21,438
Response measure		BASDAI50	ASAS20	£45,037	£21,231	£21,137	£19,227	£22,046
Long-term discontinuation rate (annual)		6.1%	15.0%	£45,131	£19,612	£19,609	£15,325	£20,463
			23.7%	£46,951	£19,033	£19,045	£12,692	£19,892
Rebound assumption		Rebound to baseline	Rebound to conventional	£52,327	£26,817	£26,799	£24,458	£27,772
SAE disutility*	TNF-alpha inhibitors	0.01	0.1	£45,891	£21,432	£21,443	£19,423	£22,659
	Conventional therapy	0.01	0.1	£44,519	£21,144	£21,124	£19,003	£22,003
Annual BASFI progression	Conventional therapy	0.07	0.03	£54,545	£28,150	£28,128	£25,744	£29,132
			0.09	£40,435	£18,050	£18,030	£16,000	£18,867

All values were calculated using deterministic analyses. * varied for TNF-alpha inhibitor, kept same for conventional therapy and vice versa. ASAS, Assessment in Ankylosing Spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; SAE, serious adverse event; TNF, tumour necrosis factor.

Finally, the economic model considers etanercept with a dosing regimen of 50mg every week and certolizumab pegol with a dosing regimen of 400mg once monthly. There is no consensus in clinical practice as to which dose should be used. To test whether the assumption we used impacted the incremental cost-effectiveness of these TNF-alpha inhibitors, an additional analysis was conducted in which etanercept 25mg twice weekly and certolizumab pegol 200mg (every 2 weeks) was used. With the altered dosing frequencies, the ICER for etanercept 25mg versus conventional therapy was £21,984 (compared to £22,177 for etanercept 50mg) and the ICER for certolizumab pegol 200mg versus conventional therapy was £19,176 (compared to £19,153 for certolizumab pegol 400mg).

6.9. Validation

The model was based on that used in the manufacturer's submission for NICE TA233 and the model described by McLeod *et al*. 2007 (from NICE TA143). As stated during the appraisal of NICE TA233, the validation of the model was performed by two clinical experts, who were asked to evaluate a model analysis plan (containing a compilation of the main assumptions, model structure, and data sources). Changes were made to reflect the experience and knowledge of the clinicians. Following the review of the model in NICE TA233, amendments have been made to correct errors. The model was then validated by an independent health economist following these amendments.

6.10. Interpretation of the Economic Evidence

Infliximab is associated with an ICER of £43,432 when compared with conventional therapy. This value remained mostly robust when key assumptions in the model were tested through sensitivity analyses. An ICER lower than £30,000 was obtained when the upper bound of the long-term treatment costs of AS associated with the BASFI score were considered.

The economic analysis can be considered robust for a number of reasons. First, it is based on an approach which was developed for a NICE appraisal. Secondly, key elements of the model have been informed by RCT evidence in the appropriate patient population (from the GO-RAISE 5-year study). The availability of long-term data provided by the 5-year follow-up of GO-RAISE enhanced the robustness of the analysis by informing rates of long-term disease progression and discontinuation of treatment, thereby addressing a key criticism around the lack of long-term data identified in NICE TA233. Finally, the comparative efficacy of each TNF-alpha inhibitor was informed by an indirect comparison using the most recently published data; it is

important to note that the data produced by this NMA did not demonstrate any statistically significant differences between TNF-alpha inhibitors.

6.10.1. Opportunities for Resource Savings not Captured in the Modelling

Successful treatment of AS with infliximab has been linked to a reduction in hospitalisation and sick leave and with gains in productivity[22]. The current economic modelling framework does not capture the benefits of improved productivity, though in the era of Value Based Assessment, productivity gains are likely to be of key importance in decision-making. Additional benefits of infliximab include the patient support programme provided by MSD, which is designed to encourage patients to stay on their treatment thereby improving compliance and the likelihood of successful treatment outcomes, and the proven efficacy of infliximab in the management of IBD which is an EAM that can associated with AS and may increase the costs of effectively managing the disease. Finally, given appropriate local arrangements (i.e. vial sharing), infliximab could be a cost-effective resource for certain patients.

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