NICE National Institute for Health and Care Excellence

TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233)

Assessment Report

Commercial in Confidence stripped version for consultation

Produced by: CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York

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Assessment Group's Report
TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233)

Produced by CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York

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Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined

Table of Contents

Table of Tables

Table of Figures

List of abbreviations

ADA adalimumab

AE adverse event

AS ankylosing spondylitis

ASAS Assessment in Ankylosing Spondylitis

ATP Adalimumab Target Population

ASQoL Ankylosing Spondylitis Quality of Life

axSpA Axial spondyloarthritis

BASDAI Bath Ankylosing Spondylitis Disease Activity Index

BASFI Bath Ankylosing Spondylitis Functional Index

BASMI Bath Ankylosing Spondylitis Metrology Index

BASRI Bath Ankylosing Spondylitis Radiology Index

BNF British National Formulary

BSR British Society for Rheumatology

BSRBR British Society for Rheumatology Biologics Register

CEA cost-effectiveness analysis

CrI Credible interval

CIC commercial in confidence

CMA cost-minimisation analysis

CPI consumer price index

CRD Centre for Reviews and Dissemination

CUA cost–utility analysis

CZP certolizumab pegol

DCART disease-controlling antirheumatic treatment

DIC deviance information criterion

DMARD disease-modifying antirheumatic drug

EQ-5D EuroQol 5 Dimensions

ESR erythrocyte sedimentation rate

FBC full blood count

GDA Global Disease Activity

HCQ hydroxychloroquine

HLA human leucocyte antigen

HUI health utility index

HRQoL health related quality of life

ICER incremental cost-effectiveness ratio

IPD individual patient data

IQR interquartile range

ISPOR International Society forPharmacoeconomics and Outcomes Research

ITT intention-to-treat

LFT liver function test

LMA longitudinal meta-analysis

LRiG Liverpool Reviews and Implementation Group

MASES Maastricht Ankylosing Spondylitis Enthesitis Score

MFI Multidimensional Fatigue Inventory

mSASSS modified Stoke Ankylosing Spondylitis Spinal Score

MTX methotrexate

NA not applicable

NICE National Institute for Health and Clinical Excellence

NNH Number needed to harm

NR not reported

nr-axSpA Non-radiographic axial spondyloarthritis

NSAID non-steroidal anti-inflammatory drug

NYHA New York Heart Association

OLS ordinary least squares

OMERACT outcome measures in rheumatology

OR odds ratio

PBO placebo

p.a. per annum

PPP purchasing power parity

PSA probabilistic sensitivity analysis

QALY quality-adjusted life-year

QoL quality of life

RA rheumatoid arthritis

RCT randomised controlled trial

RR relative risk

SA sensitivity analysis

SAE Serious adverse event

SD standard deviation

SEM standard error of the mean

SF-36 MCS Short Form 36 mental component summary

SF-36 PCS Short Form 36 physical component summary

SIJ Sacroiliac joint

SMR standardised mortality ratio

SSZ sulfasalazine

TB tuberculosis

TNF tumour necrosis factor

U&E urea and electrolytes

VAS visual analogue scale

WMD weighted mean difference

Glossary

Adverse effect

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

Ankylosing spondylitis

A rheumatic disease that affects the spine and may lead to some degree of stiffness in the back. As the inflammation goes and healing takes place, bone grows out from both sides of the vertebrae and may join the two together; this stiffening is called ankylosis. If definite changes to spinal and/or pelvic joints are present on plain X-rays.

Articular

Of or relating to the joints.

Axial spondyloarthritis

The term axial spondyloarthritis refers to a form of arthritis in which the predominant symptom is back pain due to inflammation of spinal and/or pelvic joints. If definite changes on plain X-rays are

present, the disease is classified as ankylosing spondylitis, but if they are absent it is classified as non-radiographic axial spondyloarthritis. Further tests may indicate that in some patients non-radiographic axial spondyloarthritis is very likely to be ankylosing spondylitis, only at an earlier stage of disease.

Between-study variance

Between-study variance is a measure of statistical heterogeneity that depends on the scale of the outcome measured. It represents the variation in reported study effects over and above the variation expected given the within-study variation.

Biologic therapies (biological)

Medical preparations derived from living organisms. Includes anti-TNF drugs and other new drugs which target pathologically active T cells.

Biosimilar

An imitation biological medical product (such as an anti-TNF) usually marketed by a different manufacturer to the original biological product, once a patent has expired. The biosimilar should be similar to the original licensed product in terms of safety and efficacy.

Corticosteroid

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

Cost-benefit analysis

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

Cost-effectiveness analysis

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

Cost-utility analysis

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

Credible Interval

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

C-reactive protein (CRP)

Concentrations of this protein in the blood can be measured as a test of inflammation or disease activity, for example in AS and nr-axSpA.

Disease-modifying anti-rheumatic drugs (DMARDs)

DMARDs are drugs capable of modifying the progression of rheumatic disease. The term is, however, applied to what are now considered to be traditional disease modifying drugs, in particular sulphasalazine, methotrexate and ciclosporin, as well as azathioprine, cyclophosphamide, antimalarials, penicillamine and gold. The newer agent leflunomide may be included as a DMARD. The biologics such as etanercept and infliximab are not generally referred to as DMARDS.

Erythrocyte sedimentation rate (ESR)

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

Fixed-effect model

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

Heterogeneity

In systematic reviews heterogeneity refers to variability or differences between studies in the estimates of effects. A distinction is sometimes made between "statistical heterogeneity" (differences in the reported effects), "methodological heterogeneity" (differences in study design) and "clinical heterogeneity" (differences between studies in key characteristics of the participants, interventions or outcome measures).

I-squared (I^2)

I-squared (I^2) is a measure of "statistical heterogeneity" (differences in the reported effects). It varies between 0 and 1, where 0 indicates that the differences in reported effects are entirely consistent with the within-study uncertainty, and 1 indicates that the differences in reported effects are entirely explained by study characteristics that vary across studies.

Intention-to-treat

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

Monoclonal antibody

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

Non-steroidal anti-inflammatory drugs (NSAIDs)

Consists of a large range of drugs of the aspirin family, prescribed for different kinds of arthritis which reduce inflammation and control pain, swelling and stiffness.

Non-radiographic axial spondyloarthritis

Axial spondyloarthritis where definite changes to spinal and/or pelvic joints on plain X-rays are ***not*** present. Further tests may indicate that in some patients non-radiographic axial spondyloarthritis is very likely to be ankylosing spondylitis, only at an earlier stage of disease.

Open-label study

A type of study in which both participants and researchers know which treatment is being administered.

Placebo

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

Quality Adjusted Life Year (QALY)

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

Quality of Life

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

Random effects model

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

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

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

Relative Risk (RR) (synonym: risk ratio)

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

Sensitivity analysis

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

Tumor necrosis factor (TNF)

One of the cytokines, or messengers, known to be involved in the process of systemic inflammation.

Weighted mean difference (in meta-analysis)

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

1 Scientific Summary

1.1 Background

Spondyloarthritis (SpA) encompasses a heterogeneous group of inflammatory rheumatologic diseases. SpA can be categorised as having predominantly axial or peripheral involvement. In people with axial SpA (axSpA) the predominant symptoms are back pain and stiffness, developed before age 45. For axSpA patients to be classified as having ankylosing spondylitis (AS) imaging evidence of joint damage using X-rays is required. Patients with non-radiographic axSpA (nr-axSpA) may, or may not, have signs of sacroiliac joint inflammation on an MRI scan. The use of MRI allows for earlier detection of axSpA, since joint damage may not become evident on X-rays for many years. The prognosis for axSpA is poor, although there is some evidence that deterioration plateaus in well-established AS. Progression of the disease is difficult to predict. Conventional therapy for axSpA is limited to non-steroidal anti-inflammatory drugs (NSAIDs) and patient education and home or group exercises.

Tumour necrosis factor-alpha (TNF-α) inhibitors, also referred to as anti-TNFs, are typically used when the disease has not responded adequately to conventional therapy. Current NICE guidance recommends treatment with adalimumab, etanercept and golimumab in adults with active (severe) AS only if certain criteria are fulfilled, but it does not recommend infliximab for AS.[1, 2] Anti-TNFs for patients with nr-axSpA have not previously been appraised by NICE.

1.2 Objectives

To determine the clinical effectiveness, safety, and cost-effectiveness within the NHS of adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab, within their respective licensed indications, for the treatment of severe active AS, or severe nr-axSpA (but with objective signs of inflammation).

1.3 Methods

For the systematic review of clinical efficacy RCTs were eligible, including any open-label extensions. Adverse events data were sought from existing reviews of anti-TNFs used in any disease, and from other appropriately large studies. For studies of natural history, long-term effectiveness, adherence, and sequential use, published analyses based on large and long-term data sets (registry data) were eligible. Eligible studies were of adults with either severe active AS or severe nr-axSpA but with objective signs of inflammation (such as elevated C-reactive protein levels or a positive MRI scan). The treatments of interest were adalimumab, certolizumab pegol, etanercept, golimumab, infliximab or any of their biosimilars. The relevant comparators were conventional management strategies (either with or without placebo) and alternative anti-TNFs. Key outcomes included multiple

domain response criteria (such as ASAS 40) and measures of disease activity (BASDAI) and function (BASFI).

Fifteen databases were searched for relevant studies in July 2014. Clinical effectiveness data from RCTs were synthesised using Bayesian network meta-analysis methods. Sensitivity analyses were performed where trials at risk of bias were excluded. Results from other studies were summarised narratively.

A systematic review of cost-effectiveness studies was undertaken to assess the relevance of existing data from the perspective of the NHS. Searches were undertaken in the NHS Economic Evaluation Database (NHS EED), Medline and EMBASE. Only full economic evaluations that compared two or more options and considered both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) were included. The differences in the approaches and assumptions used across the studies were examined in order to explain any discrepancies in the findings and to identify key areas of uncertainty. A separate review of the manufacturer submissions was also undertaken and the findings compared with those found in the review of previously published studies.

The findings from the clinical and cost-effectiveness reviews were used to inform the development of a de-novo decision model to assess the cost-effectiveness of the alternative anti-TNFs in accordance with their licences for the separate indications. We developed a generalised framework for evidence synthesis that pools evidence on the change in BASDAI by considering both those studies that report this measure directly and also those that report the proportion of patients achieving a BASDAI 50 response (a ≥50% improvement in BASDAI score). We expressed BASDAI 50 as a function of the absolute change in BASDAI and we used this relationship in the extended synthesis. We also aimed to simultaneously synthesise information on BASFI (function) score, a measure that is used together with the BASDAI score to determine the long-term QALY and cost burden of the disease in the economic model. The decision model was developed in accordance with the NICE reference case. The model has a lifetime horizon (60 years) and considers costs from the perspective of the National Health Services and Personal Social Services. Health effects were expressed in terms of Quality-Adjusted Life Years (QALYs).

1.4 Results

Clinical efficacy from randomised controlled trials

After screening 2,284 titles and abstracts, 198 papers were assessed for inclusion and 28 eligible RCTs were identified, with 24 being suitable for data synthesis. All but two trials were placebo controlled (mostly up to 12 weeks). All but seven of the trials were extended into open-label active treatment-only phases. Most RCTs were judged to have a low risk of bias overall.

For the AS population the 10-16 week data showed consistent effects across the different anti-TNFs (when compared with placebo) for ASAS 20 the pooled relative risks (RR) ranging from 1.80 (certolizumab pegol) to 2.45 (infliximab); for ASAS 40 data the RRs ranged from 2.53 (certolizumab pegol) to 3.42 (adalimumab) and for BASDAI 50 the RRs ranged from 3.16 (adalimumab) to 4.86 (infliximab). Adalimumab, certolizumab pegol, etanercept and infliximab produced statistically significant and clinically important reductions in disease activity with BASDAI reductions ranging from 1.46 units (certolizumab pegol) to 2.28 units (infliximab), and function with BASFI reductions ranging from 1.1 units (certolizumab pegol) to 2.16 units (infliximab).

When analysed as a class anti-TNFs were statistically significantly more likely than placebo to result in patients with AS achieving an ASAS 20 response (RR 2.21), an ASAS 40 response (RR 3.06), and a BASDAI 50 response (RR 3.37).They also produced statistically significant improvements (calculated using mean difference in change from baseline) in: disease activity (BASDAI mean difference: -1.66 units) and function (BASFI mean difference: -1.38 units). There was little evidence of statistical heterogeneity for the key outcomes (ASAS outcomes, BASFI, BASDAI and BASDAI 50) but substantial heterogeneity was seen for other outcomes. Results of the sensitivity analyses performed for the AS studies were very similar to the main analyses.

For the nr-axSpA population five RCTs were included. When anti-TNFs were considered as a class, statistically significant improvements were found for ASAS 20 (RR 1.65); ASAS 40 (RR 2.74); BASDAI 50 (RR 2.31); BASDAI (mean difference -1.32 units); and BASFI (mean difference -0.99 units). For the disease activity, function, and responder outcomes, these common class efficacy estimates were consistently slightly smaller for nr-axSpA than for AS, most noticeably for BASFI and BASDAI 50. Statistical heterogeneity (where such estimates could be calculated) was apparent in the nr-axSpA analyses.

Long term efficacy

For AS the results showed that across all the anti-TNFs after approximately two years of treatment, around half of patients were still achieving a good level of response to therapy. Available data showed that at five years around 50% of patients were still achieving a good treatment response. However, the long-term studies produced less reliable data than the RCTs. Fewer studies were available of nr-axSpA patients, although the results were broadly similar to those seen in AS patients.

Evidence for an effect of anti-TNFs on radiographic disease progression was limited: the relatively short-term follow-up available to date and the insensitivity of x-rays as an imaging tool precluded the drawing of firm conclusions regarding the role of anti-TNFs in preventing or delaying the progression of AS; there is some data to suggest an identifiable benefit from around four years, but results from ongoing long-term studies should help to clarify this issue.

Registry data demonstrate that around 60% of patients with AS treated with a first anti-TNF will still be on treatment at 2 years. Sequential treatment with anti-TNFs can be worthwhile but the drug survival, response rates and benefits are reduced with 2nd and 3rd anti-TNFs, with the proportion of BASDAI 50 responders falling approximately 10% with each subsequent anti-TNF and the median BASDAI and BASFIs achieved increasing (worsening).

Adverse effects

Data from large systematic reviews, which included patients with a wide range of diseases, suggest that, in the short-term, anti-TNFs as a group are associated with significantly higher rates of serious infections, TB reactivation, non-melanoma skin cancer, total adverse events, and withdrawals due to AEs, when compared with control treatments. Specifically, infliximab is associated with significantly higher rates of total adverse events and withdrawals due to adverse events and that certolizumab pegol is associated with significantly higher rates of serious infections and serious adverse events. The available open-label data on adverse effects were limited by the small sample sizes and non-randomised study designs.

Cost-effectiveness reported in existing published studies and manufacturer submissions

The combined searches retrieved 210 citations. A total of six UK studies reporting on the cost-effectiveness of anti-TNFs for the treatment of AS were identified. No studies were identified for nr-axSpA. There appear marked differences between the results of the previously published industry-funded assessments in AS and the results reported in a previous independent assessment. Although all models reviewed used changes in BASDAI and/or BASFI to quantitatively model the short and longer-term costs and quality of life effects , there appeared significant variation in the assumptions employed. We identified important conceptual issues with all existing models relating to the subsequent projection of BASDAI and BASFI scores over a longer time-horizon.

Manufacturers submitted *de novo* analyses for both AS (AbbVie, UCB, Pfizer, MSD) and nr-axSpA (AbbVie, UCB, Pfizer) populations. Despite the different model structures and assumptions applied across the various manufacturer submissions, the ICERs reported for the anti-TNFs vs conventional care appeared consistent in AS. Across the separate base-case analyses, the incremental cost-effectiveness ratios (ICERs) ranged from £16,391 to £44,448 for the alternative anti-TNFs compared to conventional care alone. Infliximab was routinely reported to have the highest ICER. When infliximab was excluded from consideration, the ICERs ranged from £16,391 to £21,972 for the other anti-TNFs.

The differences in structural and parameter assumptions appear more evident in the cost-effectiveness results for the nr-axSpA population. The ICERs for adalimumab, certolizumab and etanercept ranged from between £12,866 and £50,692 per QALY. Importantly, when the results in the separate

populations were compared, no consistent relationship appeared to emerge across the manufacturer submissions regarding the cost-effectiveness on anti-TNFs in AS compared to the nr-axSpA population. Also, many of the same conceptual concerns identified from the review of published cost-effectiveness studies were also still evident.

An independent model was developed to address the conceptual concerns and areas of remaining uncertainty. Although it shared several of the assumptions and parameter estimates from the manufacturer models, it has a different conceptual structure (linking BASFI progression to evidence from radiographic assessments) and applies a more generalised framework for the synthesis of clinical effectiveness data.. The extended synthesis approach showed the effectiveness of the different anti-TNFs to be similar. Consequently, the treatment effects for the anti-TNFs were assumed to come from a 'common' distribution i.e. a 'class effect'. We developed a simulation model that allowed prediction of the conditional change scores for responders/non-responders to BASDAI50 at 12 weeks and to explore differences in the baseline BASDAI/BASFI scores according to response status.

Base-case cost-effectiveness results were presented for two alternative 'rebound' assumptions. In the rebound equal to gain scenario, the ICER of the alternative anti-TNFs varied between £19,240 (certolizumab with the proposed PAS) to £40,467 per additional QALY (infliximab) in AS patients. In the rebound to conventional care scenario, the ICER of the alternative anti-TNFs varied between £33,762 (certolizumab with the proposed PAS) to £66,529 per additional QALY (infliximab) in AS patients.

In the rebound equal to gain scenario, the ICER of the alternative anti-TNFs for nr-axSpA patients varied between £28,247 (certolizumab with the proposed PAS) to £29,784 per additional QALY (etanercept) in AS patients. In the rebound to conventional care scenario, the ICER of the alternative anti-TNFs for nr-axSpA patients varied between £32,528 (certolizumab with the proposed PAS) to £34,232 (etanercept) per additional QALY.

1.5 Discussion

The key strengths of the systematic review are the rigorous methods used, and the extensive breadth of the types of study included. The York model confers several advantages over current cost-effectiveness studies by linking changes in function to a more explicit clinical/biological process and facilitating a more formal consideration of the potential impact of anti-TNFs on function, via the specific effects these drugs have on the different processes which independently relate to this parameter.

The meta-analysis results derived from a substantial and generally high quality evidence-base demonstrated that anti-TNFs produce clinically important benefits to AS patients in terms of

improved function and reduced disease activity. Smaller benefits were seen across outcomes in patients with nr-axSpA, which was a more heterogeneous population. Less reliable data were available on long-term efficacy, though it appears that around half of patients still achieve a good level of response after around two years of treatment.

Although there are a number of important differences in approaches both amongst the different manufacturer models and compared to the York model, the comparison of ICERs based on the York rebound equal to gain scenario appear broadly consistent with those reported by the manufacturers in both populations.

1.6 Conclusions

- In both AS and nr-axSpA populations anti-TNFs produce clinically important benefits to patients in terms of improving function and reducing disease activity. The efficacy estimates were consistently slightly smaller for nr-axSpA than for AS.
- Statistical (and clinical) heterogeneity was more apparent in the nr-axSpA analyses than in the AS analyses; both the reliability of the nr-axSpA meta-analysis results and their true relevance to patients seen in clinical practice are questionable.
- In AS anti-TNFs can be assumed to have a class effect, with the treatments being equally effective.
- Effectiveness appears to be maintained over time in about 50% of patients at 2 years.
- Evidence for an effect of anti-TNFs delaying disease progression was limited; results from ongoing long-term studies should help to clarify this issue.
- Sequential treatment with anti-TNFs can be worthwhile but the drug survival, response rates and benefits are reduced with 2nd and 3rd anti-TNFs.
- The de novo model, which had addressed many of the issues of earlier evaluations, generated ICERs ranging from £19,240 to £66,529 depending upon anti-TNF and modelling assumptions.

Suggested research priorities

Randomised trials are needed to identifying the nr-axSpA population who will benefit the most from anti-TNFs. Long-term studies are needed to clarify the effect of anti-TNFs on the progression of structural damage in AS, and to help clarify the characteristics of nr-axSpA patients who go on to develop AS. Studies are also needed to better inform the efficacy estimates relating to sequential use of anti-TNFs

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2 Background

2.1 Description of health problem

Spondyloarthritis (SpA) encompasses a heterogeneous group of inflammatory rheumatologic diseases including ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis, inflammatory bowel disease-related arthritis and undifferentiated SpA.[3] SpA can be categorised as having predominantly axial (sacroiliac joints or spine) or peripheral involvement. In people with axial SpA (axSpA), the predominant symptom is back pain (due to inflammation of the sacroiliac joints, the spine, or both) but there may also be extra-articular and peripheral joint manifestations.

In practice, and in clinical trials, AS is commonly diagnosed using the modified NY criteria (Box 1); sometimes in practice radiographs may not be performed routinely (because of the radiation doses involved) or MRI may be preferred as a diagnostic tool. The recently developed Assessment of SpondyloArthritis International Society (ASAS) classification criteria encompass a broad range of patients with axSpA, including patients with AS and patients with non-radiographic axSpA (nr-axSpA).[4] All axSpA patients will have developed chronic back pain (≥ 3 months) before age 45. Classifications can be made using the imaging or clinical arms of the criteria. The imaging arm requires evidence of joint damage (erosions or fusion) due to sacroiliitis, either using X-rays (when the disease is classified as AS) or MRI (when the disease is classified as non-radiographic axSpA (nr-axSpA));[5] additionally at least one of the following SpA features is also required: inflammatory back pain, arthritis, enthesitis (heel), uveitis, dactylitis, psoriasis, Crohn's/colitis, good response to NSAIDs, family history of SpA, HLA-B27 genetic marker, and elevated CRP. People with axSpA often have the genetic marker human leukocyte antigen (HLA)-B27. To be classified as having axSpA via the clinical arm of the criteria patients have to be HLA-B27 positive and also have at least three of the aforementioned SpA features.

Box 1. Modified New York criteria for ankylosing spondylitis (1984)*

Clinical criteria:	**Radiological criterion:**
– Low back pain and stiffness for more than 3 months that improves with exercise, but is not relieved by rest. – Limitation of motion of the lumbar spine in the sagittal and frontal planes. – Limitation of chest expansion relative to normal values correlated for age and sex.	– Sacroiliitis grade >2 bilaterally or grade 3–4 unilaterally. Definite AS if the radiological criterion is associated with at least one clinical criterion

*[6]

The use of MRI allows for earlier detection of axSpA, since joint damage may not become evident on X-rays for many years. Patients with nr-axSpA may, or may not, have signs of sacroiliac joint inflammation on an MRI scan. There may be other objective signs of inflammation such as an abnormally raised erythrocyte sedimentation rate (ESR) or C-Reactive protein (CRP) level, though

these are less sensitive and specific for AS. An MRI diagnosis may therefore provide the opportunity for treatment to reduce the possibility of long-term structural damage (and associated burden of symptoms).[7] However, there is some concern that the diagnostic criteria for nr-axSpA may be too liberal and may include patients who do not have axSpA and will never progress to AS, particularly with respect to patients who are diagnosed without evidence of imaging (MRI) changes.[8-10]The differences between AS and nr-axSpA are explored further in Section 4.

Prognosis

AxSpA is a painful, progressive form of inflammatory arthritis. It mainly affects the spine but can also affect other joints, tendons and ligaments. Other areas such as the eyes and bowel can also sometimes be involved in non-radiographic and radiographic (AS) forms of axSpA.[11] The pain and stiffness of axSpA adversely affects optimal daily functioning. These symptoms are due to a combination of reversible components of the disease such as inflammation and flares, and irreversible components such as syndesmophytes and vertebral bridging (bony deposition).[12] Most patients with AS develop the first symptoms at 25-45 years of age.[13] Progression of the disease is variable, and difficult to predict.[14] There is often a delay of many years between patients first noticing symptoms, and receiving a diagnosis of axSpA. Many people with axSpA have AS, with evidence of bony deposition as well as inflammation. In later-stage AS joints and bones may fuse together, a process that can occur over a long period of time and cause restricted movement. The functional impairment due to inflammation and/or bony deposition can have a profound effect on health and quality of life and lead to withdrawal from active employment, with resultant adverse financial consequences; the burden of disease is greater in more socially-deprived patients[15] The prognosis is poor although there is some evidence that deterioration plateaus in well-established AS.[16]Paradoxically early disease (nr-axSpA) may be less readily diagnosed and patients offered fewer treatment options even though it can be as, or even more, debilitating that established AS.[17]

Ankylosing spondylitis is associated with an increased risk of death: it is estimated that patients have a standardised mortality ratio (SMR) of 1.5 or greater. The increased risk appears to be greater in men, with one study reporting a statistically significant increase in SMR of 1.63 in men but no significant increase in women (SMR 1.38) with AS.[18] This study found that, after correcting for age, gender, disease duration and pre-existing cardiovascular disease, independent predictors of increased mortality were: elevated CRP, diagnostic delay, not using NSAIDs, and work disability. According to British Society for Rheumatology (BSR) guidelines, the excess mortality is mainly accounted for by cardiac valvular disease, amyloidosis and fractures.[1] Non-radiographic axSpA affects approximately equal numbers of men and women, but men are more likely to develop AS.[19]

Epidemiology

Currently, only limited epidemiological data are available for axSpA defined according to ASAS criteria. For AS, the prevalence is thought to be around 0.25% in European populations.[20] It is around three times more common in men than in women.[21] A recent study published in the US reported an estimated AS prevalence of 0.52-0.55%, and the prevalence of axSpA as approximately 1.0-1.4%.[22] The proportion of nr-axSpA among patients with axSpA is estimated to be between 20-80%.[23] Each year in the UK, an estimated 2% of patients in a general practice will present with back pain, and up to 5% of these will show features of AS.[24]

Measurement of disease

There are a number of components and measures of disease activity in axSpA:[25] a patient's health related quality of life is determined by both by physical functioning and by disease activity. In turn, physical function is determined by spinal mobility and disease activity, and spinal mobility is determined by structural damage and inflammation of the spine.[25] In nr-axSpA a patient may have significant inflammation but no detectable structural damage, in AS a patient may have both significant inflammation and structural damage, and in late AS there may be less inflammation but extensive structural damage.

The main tools used for the assessment of various components of the disease are listed in Table 1.

Table 1 Disease assessment tools

Assessment measures		
Tool	Disease component	Description
BASDAI - Bath Ankylosing Spondylitis disease activity Index	Disease activity	Consists of a 1 through 10 scale (one being no problem and 10 being the worst problem) which is used to answer 6 questions pertaining to the 5 major symptoms of AS: Fatigue Spinal pain Joint pain / swelling Areas of localized tenderness (also called *enthesitis*, or inflammation of tendons and ligaments) Morning stiffness duration Morning stiffness severity
BASFI Bath Ankylosing Spondylitis Functional Index (BASFI)	Functional ability	Patient assesses difficulty on a ten point scale (1 is easy and 10 is impossible) for each of 10 items: Putting on your socks or tights without help or aids (e.g. sock aid Bending from the waist to pick up a pen from the floor without aid. Reaching up to a high shelf without help or aids (e.g. helping hand). Getting up from an armless chair without your hands or any other help. Getting up off the floor without help from lying on your back. Standing unsupported for 10 minutes without discomfort. Climbing 12-15 steps without using a handrail or walking aid. Looking over your shoulder without turning your body. Doing physically demanding activities (e.g. physiotherapy exercises, gardening or sports). Doing a full day's activities whether it be at home or at work.

BASMI - Bath Ankylosing Spondylitis Metrology index	Disease activity Spinal mobility	Clinician assessment of: cervical rotation, tragus to wall distance, lumbar side flexion, modified Schober's, intermalleolar distance
ASDAS	Disease activity	Calculated from BASDAI questions on spinal pain, peripheral arthritis, and duration of morning stiffness, patients global assessment of disease activity, and CRP (or ESR if CRP not available)
mSASSS	Structural damage	In the mSASSS the anterior vertebral corners of the cervical (lower border of C2 to upper border of T1) and lumbar (lower border of T12 to upper border of S1) segments (a total of 24 VCs) are scored at a lateral view, for the presence of erosion and/or sclerosis and/or squaring (1 point), syndesmophyte (2 points) and bridging syndesmophyte (3 points). The total score ranges from 0 to 72. The mSASSS has shown better reliability and sensitivity to change than other radiographic scoring methods.[26]
MRI assessments		
Measures of response		
BASDAI 50	Response criterion	≥50% improvement in BASDAI
ASAS 20	Response criterion	≥20% improvement and ≥1 unit absolute improvement (range 1-10) in 3 of 4 domains: BASFI, Spinal pain, Patient GDA and inflammation (BASDAI Q5 and 6), with no worsening of ≥20% improvement and ≥1 unit absolute in the 4th domain.
ASAS 40	Response criterion	≥40% improvement and ≥2 units absolute improvement (range 1-10) in 3 of 4 domains: BASFI, Spinal pain, Patient GDA and inflammation (BASDAI Q5 and 6), with no worsening at all in the 4th domain.
ASAS partial remission	Response criterion	A value of ≥2 units absolute improvement (range 1-10) in each of 4 domains: BASFI, Spinal pain, Patient GDA and inflammation (BASDAI Q5and 6).
ASAS 5/6	Response criterion	Improvement in 5 out of 6 domains (using pre-defined % improvements) without deterioration in the 6th domain: Pain, Patient global assessment, function, inflammation, spinal mobility, CRP
ASDAS major improvement	Response criterion	≥2 units improvements in ASDAS

Placebo response

The term 'placebo effect' can be used to describe different types of 'effect' but it generally encompasses one or more of three different meanings. Firstly, there is the temporal (before-after) change after placebo medication, in which the effects of a placebo intervention cannot be distinguished from the natural course of the disease, or regression to the mean. Secondly, there is the causal effect of placebo intervention associated with the treatment ritual, and finally the effect of all the psychological processes involved in the interaction between doctor and patient[27]For the placebo-controlled trials in AS and nr-axSpA these non-pharmacological components can be assumed to act equally in the anti-TNF and placebo arms. Results from the placebo arms measure the non-pharmacological effects and the difference between the anti-TNF and placebo arms measures the pharmacological effect. All three components of the placebo effect could be important to consider when evaluating trials in this assessment, although once the trial treatment periods have ended it is likely that the effect of the natural course of the disease becomes the most important factor of any

'placebo' effect. Estimated cost-effectiveness ratios and associated policy decisions may be sensitive to assumptions regarding the mechanism underlying placebo responses.[28]

The natural course of disease activity in AS is known to vary over time with exacerbations, or flares, being common. In a study of flares in patients with AS, clinically relevant changes in BASDAI (but not in function) were noted during minor/localised flares (which occurred in 59% of patients in any given week). Although major/generalised flares were less common (reported in 12% of patients in any given week) they were associated with clinically relevant changes in both disease activity *and* function.[29] Pain is a key component of BASDAI and the ASAS responder outcomes; a Cochrane systematic review of placebos for all clinical conditions found that placebo interventions can influence patient-reported outcomes, especially pain (and nausea).[30] The authors also concluded that it was difficult to distinguish patient-reported effects of placebo from biased reporting, and that the effect on pain varied from negligible to clinically important, even among trials with low risk of bias.

2.2 Current service provision

Management of disease

Short- and long-term treatment goals for axSpA include minimising pain and stiffness, maintaining function and posture, arresting disease progression and maintaining quality of life and ability to work. Current conventional therapy for axSpA includes acute anti-inflammatory treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy and exercise.

Conventional therapy for AS is limited to NSAIDs (despite very limited supporting clinical trial evidence)[31]and recommendations regarding appropriate physical activity. Other statements in the ASAS/EULAR recommendations for the management of AS include: analgesics such as paracetamol and opioid-like drugs may be considered for residual pain. Glucocorticoid injections into the direct site of inflammation (but not systemic) may be of benefit. The use of disease-modifying anti-rheumatic drugs (DMARDs, such as methotrexate and sulfasalazine) has been all but abandoned after evidence of lack of benefit. 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. A Cochrane review of 11 trials concluded that the current best available evidence suggests that physiotherapy is beneficial for people with AS, but that it is still not clear which treatment protocol, duration and intensity, should be recommended in the management of AS.[32] Physiotherapy is universally recommended [33] but variable in practice.

Biologic drugs are the only treatment shown to be efficacious in the treatment of symptoms and signs of disease activity in axSpA and AS. Current NICE and BSR guidance recommends treatment with

the anti-TNFs adalimumab, etanercept and golimumab in adults with active (severe) AS only if certain criteria are fulfilled, but it does not recommend infliximab for AS.[1, 2]

2.3 Description of technology under assessment

Tumour necrosis factor-alpha (TNF-alpha) inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), also referred to as anti-TNFs, are typically used when the disease has not responded adequately to conventional therapy. They target the activation of tumour necrosis factor-alpha (TNF-alpha) and its subsequent activation of downstream inflammatory processes, and as such have the potential to offer symptom control as well as altering disease progression. Adalimumab, certolizumab pegol, golimumab and infliximab are monoclonal antibodies, whereas etanercept is a recombinant human TNF receptor fusion protein.

Adalimumab, etanercept, golimumab and infliximab are licensed in the UK for the treatment of adults with severe active AS that has responded inadequately to conventional therapy. Certolizumab pegol is licensed for the treatment of adults with severe active AS whose disease has responded inadequately to, or who are intolerant of, NSAIDs.

Adalimumab, etanercept and certolizumab pegol are also licensed for the treatment of adults with severe nr-axSpA with objective signs of inflammation (including elevated C-reactive protein (CRP) and/or positive MRI), whose disease has responded inadequately to, or who are intolerant of NSAIDs. Golimumab and infliximab do not currently have a UK marketing authorisation for nr-axSpA. Current NICE guidance recommends treatment with adalimumab, etanercept or golimumab in adults with active (severe) AS only if certain criteria are fulfilled (including a stipulation that patients must have tried at least two different NSAIDs, which have failed to control symptoms), but it does not recommend infliximab for AS.[1, 2] Anti-TNFs for patients with nr-axSpA have not previously been appraised by NICE.

3 Definition of decision problem

3.1 Decision problem in terms of PICOS and other key issues

The decision problem relates to the optimal use of adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab, within their respective licensed indications, for the treatment of severe/active ankylosing spondylitis, or severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (but with objective signs of inflammation).

3.2 Previous NICE appraisals

In the previous NICE Technology Appraisal TA143, adalimumab, etanercept and infliximab were evaluated for AS, while in TA233 golimumab was evaluated for AS. A number of key areas of

uncertainty and potential limitations of the evidence base were identified from these appraisals. These include:

1. A lack of direct head-to-head trial evidence evaluating the relative efficacy and safety of the TNF-alpha inhibitors;
2. A lack of evidence on the efficacy and safety of the sequential use of TNF-alpha inhibitors;
3. The long-term effectiveness of TNF-alpha inhibitors in controlling disease activity;
4. The rate of disease progression in responders and non-responders to treatment, and those on placebo;
5. The proportion of patients who may experience a significant improvement in their condition without TNF-alpha inhibitor treatment;
6. The rate of treatment withdrawal on TNF-alpha inhibitors and the degree to which a patient's condition might be expected to rebound if therapy is withdrawn;
7. The adverse effects associated with the long-term use of TNF-alpha inhibitors;
8. The impact of TNF-alpha inhibitors on the progression of structural damage in the spine and functional disability associated with ankylosis;
9. The time horizon appropriate for considering the cost-effectiveness of TNF-alpha inhibitors;
10. A lack of registry data of patients receiving TNF-alpha inhibitors for severe active AS.

This assessment would consider each of these areas of uncertainty and identify the relevant evidence available to inform the limitations of the previous appraisals.

3.3 Overall aims and objectives of assessment

The aim of the study is to determine the clinical effectiveness, safety, and cost-effectiveness within the NHS of adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab, within their respective licensed indications, for the treatment of severe active ankylosing spondylitis, or severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (but with objective signs of inflammation). If evidence allows, the clinical- and cost-effectiveness of sequential use of these treatments will also be evaluated.

4 Assessment of Clinical Effectiveness

4.1 Methods for reviewing effectiveness

4.1.1 Inclusion criteria

Two reviewers independently screened all titles and abstracts. Full manuscripts of any titles/abstracts that were relevant were obtained where possible and the relevance of each study assessed by two reviewers according to the criteria below. Any discrepancies were resolved by consensus and, when necessary, a third reviewer was consulted. Studies available only as abstracts were included.

Study design

For the review of clinical efficacy RCTs were eligible, including any open-label extensions of RCTs. Adverse events data were sought from existing reviews and other appropriately large studies. For studies of natural history, long-term effectiveness, adherence, and sequential use, published analyses based on large and long-term data sets (including studies of registry data) were eligible.

Interventions

Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab or any of their biosimilars were eligible.

Comparators

Relevant comparators were conventional management strategies (either with or without placebo) and also the different TNF-alpha inhibitors listed above (i.e. head-to-head trials).

Participants

Studies of adults with either severe active ankylosing spondylitis or severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation (such as elevated C-reactive protein levels or a positive MRI scan) were eligible. Patients with predominantly peripheral spondyloarthritis were excluded. Data relating to serious adverse effects associated with anti-TNF agents used in other indications were also considered.

Outcomes

Studies reporting the following outcomes were eligible:

- Multiple domain response criteria: (e.g. ASAS 20, ASAS 40, ASAS 5/6 and ASAS partial remission)
- Disease activity (e.g. BASDAI)
- Functional capacity (e.g. BASFI)
- Disease progression (e.g. mSASSS)
- Pain (e.g. VAS scores)
- Peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis)
- Symptoms of extra-articular manifestations (including anterior uveitis, inflammatory bowel disease and psoriasis)
- Health-related quality of life (e.g. EQ-5D)
- Rates of treatment discontinuation and withdrawal
- Adverse events

For adverse events the evaluation specifically focussed on known possible adverse events of anti-TNFs, such as reactivation of latent tuberculosis, malignancies, non-melanoma skin cancer, severe

infections, congestive heart failure, and injection site reactions. Withdrawals due to adverse events, and events categorised as serious adverse events were also evaluated.

4.1.2 Searches

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

- MEDLINE
- EMBASE
- CINAHL Plus
- Science Citation Index
- ClinicalTrials.gov
- Cochrane Central Register of Controlled Trials
- Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effects
- International Prospective Register of Systematic Reviews (PROSPERO)
- Health Technology Assessment Database
- Conference Proceedings Citation Index - Science
- National Guidelines Clearinghouse
- NHS Evidence
- NHS Clinical Knowledge Summaries
- NHS Economic Evaluation Database

The terms for search strategies were identified through discussion within the research team, by scanning the background literature and browsing the Medline Medical Subject Headings (MeSH). No date or language limits were applied. As several databases were searched, some degree of duplication resulted. To manage this issue, the titles and abstracts of bibliographic records were imported into Endnote bibliographic management software to remove duplicate records. The full search strategies used in each database are listed in Appendix 1.

4.1.3 Data extraction

Data relating to study design, outcome results and quality were extracted by one reviewer using a standardised data extraction form and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus, and when necessary, a third reviewer was consulted. Data from studies with multiple publications were extracted and reported as a single study. Data were also extracted from the manufacturer submissions when they were not available from other sources. Clinicaltrials.gov records and relevant FDA or EMA reports were also used to extract any missing data. Where data could only be estimated from graphs, the estimates used in the previous assessment report[34] were used when available. In light of the multi-domain outcomes which incorporated pain

scores (the ASAS and BASDAI outcomes), it was decided that pain scores on their own would not be extracted.

4.1.4 Critical appraisal

The quality of RCTs was assessed using the Cochrane risk of bias tool,[35] with additional assessments made for baseline imbalance of important prognostic indicators.[36] The relevant prognostic and treatment response indicators were identified from both published research and clinical advice. The risk of bias assessments were performed by one reviewer, and independently checked by a second. Disagreements were resolved through consensus, and when necessary, a third reviewer was consulted. Open-label extension studies were evaluated based on the imputation methods and patient withdrawal criteria used.

4.1.5 Methods of data synthesis

This section describes the data set construction and meta-analyses conducted for the different outcomes individually. Section 6 provides detailed evidence synthesis methods that incorporate different outcomes within one analysis, and presents clinical outcome estimates appropriate for the economic model.

Results of the data extraction in terms of study characteristics and quality assessment are presented in Tables and summarised narratively. Results of open-label studies, drug survival and switching studies, and natural history studies were also summarised narratively. Since several of the RCTs were placebo-controlled up to 24 weeks, only time points beyond 24 weeks were evaluated in the open-label studies. Adverse event data from the RCTs were pooled when enough data was identified, otherwise the adverse event data and the other studies relating specifically to adverse events were summarised narratively.

Clinical effectiveness data were synthesised using Bayesian meta-analysis methods. The main analysis was of outcomes reported from 10 to 16 weeks. A sensitivity analysis was done of outcomes reported from 24 to 30 weeks.

Dosage and pooling of trial arms

The doses included in the analyses were:

- adalimumab: 40mg every other week,
- certolizumab pegol: 200mg every 2 weeks, 400mg every 4 weeks
- etanercept: 25mg twice weekly, 50mg weekly
- golimumab: 50mg every month
- infliximab: 5mg/kg at 0,2,6 + weeks

Golimumab of 100mg every 4 weeks was excluded when it was not used according to its licence.

Data from active treatment arms were pooled in trials which studied different doses. This occurred for certolizumab pegol 200mg every 2 weeks and 400mg every 4 weeks; and etanercept 25mg twice weekly and 50mg weekly.

Data imputation and assumptions

Medians were treated as means. Although the median may not be exactly the same as the mean, the median was considered to give sufficiently accurate information. Standard deviations were estimated from inter-quartile ranges, the method of which is described in Appendix 2. Where no standard deviation was reported, the highest standard deviation from the other trials was used as a conservative estimate.

In the meta-analyses, 'change from baseline' outcomes were used in the analysis for continuous outcomes. Where these were not reported, but adequate baseline and final value outcomes were reported, the change from baseline and its standard deviation were derived from the baseline and final values and their standard deviations. The detailed methods are described in Appendix 2.

The imputation of change from baseline or final values required a within-trial correlation estimate, and trials that reported the standard deviations of baseline, change from baseline and final values were used to estimate the within-trial correlation. For BASDAI the within-study correlation varied from 0.33 to 0.67 across four trials. Given the small samples of some trials the within-study correlation can vary significantly from trial to trial. For the base case analysis, a correlation estimate of 0.3 was used and an estimate of 0.7 was tested in sensitivity analysis. For the calculation of final values, the lowest possible correlation was used when 0.3 or 0.7 were not feasible solutions (see Appendix 2).

Change from baseline was imputed for three trials for BASDAI, five trials for BASFI, one trial for BASMI, two trials for SF-36pcs, and one trial for SF-36mcs. For each of these outcomes, one of the imputations was for a trial with a non-radiographic population.

Binary event outcomes

Odds ratios were derived for binary event outcomes. Relative risks were also derived from the odds ratios using the placebo absolute risks estimated from all the trials measuring the relevant outcome within weeks 10 to 16. The relative risk estimates are therefore based on the population distribution of the trials across the interventions. As the placebo absolute risk was based on more trials than those informing the odds ratios for some outcomes, the 95% credible interval estimates of the relative risk were narrower than the credible interval estimates of the odds ratio. The placebo absolute risk was estimated using both fixed- and random-effect models within WinBUGS. Since the random- effect model for the placebo absolute risk was a better fit than the fixed effect model according to the DIC

statistic, the placebo absolute risks from the random effect models were used. For the ASAS outcomes, fewer trials reported the greater response outcomes, so a prior distribution was used for the between-study standard deviation based on the closest ASAS outcome (see Appendix 2).

Analyses

Analyses were conducted in WinBUGS. See Section 6 for more details on the models. For each outcome, multiple-treatment meta-analyses were conducted assuming that the treatments had independent effects (related to models A1 (fixed effect) and A2 (random effects) in Section 6). They were also run assuming that they had a common class effect (related to models A3 (fixed effect) and A4 (random effects) in Section 6), and the DIC statistic was used to determine the model that best fitted the data. The random effect models with independent treatment effects were assumed to have a common between-study variance across the comparisons in the network.

The sensitivity of random effect models to the between-study standard deviation priors was tested. I^2 statistics for heterogeneity were calculated for random effect models that were insensitive to change in the prior distribution for the between-study standard deviation. Results for random effect models when the results were not sensitive to prior distributions.

4.2 Clinical Effectiveness Results

4.2.1 Quantity and quality of research available

The electronic database searches identified 2,284 references. After screening titles and abstracts, full copies of 198 papers were assessed for inclusion in the review. Three trials of axSpA populations were excluded because results were not available separately for the ankylosing spondylitis and nr-axSpA populations.[37-39] One study of adalimumab appeared likely to be eligible, but was excluded as it was only available as a ClinicalTrials.gov record, without any results or further study details.[40] One excluded study was an ongoing trial of golimumab (called GO-AHEAD).[41]

Twenty-eight eligible RCTs were identified, with 24 being suitable for data synthesis. Three etanercept trials were not suitable for data synthesis because the study durations were only six weeks,[42-44] and one infliximab trial was unsuitable because a (currently) unlicensed dose (3mg/kg) had been studied.[45] The Barkham 2009 trial of infliximab in nr-axSpA patients (see Table 2) was included in the clinical efficacy section because, even though infliximab is not currently licensed for patients with nr-axSpA, the dose used in this trial was the same as that licensed for AS. Furthermore, there was no reason to think it could not be considered in the same class as the other anti-TNFs when treating a nr-axSpA population. The results of the trial therefore had the potential to be useful to help inform the relative efficacy of anti-TNFs for nr-axSpA.

Of the seventeen RCTs in which participants were studied beyond the randomised phase (i.e. in open-label studies) 71 additional full publications or conference abstracts were identified. Figure 1 illustrates the flow of studies through the review process.

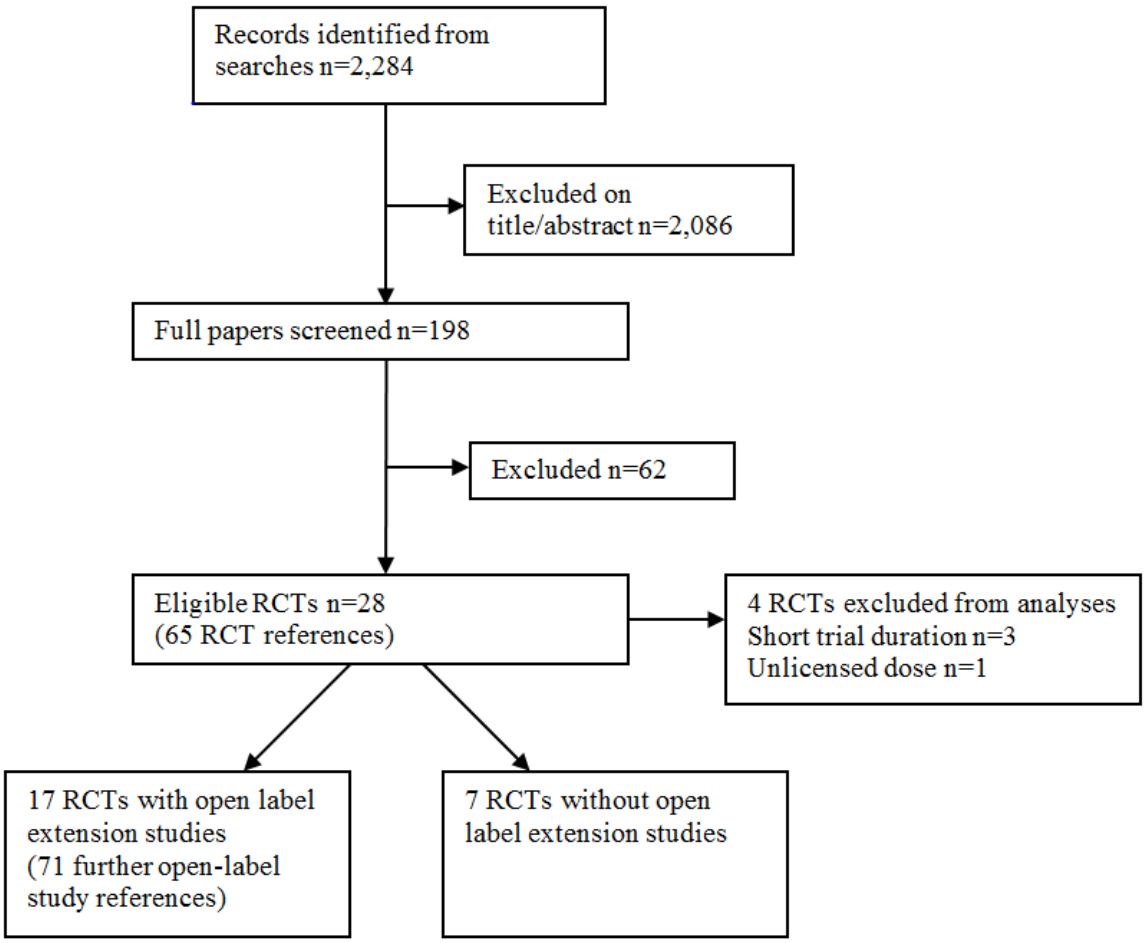


Figure 1 Flowchart showing the number of studies identified and included

Study characteristics

Table 2 lists the 24 eligible RCTs (and all the RCT-related references) which were eligible for inclusion in the network meta-analysis. Six trials compared adalimumab versus placebo, one compared certolizumab pegol versus placebo, seven compared etanercept versus placebo, three compared golimumab versus placebo, five compared infliximab versus placebo, one compared etanercept with infliximab and one compared infliximab with an infliximab biosimilar (Inflectra). Most placebo-controlled phases lasted for 12 weeks. All but seven of the trials were extended into open-label (unblinded) phases, with 11 studies having a total duration of at least a year.

Of the trials suitable for analysis, most were conducted in Europe and/or North America; four were conducted in China. Four studies recruited a nr-axSpA population, 19 an ankylosing spondylitis population and one recruited both populations.[46] Table 3 details the baseline characteristics of the populations studied. In the nr-axSpA studies around half the participants were male, whereas in the AS studies around three-quarters were male. All trials recruited participants with active disease: half the trials specified that participants had to have failed one or more NSAID, and a BASDAI score of ≥4 was used as an entry requirement in most, with the exception of six early trials where a BASDAI criterion was not stated. [47-51]Notwithstanding these entry criteria, the recruited participants mostly still took an NSAID (between around 80-90% of participants, though reported in only 12 trials) and had quite high mean (or median) BASDAI scores: most were between 5.5 and 6.5 (the range across all trial arms was 5.3 to 7). BASFI scores varied more widely, ranging between 3.2 and 6.7. Variation in CRP levels was also apparent, with lower values in the nr-axSpA trials being evident. Trials which reported both mean and median CRP showed skewed distributions, with means being higher than medians.[46, 52, 53] The upper limits of normal used for defining elevated CRP in the nr-axSpA trials were either unclear[52] or varied, being 3mg/l,[54] 6mg/l[55]or 7.9mg/l.[46] One nr-axSpA study recruited only MRI-positive patients.[56] In the remaining nr-axSpA trials the proportion of MRI-positive patients ranged from 51%[52] to 81%.[54]

Table 2 General trial characteristics

Study	Interventions	Anti-TNF dose	Country/ Continent	Population	Duration of placebo-controlled phase (weeks)	Total duration of study, including any open-label extension phase
Haibel 2008[55, 57, 58]	Adalimumab Placebo	40mg every other week	Germany	nr-axSpA with inflammation Inadequate response /intolerance to NSAIDs	12	1 year
Hu 2012[59]	Adalimumab Placebo	40 mg every other week	China	Ankylosing spondylitis Inadequate response /intolerance to NSAIDs	12	24 weeks
Huang 2014[60]	Adalimumab Placebo	40 mg every other week	China	Ankylosing spondylitis Inadequate response /intolerance to NSAIDs	12	24 weeks
Lambert 2007[61]	Adalimumab Placebo	40 mg every other week	Canada	Ankylosing spondylitis Inadequate response to an NSAID or DMARD	12	1 year
ABILITY-1 2013[52, 62]	Adalimumab Placebo	40mg every other week	Australia, Europe, North America	nr-axSpA with inflammation Inadequate response/ contraindication to NSAIDs	12	3 years
ATLAS 2006[63-65]	Adalimumab Placebo	40 mg every other week	USA, Europe	Ankylosing spondylitis Inadequate response to an NSAID or DMARD	12	5 years
RAPID-axSpA 2014[46, 66-71]	Certolizumab pegol Placebo	200mg every 2 weeks, or 400mg every 4 weeks	Europe, North America, Latin America	Ankylosing spondylitis nr-axSpA with inflammation Inadequate response /intolerance to NSAIDs	12	96 weeks
Barkham 2010[72]	Etanercept Placebo	25mg twice weekly	UK	Ankylosing spondylitis	12	12 weeks
Davis 2003[47, 73]	Etanercept Placebo	25mg twice weekly	North America, Europe	Ankylosing spondylitis	24	168 weeks

Study	Interventions	Anti-TNF dose	Country/ Continent	Population	Duration of placebo-controlled phase (weeks)	Total duration of study, including any open-label extension phase
Dougados 2011[74, 75]	Etanercept Placebo	50mg weekly	Europe	Ankylosing spondylitis Inadequate response to NSAIDs	12	24 weeks
Dougados 2014[54, 76, 77]	Etanercept Placebo	50mg weekly	Europe, Asia, South America	nr-axSpA Inadequate response to NSAIDs	12	48 weeks
Gorman 2002[49, 78-80]	Etanercept Placebo	25mg twice weekly	USA	Ankylosing spondylitis	16	40 weeks
Calin 2004[48, 81, 82]	Etanercept Placebo	25 mg twice weekly	Europe	Ankylosing spondylitis	12	5 years
Van der Heijde 2006[51, 83]	Etanercept Placebo	25 mg twice weekly, or 50mg weekly	Europe	Ankylosing spondylitis	12	12 weeks
Giardina 2010[84, 85]	Etanercept Infliximab	50mg weekly; 5mg/kg (at week 0,2,6 and every 6 weeks)	Italy	Ankylosing spondylitis Inadequate response to NSAIDs	N/A	12 weeks
GO-RAISE 2008[86-90]	Golimumab Placebo	50mg or 100mg every 4 weeks	North America, Europe, Asia	Ankylosing spondylitis	16	4 years
Bao 2014[53, 91]	Golimumab Placebo	50mg every 4 weeks	China	Ankylosing spondylitis	14	1 year
Tam 2014[92]	Golimumab Placebo	50mg every 4 weeks	China (Hong Kong)	Ankylosing spondylitis Inadequate response to NSAIDs	24	1 year
Barkham 2009 [56, 93]	Infliximab Placebo	5 mg/kg (at 0, 2, 6, and 12 weeks)	UK	nr-axSpA with inflammation	16	16 weeks
Braun 2002[94, 95]	Infliximab Placebo	5mg/kg (at weeks 0,2,6)	Germany	Ankylosing spondylitis	12	8 years

Study	Interventions	Anti-TNF dose	Country/ Continent	Population	Duration of placebo-controlled phase (weeks)	Total duration of study, including any open-label extension phase
Marzo-Ortega 2005[50]	Infliximab+methotrexate Placebo+methotrexate	5mg/kg (at weeks 0,2,6,14,22)	UK	Ankylosing spondylitis	30	30 weeks
Van den Bosch 2002[96]	Infliximab Placebo	5mg/kg (at weeks 0,2,6)	Belgium	Ankylosing spondylitis	12	12 weeks
ASSERT[97-104]	Infliximab Placebo	5mg/kg (at weeks 0,2,6,12,18)	North America, Europe	Ankylosing spondylitis Inadequate response /intolerance to NSAIDs	24	2 years
PLANETAS 2013[105, 106]	Inflectra (CT-P13) Infliximab	5mg/kg 5mg/kg	Europe, Asia, Latin America	Ankylosing spondylitis	N/A	2 years (using randomised interventions up to 54 weeks)

Table 3 Baseline characteristics of trial populations

Trial	Patient Group	Trial arm	n	% Male	Mean or *median* age (SD)	% on an NSAID	Mean or *median* symptom duration (years)	Mean (SD) [SE] or *median (IQR)* BASDAI	Mean (SD) or *median (IQR)* BASFI	Mean (SD) or *median (IQR)* BASMI	Mean or *median* CRP mg/L, (SD)	% HLA-B27 +ve	Mean (SD) or *median (IQR)* SF-36 MCS	Mean (SD) or *median (IQR)* SF-36 PCS	Mean (SD)or *median* ASQoL
Haibel 2008[55]	nr-axSpA	ADA	22	41	38	NR	7	6.5 (1.2)	5.4 (2)	1.3 (1.2)	6.2 (5.8)	59	41.3 (12.5)	28.8 (7.6)	10.8 (3.7)
	nr-axSpA	PLA	24	50	37	NR	8	6.2 (1.3)	4.9 (1.6)	1.3 (1.6)	7.8 (7.0)	75	43.6 (11.1)	30.7 (6)	9.5 (3)
Hu 2012[59]	AS	ADA	26	92	28.2 (6.9)	NR	7.4	5.9 (1.4)	3.7 (2.1)	-	24.6	96	-	-	-
	AS	PLA	20	100	27.4 (7.2)	NR	7.6	6.2 (1.1)	3.9 (2)	-	32.1	95	-	-	-
Huang 2014[60]	AS	ADA	229	81	30.1 (8.7)	80	8.1	6.0 (1.4)	4.3 (2.3)	3.4 (1.4)	22.4 (24)	96	36.2 (10.7)	33.8 (7)	-
	AS	PLA	115	83	29.6 (7.5)	78	7.7	6.2 (1.4)	4.4 (2.3)	3.4 (1.5)	23 (30)	95	35 (10.6)	32.2 (6.7)	-
Lambert 2007[61]	AS	ADA	38	76	41.9 (11.1)	NR	14.5	6.2 (1.7)	5.3 (2)	-	18	87	-	-	-
	AS	PLA	44	82	40 (10.9)	NR	12.1	6.5 (1.6)	5.6 (2.2)	-	23	82	-	-	-
ABILITY-1 2013[52]*	nr-axSpA	ADA	[redacted]												
	nr-axSpA	PLA	[redacted]												
ATLAS 2006 [63]	AS	ADA	208	76	41.7 (11.7)	80	11.3	6.3 (1.7)	5.2 (2.2)	3.8 (2.2)	18	78	43.4 (12)	32.9 (8)	10.2 (4)
	AS	PLA	107	74	43.4 (11.3)	79	10	6.3 (1.7)	5.6 (2.2)	4.2 (2.1)	22	79	44.4 (12)	31.8 (8)	10.6 (4)
RAPID-axSpA 2014[46]	AS	CER 200mg	65	72	41 (10.8)	91	*8.8*	6.5 (1.7)	5.6 (2.3)	4.2 (1.6)	*14*	82	-	-	-
	AS	CER 400mg	56	73	41.9 (11.5)	91	*8.8*	6.2 (1.3)	5.7 (2.3)	4.3 (1.8)	*12.9*	79	-	-	-
	AS	PLA	57	72	41.6 (12.8)	90	*10.2*	6.4 (1.9)	6.0 (2)	4.7 (1.6)	*16.6*	84	-	-	-
RAPID-axSpA 2014)[46]	nr-axSpA	CER 200mg	46	44	36.6 (13)	83	*4.8*	6.5 (1.4)	4.8 (2.2)	3.1 (1.4)	*10*	74	-	-	-
	nr-axSpA	CER 400mg	51	53	37.5 (10.8)	86	*7.3*	6.6 (1.6)	5.1 (2.4)	3.3 (1.5)	*12.1*	73	-	-	-

Trial	Patient Group	Trial arm	n	% Male	Mean or *median* age (SD)	% on an NSAID	Mean or *median* symptom duration (years)	Mean (SD) [SE] or *median (IQR)* BASDAI	Mean (SD) or *median (IQR)* BASFI	Mean (SD) or *median (IQR)* BASMI	Mean or *median* CRP mg/L, (SD)	% HLA-B27 +ve	Mean (SD) or *median (IQR)* SF-36 MCS	Mean (SD) or *median (IQR)* SF-36 PCS	Mean (SD)or *median* ASQoL
	nr-axSpA	PLA	50	48	38 (11.8)	82	*4.5*	6.4 (1.5)	4.9 (2.2)	3.1 (1.6)	*13.5*	78	-	-	-
Barkham 2010[72]	AS	ETA	20	75	40.8 (9.7)	NR	*11*	6.1 (1.7)	5.6 (2.0)	-		NR	-	-	-
	AS	PLA	20	85	39.4 (10.1)	NR	*20*	5.5 (1.7)	5.3 (1.8)	-		NR	-	-	-
Davis 2003[47]	AS	ETA	138	76	42.1	91	10.1	5.8 [0.15]	5.2	-	19	84	-	-	-
	AS	PLA	139	76	41.9	92	10.5	6.0 [0.14]	5.6	-	20	84	-	-	-
Dougados 2011[74]	AS	ETA	39	95	46 (11)	NR	19	6.4 (1.2)	6.3 (2.0)	5.7 (1.4)	25 (31)	79	-	-	-
	AS	PLA	43	91	48 (10)	NR	23	5.8 (1.5)	5.7 (1.9)	5.8 (1.3)	17 (19)	86	-	-	-
Dougados 2014[54]**	nr-axSpA	ETA	106	64	31.9 (7.8)	[redacted]	2.4	[redacted]	[redacted]	1.4 (1.3)	6.8	67	-	[redacted]	[redacted]
	nr-axSpA	PLA	109	57	32 (7.8)	[redacted]	2.5	[redacted]	[redacted]	1.2 (1.3)	6.4	76	-	[redacted]	[redacted]
Gorman 2002[49]	AS	ETA	20	65	[redacted]	80	[redacted]	-	4.5 (2.1)	-	20	95	-	-	-
	AS	PLA	20	90	[redacted]	95	[redacted]	-	3.2 (2.5)	-	15	90	-	-	-
Calin 2004[48]	AS	ETA	45	80	45.3 (9.5)	89	15.0	6.1	6.0	-	*154*	NR	-	-	-
	AS	PLA	39	77	40.7 (11.4)	85	9.7	5.9	5.7	-	*97*	NR	-	-	-
Van der Heijde 2006[51]	AS	ETA 25mg	150	76	39.8 (10.7)	85	10.0	5.9(1.7)	5.8 (2.0)	-	19.8 (20.8)	NR	-	-	-
	AS	ETA 50mg	155	70	41.5 (11)	80	9.0	6.2 (1.7)	6.1 (2.0)	-	21.7 (24.6)	NR	-	-	-
	AS	PLA	51	78	40.1 (10.9)	78	8.5	6.1 (1.4)	6.0 (1.9)	-	22 (22.9)	NR	-	-	-
Giardina 2010[84]	AS	ETA	25	80	32.6 (6.8)	NR	15.7	6.6 (1.1)	6.5 (1.1)	3.9 (1.7)	22.9	96	-	-	-
	AS	INF	25	76	31.9 (9.2)	NR	15.4	6.5 (1.2)	6.1 (0.9)	3.7 (1.6)	25	92	-	-	-
GO-	AS	GOL	138	74	*38*	90	*11*	*6.6 (5.6,*	*5 (3.2,*	*3 (2, 4)*	11	82	*46.5*	*29.7 (22.5,*	-

Trial	Patient Group	Trial arm	n	% Male	Mean or *median* age (SD)	% on an NSAID	Mean or *median* symptom duration (years)	Mean (SD) [SE] or *median (IQR)* BASDAI	Mean (SD) or *median (IQR)* BASFI	Mean (SD) or *median (IQR)* BASMI	Mean or *median* CRP mg/L, (SD)	% HLA-B27 +ve	Mean (SD) or *median (IQR)* SF-36 MCS	Mean (SD) or *median (IQR)* SF-36 PCS	Mean (SD)or *median* ASQoL
RAISE 2008[86]		50mg						*7.6)*	*6.7)*				*(36.8,54.1)*	*35.3)*	
	AS	GOL 100mg	140	70	*38*	88	*9.5*	*7 (6.0, 7.9)*	*5.4 (3.4, 7.3)*	*3 (2, 5)*	9	84	*43.1 (33.5,53.5)*	*29.8 (25.2, 35.5)*	-
	AS	PLA	78	71	*41*	92	*16.0*	*6.6 (5.7, 7.7)*	*4.9 (3.5, 6.8)*	*4 (2, 5)*	11.5	85	*46.2 (37.1,54.8)*	*28.3 (23.8, 34.1)*	-
Bao 2014[53]	AS	GOL	108	83	30.5 (10.3)	67	6.8	6.6 (1.3)	5 (2.4)	4 (1.9)	20.6	-	36.5 (10.5)	33.2 (7.8)	-
	AS	PLA	105	83	30.6 (8.6)	72	7.5	6.5 (1.5)	5 (2.4)	3.8 (1.6)	18.6	-	36.2 (11.5)	33.9 (7.7)	-
Tam 2014[92]	AS	GOL	20	90	35.6 (9.9)	85	8.0	6.2 (1.0)	4.6 (1.9)	5.0 (4.0,7.0)	23.9 (18.6)	-	-	-	-
	AS	PLA	21	90	34.2 (10)	100	11.0	6.2 (1.5)	4.1 (2.3)	3 (2.0, 5.5)	19.9 (14.0)	-	-	-	-
Barkham 2009[56]	nr-axSpA	INF	20	75	29.5	90	13.4	5.9	4.4	-	*5*	100	-	-	10
	nr-axSpA	PLA	20	75	28.2	90	17.2	5.8	4.1	-	*11.5*	100	-	-	11
Braun 2002[94]	AS	INF	34	68	40.6 (8)	NR	16.4	6.5 (1.2)	5.4 (1.8)	3.7 (2.0)	24	91	51.5 (22.6)	46.5 (22.6)	-
	AS	PLA	35	63	39 (9.1)	NR	14.9	6.3 (1.4)	5.1 (2.2)	3.7 (2.2)	18	88	65.4 (18.4)	47.6 (23.4)	-
Marzo-Ortega 2005[50]	AS	INF	28	82	41	89	*8*	6.5 (1.9)	*6.7*	-	*30.5*	96	-	-	*14*
	AS	PLA	14	79	39	86	*10*	6.6 (2.1)	*6*	-	*30*	86	-	-	*13.5*
Van den Bosch 2002[96]	AS	INF	9	78	44.3	NR	10	*5.9*	*4.7*	*5*	41.0	89	-	-	-
	AS	PLA	12	83	46.4	NR	17	*5.3*	*5.9*	*4*	25.7	75	-	-	-
ASSERT 2005[97]	AS	INF	201	78	*40*	NR	7.7	*6.6 (5.2,7.1)*	*5.7 (4.5,7.1)*	-	15	87	*47.6 (37.6, 54.9)*	*28.8 (23.8, 33.7)*	-
	AS	PLA	78	87	*41*	NR	13.2	*6.5 (5.3,7.6)*	*6 (4.1,7.2)*	-	17	89	*45 (33.7, 55.5)*	*30.1 (24.9, 36.2)*	-
Park	AS	INFC	125	79	*38*	NR		6.7 (1.4)	6.2 (1.9)	4 (2.1)	*11*	-	-	-	-

Trial	Patient Group	Trial arm	n	% Male	Mean or *median* age (SD)	% on an NSAID	Mean or *median* symptom duration (years)	Mean (SD) [SE] or *median (IQR)* BASDAI	Mean (SD) or *median (IQR)* BASFI	Mean (SD) or *median (IQR)* BASMI	Mean or *median* CRP mg/L, (SD)	% HLA-B27 +ve	Mean (SD) or *median (IQR)* SF-36 MCS	Mean (SD) or *median (IQR)* SF-36 PCS	Mean (SD)or *median* ASQoL
2013[105]	AS	INF	125	82	*38*	NR		6.6 (1.6)	6.2 (2.2)	4.1 (2.1)	*14*	-	-	-	-

* Licensed population ** Includes a small proportion (12%) of unlicensed patients

Risk of bias

Results of the risk of bias judgements are presented in Table 4. Further details, including judgement reasons, and the prognostic indicators of important baseline imbalance, are available in Appendix 3. Most trials were judged to have a low risk of bias overall; where possible bias was detected there was little indication to suggest that this varied across the different ant-TNF trials.

Over half the trials did not report adequate details about methods of randomisation and allocation concealment, though in the majority of those trials (8 out of 14) an assessment could be made of whether groups were balanced in all five of the important prognostic indicators of treatment response. Using both randomisation method details and a baseline assessment to judge the risk of selection bias, 15 trials were judged as having a low risk of selection bias, five trials were judged as having an unclear risk,[51, 55, 72, 91, 107] and four a high risk;[48, 49, 56, 96] in one of these four trials the risk was deemed likely to be due to a chance effect.[49]

The risk of performance bias arising from lack of blinding of participants and personnel was low in 20 trials, unclear in three trials[46, 59, 61] and high in the one head-to-head trial, where blinding would have been difficult to achieve due to the different modes and timings of delivery (weekly injection for etanercept versus six-weekly infusion for infliximab).[84] All except one of the trials were at low risk of detection bias, since they were all adequately placebo-controlled (except the head-to-head trial), with nearly all the key outcomes being self-reported by patients (a noTable exception being BASMI). The blinded patients were the outcome assessors, and the effect of any unblinded study personnel on patient questionnaire responses was likely to be minimal at most. The proportion of patients withdrawing or dropping-out of trials was generally low; most trials received low risk judgements for attrition bias. In two of the trials with unclear risk judgements, there were nevertheless reasons to suspect the possibility of important bias (see Appendix 3). [59, 72] Of the studies with missing data which also reported details on the populations and imputations used in analyses 'last observation carried forward' (LOCF) was used; this was done using a modified ITT approach in just over half the trials (in which patients had to have received at least one dose of treatment), and an ITT approach in the remaining trials (see Appendix 3). There was no evidence of reporting bias in any of the trials with all being judged as low risk, except for one trial with an unclear risk of bias.[59]

Table 4 Risk of bias assessment results

Trial	Bias domain							
	1 Sequence generation	**2 Allocation concealment**	**3 Important baseline imbalance**	**Selection bias based on 1, 2, and 3.**	**4 Blinding of participants and personnel**	**5 Blinding of outcome assessment**	**6 Incomplete outcome data**	**7 Selective reporting**
	Risk of bias judgement							
Adalimumab versus placebo								
Haibel 2008[55]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low
Hu 2012[59]	Unclear	Unclear	Low	Low	Unclear	Low	Unclear	Unclear
Huang 2014[60]	Low	Low	Low	Low	Low	Low	Low	Low
Lambert 2007[61]	Unclear	Unclear	Low	Low	Unclear	Low	Low	Low
ABILITY-1 2013[52]	Low	Low	Low	Low	Low	Low	Low	Low
ATLAS 2006[63]	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Certolizumab pegol versus placebo								
RAPID-axSpA 2014[46]	Low	Low	Low	Low	Unclear	Low	Low	Low
Etanercept versus placebo								
Barkham 2010[72]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	Low
Davis 2003[47]	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Dougados 2011[74]	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Dougados 2014[54]	Low	Low	Low	Low	Low	Low	Low	Low

Trial	Bias domain							
	1 Sequence generation	**2 Allocation concealment**	**3 Important baseline imbalance**	**Selection bias based on 1, 2, and 3.**	**4 Blinding of participants and personnel**	**5 Blinding of outcome assessment**	**6 Incomplete outcome data**	**7 Selective reporting**
	Risk of bias judgement							
Gorman 2002[49]	Low	Low	High*	High*	Low	Low	Low	Low
Calin 2004[48]	Unclear	Unclear	High	High	Low	Low	Low	Low
Van der Heijde 2006[51]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low
Etanercept versus Infliximab								
Giardina 2010[84]	High	High	Low	Low	High	High	Low	Low
Golimumab versus placebo								
GO-RAISE 2008[86]	Low	Low	Low	Low	Low	Low	Low	Low
Bao 2014[53]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	Low
Tam 2014[92]	Low	Unclear	Unclear	Unclear	Low	Low	Low	Low
Infliximab versus placebo								
Barkham 2009 [56]	Unclear	Unclear	High	High	Low	Low	Low	Low
Braun 2002[94]	Low	Low	Low	Low	Low	Low	Low	Low
Marzo-Ortega 2005[50]	Low	Low	Unclear	Low	Low	Low	Unclear	Low
Van den Bosch 2002[96]	Unclear	Unclear	High	High	Low	Low	Low	Low
ASSERT[97]	Unclear	Unclear	Low	Low	Low	Low	Low	Low

Trial	Bias domain							
	1 Sequence generation	**2 Allocation concealment**	**3 Important baseline imbalance**	**Selection bias based on 1, 2, and 3.**	**4 Blinding of participants and personnel**	**5 Blinding of outcome assessment**	**6 Incomplete outcome data**	**7 Selective reporting**
	Risk of bias judgement							
Infliximab versus biosimilar infliximab (Inflectra)								
PLANETAS 2013[105]	Low	Low	Unclear	Low	Low	Low	Low	Low

* Judged likely to be due to chance

4.2.2 Clinical effectiveness results – efficacy results from RCTs

Individual results for all 24 trials are presented in Appendix 4.

Exclusions from the meta-analyses

Of the trials with results at between 10 and 16 weeks, one small head-to-head trial (n=50) comparing etanercept with infliximab was excluded, since it was redundant in a class effect model (in addition blinding was not feasible in this trial).[84] One trial[105] was excluded because it compared infliximab and inflectra, and therefore did not include any of the relevant comparators needed for meta-analysis. The maximum number of studies included for any one outcome was 16.

Exclusions from the sensitivity analyses

Five studies were excluded in the sensitivity analyses due to risk of bias judgements.[48, 49, 59, 72, 96] Further details can be found in Appendix 3. A sensitivity analysis of the nr-axSpA trials was not performed since the only trial judged to have a high risk of bias had only 40 patients;[56] any effect arising from the removal of such a small study would have been likely to have been minimal.

The best model

Models were run where it was assumed that:

- there were different independent treatment effects, or
- there was just one treatment class effect

In addition, fixed-effect and random-effects models were run where there were sufficient data. These models relate to models A1, A2, A3 and A4 in Section 6. For the non-radiographic population, there were very few studies and therefore only fixed-effect analyses were conducted.

The DIC and I^2 results for each outcome (other than injection site reactions) are shown for the AS population in Table 5 and for the nr-axSpA population in Table 6. The lower the DIC for a given outcome, the better the model fit. I^2 varies between 0% and 100%, with 0% representing no heterogeneity in the results and 100% indicating that all of the variation in the results can be explained by heterogeneity. The greater the value of I^2, the more likely it is that a random-effects model would be a better fit. But this is not always the case as if there are few studies then there will be significant uncertainty around the between-study variance and therefore the I^2 also. Random-effect model results and I^2 results are not presented for some outcomes due to sensitivity to prior distributions in the model.

Table 5: The AS population model DIC statistics

	DIC				I^2
	Independent- effects		Class-effect		
Outcome	Fixed Effect	Random Effects	Fixed Effect	Random Effects	
Related model in Section 6	A1	A2	A3	A4	
BASDAI50	16.82	-	10.86	12.71	21%
BASDAI	16.76	18.22	13.53	15.12	21%
BASFI	18.96	20.87	14.79	16.80	10%
ASAS20	10.68	17.05	9.98	8.73	16%
ASAS40	10.36	14.07	8.50	10.29	27%
ASAS50	8.38	-	6.68	8.11	52%
ASAS70	2.92	-	-	-	-
BASMI	-0.87	-	0.12	-3.01	77%
SF36 PCS	19.64	-	20.20	17.71	76%
MASES	5.99	-	4.17	-	-
SF36 MCS	19.20	-	16.67	18.26	47%

Table 6: The nr-axSpA population model DIC statistics

	DIC				I^2
	Independent- effects		Class-effect		
Outcome	Fixed Effect	Random Effects	Fixed Effect	Random Effects	
Related model in Section 6	A1	A2	A3	A4	
BASDAI50	6.74	-	4.85	-	-
BASDAI	10.80	-	11.07	11.51	69%
BASFI	11.45	-	13.74	10.70	83%
ASAS20	6.72	-	5.23	-	-
ASAS40	11.17	-	7.96	9.30	49%
ASAS50	-	-	-	-	-
ASAS70	-	-	-	-	-
BASMI	1.80	-	4.74	2.42	89%
SF36 PCS	16.67	-	20.18	-	-
MASES	-	-	-	-	-
SF36 MCS	14.61	-	14.08	-	-

Overall, assuming a class effect for the treatments produced a better-fitting model than assuming independent treatment effects. In addition, a fixed-effect analysis was more often than not appropriate. The mean and median effects of the two analyses were also similar. Hence, the fixed-effect results are reported in this section: these represent a common class-effect.

For AS the common class effect model was found to be a much better fit than the independent treatment effect model . As described in Section 6 the exchangeable class effect model, not explored here, also fitted the data well, though not so well as the common class effect model. It should be noted here that the common class effect model may possibly underestimate the uncertainty around the treatment effect estimate. As explained in Section 6, if the differences between treatments is due to systematic differences in study design between treatments, then an exchangeable class effect model may be appropriate. However, if in fact there is a true difference between treatments, such as between infliximab and the other TNF-inhibitors then an exchangeable class effect model may overestimate the uncertainty around the effect estimates. Since the common class effect model had a lower DIC than the exchangeable class effect model, this is the model evaluated in this section. The economic model explores the assumption that treatment effect differences are in fact due to systematic differences in study design between treatments.

Since there was very little difference between the results where change from baseline was imputed assuming a within-study correlation of 0.3 or 0.7, only the results assuming a within-study correlation of 0.3 are reported here. Comparison of the results assuming different within-study correlations are presented in the appendix for BASDAI change from baseline.

4.2.2.2 Individual anti-TNFs compared with placebo

Binary responder outcomes at between 10 and 16 weeks

The results of the analyses of the responder outcomes at 10-16 weeks for patients with AS are presented in Table 7.

Table 7 Results versus placebo for AS population – response outcomes at between 10 and 16 weeks

		Number of trials (number of patients) Relative risk (95% CrI) Odds ratio (95% CrI) ASAS 20	ASAS 40	ASAS 50	BASDAI 50
Adalimumab	Main analysis	3 (741) 2.28 (1.98 to 2.62) 4.52 (3.23 to 6.33)	2 (659) 3.42 (2.57 to 4.55) 5.67 (3.56 to 8.97)	1 (82) 2.75 (1.11 to 5.45) 3.58 (1.12 to 11.17)	2 (659) 3.16 (2.40 to 4.16) 4.68 (3.14 to 7.03)
	Sensitivity analysis	3 (741) 2.27 (1.97 to 2.62) 4.52 (3.23 to 6.33)	2 (659) 3.34 (2.53 to 4.40) 5.67 (3.56 to 8.97)	As above	2 (659) 3.11 (2.37 to 4.09) 4.68 (3.14 to 7.03)
Certolizumab pegol	Main analysis	1 (178) 1.80 (1.24 to 2.39) 2.61 (1.37 to 5.01)	1 (178) 2.53 (1.47 to 3.98) 3.38 (1.59 to 7.15)	- -	1 (178) 3.60 (2.02 to 5.74) 5.97 (2.39 to 15.03)
	Sensitivity analysis	1 (178) 1.80 (1.24 to 2.39) 2.61 (1.37 to 5.01)	1 (178) 2.49 (1.46 to 3.87) 3.38 (1.59 to 7.15)	- -	1 (178) 3.53 (2.00 to 5.58) 5.97 (2.39 to 15.03)
Etanercept	Main analysis	5 (839) 2.23 (1.93 to 2.55) 4.23 (3.05 to 5.88)	3 (478) 2.75 (1.88 to 3.88) 3.86 (2.21 to 6.72)	2 (359) 3.43 (2.40 to 4.90) 5.04 (2.98 to 8.51)	3 (478) 3.17 (2.20 to 4.49) 4.74 (2.71 to 8.28)
	Sensitivity analysis	3 (715) 2.17 (1.84 to 2.53) 3.98 (2.78 to 5.73)	2 (436) 2.65 (1.80 to 3.72) 3.72 (2.11 to 6.53)	As above	2 (436) 3.03 (2.08 to 4.31) 4.50 (2.52 to 8.01)
Golimumab	Main analysis	2 (429) 2.14 (1.75 to 2.53) 3.82 (2.47 to 5.86)	2 (429) 3.11 (2.24 to 4.26) 4.77 (2.85 to 7.98)	- -	2 (429) 3.57 (2.51 to 5.00) 5.85 (3.31 to 10.28)
	Sensitivity analysis	2 (429) 2.13 (1.74 to 2.53) 3.82 (2.47 to 5.86)	2 (429) 3.05 (2.21 to 4.13) 4.77 (2.85 to 7.98)	- -	2 (429) 3.50 (2.48 to 4.88) 5.85 (3.31 to 10.28)
Infliximab	Main analysis	2 (111) 2.45 (1.73 to 3.06) 5.54 (2.41 to 12.71)	- -	1 (69) 5.59 (2.44 to 9.81) 14.71 (3.07 to 72.69)	1 (69) 4.86 (2.41 to 7.82) 12.07 (3.09 to 46.37)
	Sensitivity analysis	2 (111) 2.44 (1.72 to 3.06) 5.54 (2.41 to 12.71)	- -	As above	1 (69) 4.72 (2.38 to 7.54) 12.07 (3.09 to 46.37)
Anti-TNFs as a class	Main analysis	13 (2298) 2.21 (2.01 to 2.43) 4.12 (3.40 to 4.99)	8 (1744) 3.06 (2.52 to 3.76) 4.61 (3.51 to 6.05)	4 (510) 3.51 (2.55 to 4.86) 5.23 (3.31 to 8.27)	9 (1813) 3.37 (2.75 to 4.16) 5.22 (4.00 to 6.79)
	Sensitivity analysis	11 (2174) 2.18 (1.97 to 2.42) 4.04 (3.32 to 4.92)	7 (1702) 2.99 (2.47 to 3.66) 4.57 (3.48 to 6.02)	As above	8 (1771) 3.29 (2.68 to 4.07) 5.16 (3.94 to 6.72)

ASAS improvement criteria: ASAS 20, ASAS 40, ASAS 50 and ASAS 70

For the AS population ASAS 20 data were available for all five anti-TNFs, although the number of participants studied varied considerably, ranging from 839 patients in five etanercept trials, to 111 patients in two infliximab trials. A consistent effect was evident across the treatments with the pooled relative risks ranging from 1.80 (certolizumab pegol) to 2.45 (infliximab). ASAS 40 data were available for four anti-TNFs (no data were available for infliximab); the amount of data available ranged from 178 patients in one certolizumab trial, to 659 patients in 2 adalimumab trials. Again a consistent effect was found, with relative risks ranging from 2.53 (certolizumab pegol) to 3.42 (adalimumab); all the relative risks were greater than the corresponding ASAS 20 estimates. For ASAS 50 there were two trials of etanercept (totalling 359 participants) and small single trials in adalimumab (n=82) and infliximab (n=69). A wider range of relative risks and credible intervals resulted, ranging from 2.75 (adalimumab) to 5.59 (infliximab) which may be a consequence of the smaller numbers of patients studied. Only two trials, both of etanercept (n=359), reported actual numbers of ASAS70 responders. Pooling of these data showed that patients taking etanercept were more than three times more likely to be ASAS 70 responders compared with patients taking placebo (RR 3.59, 95% CrI 2.18 to 5.87).

For the nr-axSpA population, each of the relative risks for certolizumab pegol and etanercept were based on single, quite large trials; the estimate for adalimumab was based on a similar number of patients (to etanercept and certolizumab) across two trials, whereas infliximab was represented by a single small trial (n=40). ASAS 20 results were similar across treatments but for ASAS 40 heterogeneity of effect appeared evident; the smallest estimate was for etanercept and the largest estimate was seen in the small infliximab trial (Table 8). However, this infliximb trial was the only nr-axSpA trial judged to be at high risk of bias. Only one trial (RAPID-axSpA) reported ASAS 50 or ASAS 70 results. For ASAS 50 the relative risk was 4.23 (95% CrI 1.84 to 9.72; OR 5.96 (95% CrI 2.40 to 14.80)). For ASAS 70 the relative risk was 4.58 (95% CrI 1.37 to 15.40; OR 5.42, 95% CrI 1.54 to 19.11).

BASDAI 50

For the AS population BASDAI 50 data were available for all five anti-TNFs; the number of participants studied varied widely, ranging from 69 patients in one infliximab trial to 659 patients in two adalimumab trials. Although a consistent beneficial effect was evident across treatments, some heterogeneity of effect could be seen with the relative risks ranging from 3.16 (adalimumab) to 4.86 (infliximab).

For the nr-axSpA population the relative risks were lower than for the AS population being 2.52 (95% CrI 1.65 to 3.83, 2 trials) for adalimumab, 2.80 (95% CrI 1.71 to 4.47, 1 trial) for certolizumab, and 1.92 (95% CrI 1.27 to 2.82, 1 trial) for etanercept (Table 8).

Results of the AS sensitivity analyses were very similar to the main analyses (Table 7).

Table 8 Results versus placebo for nr-axSpA population – response outcomes at 10-16 weeks

	Number of trials (number of patients) Relative risk (95% CrI) Odds ratio (95% CrI)		
	ASAS 20	**ASAS 40**	**BASDAI 50**
Adalimumab	2 (188)	2 (188)	2 (188)
	1.92 (1.47 to 2.56) 3.71 (2.02 to 6.75)	3.14 (1.99 to 4.68) 5.04 (2.44 to 10.32)	2.52 (1.65 to 3.83) 3.97 (1.97 to 7.86)
Certolizumab pegol	1 (147)	1 (147)	1 (147)
	1.59 (1.10 to 2.21) 2.32 (1.15 to 4.67)	3.04 (1.74 to 4.81) 4.75 (2.01 to 11.17)	2.80 (1.71 to 4.47) 4.92 (2.09 to 11.58)
Etanercept	1 (215)	1 (215)	1 (215)
	1.46 (1.08 to 1.94) 1.94 (1.13 to 3.37)	2.07 (1.26 to 3.20) 2.55 (1.32 to 4.92)	1.92 (1.27 to 2.82) 2.45 (1.37 to 4.43)
Infliximab	-	1 (40)	-
	-	3.63 (1.41 to 6.44) 6.85 (1.52 to 31.03)	-
Anti-TNFs as a class	4 (550)	5 (590)	4 (550)
	1.65 (1.37 to 2.04) 2.52 (1.78 to 3.59)	2.74 (2.08 to 3.62) 3.92 (2.61 to 5.91)	2.31 (1.76 to 3.10) 3.33 (2.24 to 4.96)

Continuous outcomes at between 10 and 16 weeks

The results of the analyses of the continuous efficacy outcomes for patients with AS are presented in Table 9.

For the AS population, when compared with placebo, adalimumab (n=705), certolizumab pegol (n=178), etanercept (n=483) and infliximab (n=132) produced statistically significant reductions in disease activity, when assessed using BASDAI. The magnitude of the reductions in change from baseline BASDAI score ranged from 1.46 units (certolizumab pegol) to 2.28 units (infliximab). None of the three golimumab trials reported BASDAI as a continuous outcome. The amount of data available for BASFI in patients with AS ranged from 132 patients in three infliximab trials, to 523 patients in five etanercept trials. When compared with placebo, all five anti-TNFs produced statistically significant improvements in function. The magnitude of the reductions in change from baseline BASFI score ranged from 1.1 units (certolizumab pegol) to 2.16 units (infliximab). When compared with placebo, statistically significant improvements in BASMI scores were found for AS patients taking adalimumab (mean difference in change from baseline: -0.37, 95% CrI -0.50 to -0.23) and etanercept (mean difference in change from baseline: -0.37, 95% CrI -0.65 to -0.09), but not for certolizumab pegol (mean difference in change from baseline: -0.26, 95% CrI -0.55 to 0.03) and golimumab (mean difference in change from baseline: -0.11, 95% CrI -0.26 to 0.04). Results for SF-36 MCD, SF-36 PCS and ethesitis (MASES) are presented in Table 9.

For the nr-axSpA population, a heterogeneity of effect on BASDAI and BASFI appears evident from the relative risks of the individual anti-TNFs. The smallest estimates were for etanercept and the

largest estimates were seen in the small infliximab trial, although this trial was the only nr-axSpA trial judged to be at high risk of bias (Table 10).

Results of the AS sensitivity analyses were very similar to the main analyses (Table 9).

When the mean baseline BASDAI and BASFI are presented by treatment response at week 12 (or 14 for golimumab) for three of the five anti-TNFs (see Appendix 6), it can be seen that in patients with AS and patients with nr-axSpA, on average baseline BASDAI does not differ greatly between responders and non-responders either to placebo or to active anti-TNF therapy. In patients with AS or nr-axSpA from the trials of adalimumab (ATLAS and M10-791) and golimumab (GO-RAISE) on average baseline BASFI was higher in non-responders compared with responders. However, this was not seen in the etanercept trials.

Table 9 Results versus placebo for AS population – continuous outcomes at 10-16 weeks

		Number of trials (number of patients) Mean difference in change from baseline (95% CrI)					
		BASDAI	**BASFI**	**BASMI**	**SF-36 PCS**	**SF-36 MCS**	**MASES**
Adalimumab	Main analysis	3 (705)	2 (390)	2 (659)	2 (659)	2 (659)	2 (659)
		-1.55 (-1.88 to -1.22)	-1.25 (-1.63 to -0.87)	-0.37 (-0.50 to -0.23)	3.53 (2.37 to 4.68)	1.41 (-0.19 to 3.02)	-0.50 (-0.89 to -0.11)
	Sensitivity analysis	2 (659)	1 (344)	Same as above	Same as above	Same as above	Same as above
		-1.55 (-1.89 to -1.21)	-1.28 (-1.68 to -0.88)				
Certolizumab pegol	Main analysis	1 (178)	1 (178)	1 (178)	1 (178)	1 (178)	-
		-1.46 (-2.17 to -0.74)	-1.10 (-1.83 to -0.37)	-0.26 (-0.55 to 0.03)	5.64 (3.64 to 7.66)	1.25 (-2.08 to 4.61)	-
	Sensitivity analysis	Same as above	Same as above	Same as above	Same as above	Same as above	-
							-
Etanercept	Main analysis	4 (483)	5 (523)	1 (82)	-	-	-
		-1.75 (-2.14 to -1.37)	-1.43 (-1.82 to -1.04)	-0.37 (-0.65 to -0.09)	-	-	-
	Sensitivity analysis	2 (359)	2 (359)	Same as above	-	-	-
		-1.72 (-2.16 to -1.29)	-1.29 (-1.76 to -0.84)		-	-	-
Golimumab	Main analysis	-	2 (429)	2 (429)	2 (429)	2 (429)	1 (216)
		-	-1.45 (-1.84 to -1.05)	-0.11 (-0.26 to 0.04)	5.06 (3.71 to 6.40)	2.75 (1.08 to 4.40)	-0.70 (-1.53 to 0.11)
	Sensitivity analysis	-	Same as above	Same as above	Same as above	Same as above	Same as above
		-					
Infliximab	Main analysis	3 (132)	3 (132)	-	-	-	-
		-2.28 (-3.18 to -1.38)	-2.16 (-3.18 to -1.12)	-	-	-	-
	Sensitivity analysis	2 (111)	2 (111)	-	-	-	-
		-2.18 (-3.14 to -1.21)	-1.94 (-3.07 to -0.80)	-	-	-	-
Anti-TNFs as a class	Main analysis	11 (1498)	13 (1652)	6 (1348)	5 (1266)	5 (1266)	3 (875)
		-1.66 (-1.88 to -1.43)	-1.38 (-1.59 to -1.18)	-0.27 (-0.36 to -0.18)	4.40 (3.60 to 5.21)	1.93 (0.12 to 3.72)	-0.54 (-0.89 to -0.19)
	Sensitivity analysis	7 (1305)	8 (1419)	Same as above	Same as above	Same as above	Same as above
		-1.63 (-1.88 to -1.39)	-1.34 (-1.57 to -1.12)				

Table 10 Results versus placebo for nr-axSpA population – continuous outcomes at 10-16 weeks

Number of trials (number of patients) Mean difference in change from baseline (95% CrI)					
	BASDAI	**BASFI**	**BASMI**	**SF-36 PCS**	**SF-36 MCS**
Adalimumab	2 (188)	2 (188)	2 (188)	2 (188)	2 (188)
	-1.23 (-1.83 to -0.62)	-0.90 (-1.44 to -0.36)	-0.02 (-0.24 to 0.20)	4.98 (2.74 to 7.20)	1.13 (-1.86 to 4.13)
Certolizumab pegol	1 (147)	1 (147)	1 (147)	1 (147)	1 (147)
	-1.85 (-2.83 to -0.88)	-1.90 (-2.87 to -0.94)	-0.55 (-0.89 to -0.20)	6.99 (4.23 to 9.76)	4.01 (0.44 to 7.53)
Etanercept	1 (215)	1 (215)	-	-	-
	-0.70 (-1.54 to 0.12)	-0.60 (-1.16 to -0.06)	-	-	-
Infliximab	1 (40)	1 (40)	1 (40)	1 (40)	-
	-2.67 (-4.21 to -1.13)	-2.24 (-3.67 to -0.80)	0.00 (-0.44 to 0.44)	2.10 (-0.21 to 4.37)	
Anti-TNFs as a class	5 (590)	5 (590)	4 (375)	4 (375)	3 (335)
	-1.32 (-1.74 to -0.90)	-0.99 (-1.34 to -0.64)	-0.15 (-0.32 to 0.02)	4.41 (3.04 to 5.81)	2.33 (0.07 to 4.62)

4.2.2.3 Individual anti-TNFs compared with each other

For efficacy outcomes, all of the comparisons that could be made between different anti-TNFs at 10-16 weeks resulted in no statistically significant differences between treatments. For the full results see Appendix 5.

One small trial, which could not be included in the meta-analysis (see section 4.2.2), compared infliximab with etanercept in a two year unblinded randomised study of 50 AS patients.[84] At 12 weeks there were statistically significant differences between groups in terms of BASDAI (3.5 versus 5.6, $p<0.005$) and BASFI (3.5 versus 5, $p<0.005$), favouring treatment with infliximab. By week 48, the BASDAI and BASFI scores were almost identical across the treatment groups (data were only presented graphically). Also at 12 weeks, 19 of 25 infliximab patients were ASAS 20 responders, versus 15 of 25 etanercept patients (not a statistically significant difference). This study concluded that infliximab produces a more rapid clinical improvement, but, at the end of the study, treatment with both etanercept and infliximab was effective and safe. The results of this trial may explain why, at 10-16 weeks, the meta-analysis results for infliximab were a little better than those of the other anti-TNFs.

Another trial which could not be included in the meta-analysis compared infliximab with an infliximab biosimilar called Inflectra in 250 AS patients.[105] The ASAS 40 response rates at week 14 were 42% for inflectra and 46% for infliximab (OR 0.85, 95% CI 0.51 to 1.42) and at week 30 they were 52% for inflectra and 47% for infliximab (OR 1.19, 95% CI 0.70 to 2.00). At week 14 BASDAI median change from baseline scores were identical (-2.7) and at week 30 they differed slightly (-3.1 Inflectra vs -2.5 infliximab). For BASFI the median change from baseline scores were -2.2 Inflectra

versus -2.4 infliximab at week 14, and -2.6 Inflectra versus -2.2 infliximab at week 30. The study concluded that Inflectra had a comparable efficacy and safety profile to that of infliximab.

4.2.2.4 Anti-TNFs as a class compared with placebo

Within this section the class effect, calculated as a common effect across all the TNF-inhibitors under consideration, assumes a single treatment effect for all the TNF-inhibitors. It is calculated as the pooled treatment effect using a fixed effect model. The common class effect model may possibly underestimate the uncertainty around the treatment effect estimate. As explained in chapter 6, if the differences between treatments is due to systematic differences in study design between treatments then an exchangeable class effect model may be appropriate. However, if in fact there is a true difference between treatments, such as between infliximab and the other TNF-inhibitors then an exchangeable class effect model may overestimate the uncertainty around the mean class effect estimates. Since the common class effect model had a lower DIC than the exchangeable class effect model, this is the model evaluated in this chapter. The economic model in chapter 7 explores the assumption that treatment effect differences are in fact due to differences in study design between treatments.

Binary responder outcomes at between 10 and 16 weeks

ASAS improvement criteria: ASAS 20, ASAS 40, ASAS 50 and ASAS 70

When compared with placebo, anti-TNFs as a common class were more than twice as likely to result in patients with AS achieving an ASAS 20 response (RR 2.21, 95% CrI 2.01 to 2.43, 13 trials, Table 7). Anti-TNFs were also around three times as likely to result in patients achieving an ASAS 40 response (RR 3.06, 95% CrI 2.52 to 3.76, 8 trials) and three and a half times as likely to result in patients achieving an ASAS 50 response (RR 3.51, 95% CrI 2.55 to 4.86, 4 trials). Only two trials, both of etanercept, reported data suitable for the ASAS 70 analysis; the results are presented in section 4.2.2.2 below. There was little evidence of heterogeneity for ASAS 20 (I^2=16%) and ASAS 40 I^2=27%), but heterogeneity was evident for ASAS 50 (I^2=52%). For ASAS 50 three of the four trials were small (i.e. fewer than 100 participants), which may partly explain the heterogeneity estimate.

For the nr-axSpA population anti-TNFs as a common class were statistically significantly more effective than placebo, although the relative risks being lower than for the AS population. For ASAS 20 the relative risk was 1.65 (95% CrI 1.37 to 2.04, 4 trials) and for ASAS 40 the relative risk was 2.74 (95% CrI 2.08 to 3.62, 5 trials). Only one trial presented ASAS 50 and ASAS 70 results (see section 4.2.2). A heterogeneity estimate could only be calculated for ASAS 40 (I^2=49%).

BASDAI 50

Anti-TNFs as a common class resulted in patients with AS being more than three times more likely to achieve a BASDAI 50 response when compared with patients taking placebo (RR 3.37, 95% CrI 2.75 to 4.16, 9 trials). There was little evidence of heterogeneity (I^2=21%).

For the nr-axSpA population anti-TNFs as a common class were also statistically significantly more effective than placebo in terms of achieving a BASDAI 50, although the relative risk being lower than for the AS population (RR 2.31, 95% CrI 1.76 to 3.10, 4 trials). Results of the AS sensitivity analyses were very similar to the main analyses (Table 4).

Binary responder outcomes at between 24 and 30 weeks

Four AS trials reported outcomes at between 24 and 30 weeks (see Table 2). Anti-TNFs as a common class were statistically significantly more effective than placebo at 24-30 weeks; for ASAS 20 the relative risk was 1.69 (95% CrI 1.30 to 2.14, 4 trials). No studies reported BASDAI 50 or ASAS 70 results, and only single studies reported on ASAS 40 (RR 4.01, 95% CrI 2.13 to 7.55),[97] and ASAS 50 (RR 4.17, 95% CrI 2.45 to 7.12).[47]

Continuous outcomes at between 10 and 16 weeks

When considered together as a group compared with placebo (Table 9), treatment with an anti-TNF in patients with AS produced statistically significant improvements (calculated using mean difference in change from baseline) in: disease activity (BASDAI mean difference: -1.66 units, 95% CrI -1.88 to -1.43, 11 trials); function (BASFI mean difference: -1.38 units, 95% CrI -1.59 to -1.18, 13 trials); spinal mobility (BASMI mean difference: -0.27 units, 95% CrI -0.36 to -0.18); physical health (SF-36 PCS mean difference: 4.40, 95% CrI 3.60 to 5.21, 5 trials); mental health (SF-36 MCS mean difference: 1.96, 95% CrI 0.87 to 3.05, 5 trials); and enthesitis (MASES mean difference: -0.54, 95% CrI -0.89 to -0.19, 3 trials). There was little evidence of heterogeneity for BASDAI (I^2=21%) and BASFI (I^2=10%), but evidence of substantial heterogeneity for BASMI (I^2=77%), SF-36 PCS (I^2=76%) SF-36 MCS (I^2=47%) and MASES (I^2=91%).

In the nr-axSpA population the mean differences achieved with anti-TNFs (Table 10) were also statistically significant, although slightly lower than for the AS population. For BASDAI the mean difference was -1.32 units (95% CrI -1.74 to -0.90, I^2=69%) and for BASFI the mean difference was -0.99 units (95% CrI -1.34 to -0.64, I^2=83%) but there was evidence of substantial heterogeneity. The results for SF-36 MCS and SF-36 PCS were similar to those for AS (Table 10).

Results of the AS sensitivity analyses were very similar to the main analyses (Table 9). Because the results of the independent treatment effects showed a trend that infliximab had a greater, although not statistically significant, effect on the change in BASDAI and BASFI from baseline, an additional

sensitivity analysis was conducted where infliximab was assumed to be different to the rest of the ant-TNFs. The results are presented in Table 11. The low weight of evidence available for infliximab ensures that the class effect for the other anti-TNFs does not change greatly. Although it is possible that infliximab has a greater effect than the other anti-TNFs at least at 12 weeks, there is no strong evidence from these analyses to suggest that it does.

Table 11: The difference in change from baseline for BASDAI and BASFI assuming all TNFs have the same effect and assuming infliximab may be different

	BASDAI		BASFI	
	Mean	95% CrI	Mean	95% CrI
All TNFs	-1.66	(-1.88 to -1.43)	-1.38	(-1.59 to -1.18)
TNFs other than infliximab	-1.62	(-1.85 to -1.38)	-1.35	(-1.56 to -1.14)
Infliximab	-2.28	(-3.18 to -1.38)	-2.15	(-3.18 to -1.11)

Continuous outcomes at between 24 and 30 weeks

Four AS trials reported outcomes at between 24 and 30 weeks (see Table 2). The mean differences in change from baseline were -1.98 units (95% CrI -2.27 to -1.68, 4 trials) for BASDAI, -0.87 units (95% CrI -1.11 to -0.62, 3 trials)[47, 50, 97] for BASFI, and -1.00 units (95% CrI -1.19 to -0.81, 2 studies)[92, 97] for BASMI. One study reported SF-36 outcomes, with differences of 9.40 (95% CrI 7.88 to 10.92) for SF-36-PCS and 0.70 (95% CrI -1.36 to 2.76) for SF-36-MCS.[97]

4.2.2.5 Outcomes not included in the meta-analyses

Very little data was available on peripheral symptoms (other than enthesitis – see MASES results above) or symptoms of extra-articular manifestations. One trial reported five cases of inflammatory bowel disease flare up to the 24 week time point; three occurred in patients on etanercept, and 2 in patients on placebo.[47] Another study reported that there were no cases of inflammatory bowel disease at 12 weeks.[51]Incidence of uveitis was also reported in one trial; up to the 24 week time point there were three cases in the etanercept arm and 8 cases in the placebo arm.[47]

[redacted]. A study of adalimumab reported no statistically significant difference in EQ-5D between groups at 12 weeks (0.78 for adalimumab versus 0.72 for placebo, p=0.32).[55]

For ASQoL – a quality of life instrument specific to ankylosing spondylitis - ATLAS was the only trial which reported results together with SDs or SEs; significant improvements were found favouring treatment with adalimumab at week 12 (mean change from baseline -3.2 (SD 0.3) for adalimumab versus -1 (SD 0.4) for placebo).[64] Similar statistically significant results were reported in an etanercept

trial at 12 weeks (mean change from baseline -3.3 for etanercept versus -0.1 for placebo, p=0.02)[72] and in an infliximab trial at 16 weeks (mean change from baseline -6.2 for infliximab versus -1 for placebo, p=0.007).[56] Another small study of infliximab did not find a significant difference between groups at 30 weeks (p=0.14).[50]

4.2.2.6 'Placebo' response in AS and nr-axSpA

To inform insight into the extent of any 'placebo' effects (outlined in section 2.1), Table 12 compares the placebo response rates in trials which reported ASAS 20 results and at least one of ASAS 40 or BASDAI 50 results. These data highlight the relatively high rates of ASAS 20 response (median 31%, range 21% to 40%) when compared with ASAS 40 response (median 15%, range 10% to 23%) and BASDAI 50 response (median 16%, range 5% to 24%).

However, the extent of the 'placebo' response on the ASAS 20 results might result in an underestimation of anti-TNF efficacy, notably when ASAS 20 is the only ASAS improvement outcome reported in a trial. An increase in the likelihood of being a responder (i.e. the relative risks when compared with placebo) when moving up the ASAS thresholds seems apparent from the results in section 4.2.2.1. This might be explained by considering the subset of patients who achieve an ASAS 20 response largely due to regression to the mean (i.e. due to natural variation in repeated data measurements, such as patients transitioning from flare at randomisation to no flare at 12 weeks). For those patients who experience regression to the mean after taking an anti-TNF, the true benefit of treatment may be hidden in the ASAS 20 outcome for some patients, and the proportion of ASAS 20 responders might therefore differ only moderately between the anti-TNF and placebo groups. As the bar for response is raised - from ASAS 20 through to ASAS 70 - this difference in the proportion of responders between active treatment and placebo groups is likely to increase as an effect due to regression to the mean becomes less likely. The diluting effect of a placebo response on the relative risks therefore diminishes as the ASAS thresholds increase (and more informative estimates of treatment benefit can be seen). Regardless of the reason, these results highlight the limited applicability of ASAS 20 as a clinically informative outcome measure. ASAS 20 was nevertheless was the most commonly reported responder outcome across the trials.

Table 12 Comparison of placebo response rates in trials reporting ASAS 20 results together with ASAS 40 or BASDAI 50 results

				Number of responders			% of responders			Difference in response (%)		
Population and study	**Placebo compared with**	**Time point (weeks)**	**Number of patients on placebo**	**ASAS 20**	**ASAS 40**	**BASDAI 50**	**ASAS 20**	**ASAS 40**	**BASDAI 50**	**ASAS 20 vs ASAS 40**	**ASAS 20 vs BASDAI 50**	**ASAS 40 vs BASDAI 50**
nr-axSpA [55]	Adalimumab	12	24	6	3	5	25%	13%	21%	13%	4%	-8%
AS [60]	Adalimumab	12	115	35	11	19	30%	10%	17%	21%	14%	-7%
nr-axSpA [52]	Adalimumab	12	73	23	10	10	32%	14%	14%	18%	18%	0%
AS[63]	Adalimumab	12	107	22	14	17	21%	13%	16%	7%	5%	-3%
AS[46]	Certolizumab	12	57	21	11	6	37%	19%	11%	18%	26%	9%
nr-axSpA [46]	Certolizumab	12	50	20	8	8	40%	16%	16%	24%	24%	0%
AS[74]	Etanercept	12	43	14	10	10	33%	23%	23%	9%	9%	0%
nr-axSpA [54]	Etanercept	12	109	39	17	26	36%	16%	24%	20%	12%	-8%
AS[51]	Etanercept	12	51	19	11	10	37%	22%	20%	16%	18%	2%
AS[86]	Golimumab	14	78	17	12	12	22%	15%	15%	6%	6%	0%
AS[53]	Golimumab	14	105	26	10	5	25%	10%	5%	15%	20%	5%
AS[94]	Infliximab	12	35	10		3	29%	-	9%	-	20%	-

Summary of the RCT clinical efficacy results

For both the AS and nr-axSpA populations the results of the meta-analyses demonstrated that anti-TNFs produce statistically significant and clinically relevant benefits to patients in terms of improving function and reducing disease activity. The common class effect model used may have underestimated the uncertainty in the effect estimates. Although there is a possibility that infliximab is more effective than other TNF inhibitors at least at 12 weeks, there is no strong evidence to support this. For the disease activity, function, and responder outcomes, the class efficacy estimates were consistently slightly smaller for nr-axSpA than for AS, most noticeably for BASFI and BASDAI 50.

The included RCTs were generally subject to low risks of bias and no important variation in baseline characteristics was evident, with the exception of CRP levels; in the nr-axSpA trial populations CRP levels were much lower than in the AS populations. Although heterogeneity of CRP levels was evident across both the AS trials and the nr-axSpA trials, in almost all the AS trials the CRP levels were higher than the 14mg/l threshold identifed as being a key predictor of treatment response (in AS, higher CRP levels are associated with an increased likelihood of BASDAI 50 response).[108] In the nr-axSpA trials only the RAPID-axSpA population came close to this cut-off. These lower CRP levels may therefore have had an impact on the efficacy estimates for the nr-axSpA population.

Statistical heterogeneity was more apparent in the nr-axSpA analyses than in the AS analyses. This may be due to both clinical heterogeneity in the nr-axSpA trials (such as variation in CRP thresholds, or the proportion of MRI positive patients), and the fact that fewer studies were available for analysis. In light of the statistical heterogeneity across the nr-axSpA trials, both the reliability of the nr-axSpA pooled estimates and their true relevance to patients seen in clinical practice are questionable.

The clinical relevance of the efficacy of anti-TNFs can be evaluated in part by considering the literature on minimum clinically important differences (MCID) or improvements (MCII). In a study of 125 AS patients, Pavy et al[109] reported a MCID of 1 unit (or a 20% relative change) for BASDAI and 0.7 units (17.5% relative change) for BASFI. All the effect estimates from this review for both BASDAI and BASFI were considerably higher than these MCIDs. The small effect on spinal mobility (a group effect reduction of around 0.3 BASMI units) appears unlikely to be clinically important.

4.2.2.7 Summary of some key issues arising from the FDA assessments of the ABILITY-1 and Rapid-axSpA trials

The FDA Arthritis Advisory Committee met in July 2013 to discuss licence applications for adalimumab for patients with active nr-axSpA (with objective signs of inflammation) and certolizumab pegol for patients with active axial spondyloarthritis, including patients with ankylosing spondylitis. An important issue which arose in both trials was the differences in diagnoses arising

from x-ray images evaluated centrally, when compared with images being evaluated locally. The implications for efficacy were explored via further analyses.

Rapid-axSpA trial (certolizumab pegol)

This trial aimed to recruit *both* AS and nr-axSpA patients.[46] The nr-axSpA patients had to have a positive MRI *or* an elevated CRP; the definition used for CRP elevation was 7.9mg/L.

Comparison of AS and nr-axSpA population characteristics

In AS males predominated (72%), whereas in nr-axSpA the male to female ratio was roughly equal. The AS population had a mean age of 41.5 years, which was around four years older than the nr-axSpA population. Baseline BASFI, BASMI and CRP levels suggested more functional and mobility impairment and more inflammation in the AS group when compared with the nr-axSpA group. However, baseline back pain severity and BASDAI scores were similar between the AS and nr-axSpA subgroups (Table 13).

Methods used to evaluate x-ray images

In the trial, many patients had their disease re-classified when x-ray images were evaluated centrally, rather than being evaluated locally. Two readers were involved in the central evaluation of the x-ray images, they were blinded to both the assigned subgroup and the treatment group; a third reader was used in cases of disagreement. 21% of locally-classified AS patients were re-classified as nr-axSpA by central readers and 51% of locally-classified nr-axSpA patients were re-classified as AS by the central readers. Based on the central assessments 184 patients had AS and 98 patients had nr-axSpA. Central reads could not be made for 43 patients as x-rays were not available (37 AS patients and 6 nr-axSpA patients).

ABILITY-1 trial (adalimumab)

This trial intended to recruit only nr-axSpA patients, although this included patients (n=43) who had nr-axSpA but *neither* a positive MRI nor an elevated CRP.[52] The population with these 43 patients excluded is referred to as the 'adalimumab target population' (ATP). As in the Rapid-axSpA trial, central re-reading of x-rays was performed (in addition to local evaluation) although this was only done for per-protocol patients, who also reached week 104 (n=102 (out of 185) patients). Thirty-eight of the 102 were identified as having AS rather than nr-axSpA. The FDA statistician analysed the results in these 38 patients and compared them to those for patients with centrally confirmed nrAxSpA. The FDA document reported results for the sub-populations based on local or central diagnosis, including ATP analyses.

Comparison of AS and nr-axSpA results and impact of reclassification in the trials

For certolizumab pegol the FDA statistical review stated that "efficacy findings were consistent in both AS and nr-axSpA subpopulations regardless of the discrepancy in pelvic x-ray readings at local or central lab for modified New York criteria" (Table 14).

For ABILITY-1 a notably higher proportion of patients in the AS subgroup responded to adalimumab (ASAS 40) when compared with placebo than of patients with confirmed nr-axSpA. This suggests that the treatment benefit in the whole trial population may be driven by benefit in AS patients rather than in nr-axSpA patients, skewing the results for the ATP (Table 14). It should be noted though that this may be an atypical AS population – the trial had intended to recruit only nr-axSpA patients.

Due to the fact that only a select group of patients could be subject to central confirmation of their nr-axSpA status, the FDA statistician explored assumptions around the proportion of true nr-axSpA patients in the whole trial population. Given that the treatment difference in the non-centrally-read patients was 23%:

- Assuming that all non-centrally read patients were true negatives and therefore including them in the analysis with the centrally read negatives, the treatment difference for the centrally-read and non-centrally read negatives was 15%.
- Assuming that a fraction (i.e., 63%) of non-centrally read patients were true negatives and including only this fraction of non-centrally read patients with the centrally read negatives, the treatment difference was 14%.

The FDA document stated that, "Because there was a differential treatment effect between the centrally-read positive and centrally-read negative, it is safe to assume that the difference of 23% is an overestimate of the treatment effect because this includes both positive and negative x-ray groups. If there is a fraction of patients who are negative in the non-centrally-read group, treatment difference among this negative group would be smaller. Therefore, the treatment difference for negative x-rays (i.e., centrally-read and non-centrally-read) should be at most 15%. Based on the data provided, the estimate of the treatment effect in ASAS40 response for nr-axSpA should be no bigger than 15%."

Overall, the results suggest reduced efficacy of anti-TNFs in the centrally diagnosed nr-axSpA population when compared with the locally diagnosed population. Nevertheless, there was noticeable variation across the two trials. In Rapid-axSpA (certolizumab) the difference between the central and local populations appears small (and is not evident for 400mg versus placebo results). Conversely, in ABILITY-1 (adalimumab) the locally diagnosed population had notably more responders than the centrally diagnosed population, though the treatment group sample sizes were small.

Table 13 Baseline characteristics of trials analysed by the FDA

Trial & Population	Characteristic									
	Age (mean)	% Male	Duration of symptoms, years (mean)	Weight, kg (mean)	% HLA-B27 positive	% on NSAIDs	CRP	% MRI positive	BASDAI (mean)	BASFI (mean)
ABILITY-1 *nr-axSpA* (n=142)	38	46	Median, 8 mean 11	80	80	81	median ~4, mean 9	51	6	4.7
Rapid-axSpA *nr-axSpA* (n=147)	37	48	median 5.5, mean 8.6	82	75	84	median 11.9 mean 16	54	6.5	4.9
Rapid-axSpA, *AS* (n=178)	42	73	median 9.1, Mean 11.9	82	82	91	median 14.3, mean 21.3	N/A	6.4	5.7

Table 14 FDA analyses - percentage differences from placebo, by method of diagnosis

Outcomes at week 12	ABILITY-1 ATP population		Rapid-axSpA							
	Local lab nr-axSpA ADA n=69, PBO n=73	Central lab nr-axSpA ADA n=25, PBO n=20	Local lab nr-axSpA CZP 200mg n=46, CZP 400mg n=51, PBO n=50		Central lab nr-axSpA CZP 200mg n=39, CZP 400mg n=35, PBO n=39		Local lab AS CZP 200mg n=65, CZP 400mg n=56, PBO n=57		Central lab AS CZP 200mg n=74, CZP 400mg n=71, PBO n=67	
	Adalimumab 40mg		CZP 200mg	CZP 400mg	CZP 200mg	CZP 400mg	CZP 200mg	CZP 400mg	CZP 200mg	CZP 400mg
ASAS 20 95% CI	28% 12 to 44	15% -14 to 44	19% 1 to 38	23% 4 to 42	23% 2 to 44	23% 1 to 44	20% 3 to 37	27% 10 to 45	17% 1 to 33	23% 7 to 39
ASAS 40 95% CI	27% 13 to 41	11% -16 to 38	32% 14 to 49	31% 14 to 48	18% 0 to 36	27% 8 to 47	21% 5 to 36	31% 14 to 47	28% 13 to 43	33% 17 to 48
BASDAI50 95% CI	25% 11 to 39	19% -8 to 46	-	-	-	-	-	-	-	-

4.2.3 Long-term efficacy results from open-label extensions of RCTs

Of the 24 included RCTs, 17 reported data from an open-label extension phase. Results for all studies are presented in Appendix 7. Considerable effort has been put into patient follow-up in anti-TNF trials with the results that data up to 5 years is available (there are data up to 8 years for infliximab but that included an involuntary treatment break and is not discussed further). The longest follow-up durations in patients with AS by anti-TNF are: adalimumab 260 weeks, etanercept 264 weeks, infliximab 156 weeks, golimumab 268 weeks ; and certolizumab pegol 96 weeks. However, the data were reported across numerous publications and in various formats. Results were reported as observed, as completer analyses, using imputation (and rarely LOCF) for non-responders and LOCF for missing continuous data, but these related to differing populations (at varying time points): all patients randomised, all patients who took active drug at any point in the study, or just during the open-label phase. The follow-up protocols were not clearly reported, with stopping rules unclear, but it appears that not all patients who did not achieve a response at ASAS 20, 40 or BASDAI 50 discontinued therapy. Therefore the results may not reflect clinical practice should response be required for treatment continuation.

Table 15 Treatment effect over time (AS only) (results calculated using NRI)

Outcome	Trial	52 weeks	104 weeks	156 weeks	5 years (approx. 264 weeks)
Adalimumab					
ASAS 20	ATLAS	193/311 (62%)[c]	135/311 (43%)[c]		111/311 (36%)[c]
ASAS 40	ATLAS	138/311 (44%)[c]	109/311 (35%)[c]		88/311 (28%)[c]
BASDAI 50	ATLAS	167/311 (54%)[c]	122/311 (39%)[c]		96/311 (31%)[c]
Certolizumab					
ASAS 20	RAPID-axSpA (AS)	(48 weeks) 89/121 (74%)[a]	(96 weeks) [redacted]		
ASAS 40	RAPID-axSpA (AS)	(48 weeks) 70/121 (58%)[a]	(96 weeks) 61/121 (50%)[a]		
BASDAI 50					
Etanercept					
ASAS 20	Calin 2004		(108 weeks) 52/81 (64%)[d]		
ASAS 40	Calin 2004		(108 weeks) 44/81 (54%)[d]		40/81 (49%)[d]
BASDAI 50	Calin 2004		(108 weeks) 42/81 (52%)[d]		39/81 (48%)[d]
Golimumab					
ASAS 20	GO-RAISE		235/356 (66%) [a]	(160 weeks) 246/356(69%)[a]	235/356 (66%)[a]
ASAS 40	GO-RAISE		203/356 (57%)[a]	(160 weeks) 208/356 (58%)[a]	203/356 (57%)[a]
BASDAI 50	GO-RAISE		199/356 (58%)[a]		199/356 (58%)[a]
Infliximab					
ASAS 20	Park 2013	(78 weeks) 125/174 (72%)[de]	(102 weeks) 127/174 (73%)[de]		
ASAS 40		(78 weeks) 93/174 (53%)[de]	(102 weeks) 101/174 (58%)[de]		
ASAS 40	ASSERT 2005	(102 weeks)	33/78 (42%)[af]		
BASDAI 50	Braun 2002	(54 weeks) 33/69 (48%)[a]	(102 weeks) 30/69 (43%)[a]		

[a]NRI imputed result calculated using number of patients randomised as denominator; [b]NRI imputed result calculated using number of patients at week 12 as denominator; [c]NRI imputed result calculated using number of patients who had received at least one dose of active as denominator; [d]NRI imputed result calculated using number of patients who had received active during open-label phase as denominator; [e]Inflectra and infliximab combined; [f]Only the subset of patients who took the 5mg dose of infliximab (remaining patients took 5 or 7.5 mg)

Table 15 presents the results based on non-responder imputation (NRI) analyses for the main studies where these results could be extracted. For AS the results show that across all the anti-TNFs after approximately two years of treatment, around half of patients are still achieving a good level of response to therapy. The results for golimumab look particularly strong with around 60% of all randomised patients achieving ASAS 40 and BASDAI 50 after 5 years. However, this is probably not reflective of clinical practice as many of the normal weight patients took the 100 mg dose of

golimumab rather than the 50 mg dose: the licence only permits the use of 100 mg dose in patients with a body weight of more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses. The equivalent results for adalimumab and etanercept are around 30% and 50%, though it is unknown if the difference may be due to differences in follow-up protocols than true treatment difference.

Table 16 Treatment effect over time (nr-axSpA only) (results calculated using NRI)

Outcome	Trial	52 weeks	104 weeks	156 weeks	5 years (approx. 264 weeks)
Adalimumab					
ASAS 20	ABILITY-1			83/142 (58%)[b]	
ASAS 40	Haibel 2008	23/46 (50%) [a]			
ASAS 40	ABILITY-1	(68 weeks) 77/142 (54%)[b]		67/142 (47%)[b]	
BASDAI 50	Haibel 2008	24/46 (52%)			
BASDAI 50	ABILITY-1	(68 weeks) 74/142(52%)[b]		70/142 (49%)[b]	
Certolizumab					
ASAS 20	RAPID-axSpA (AS)	(48 weeks) 68/97 (70%)[a]	(96 weeks) [redacted]		
ASAS 40	RAPID-axSpA (AS)	(48 weeks) 56/97 (58%)[a]	(96 weeks) 49/97 (51%)[a]		
BASDAI 50					
Etanercept					
ASAS 20	Dougados 2014	(48 weeks) [redacted]			
ASAS 40		(48 weeks) 108/205 (53%)[a]			
BASDAI 50		(48 weeks) [redacted]			

[a]NRI imputed result calculated using number of patients randomised as denominator; [b]NRI imputed result calculated using number of patients at week 12 as denominator

The long-term follow-up for nr-axSpA patients (Table 16) shows continued high proportions of responders. At one year around half of patients are achieving an ASAS 40 or BASDAI 50 level response and with certolizumab this is maintained at two years and with adalimumab at 3 years.

When the long-term data are presented as observed or as completer analyses the long-term results are similarly good: withdrawal rates are not high and a high proportion of those who remain on treatment continue to achieve a good response, see the example data available from one trial of adalimumab and one of certolizumab pegol(Table 17).

Table 17 Observed or completer analysis results

Trial, anti-TNF, population	Time point	Type of analysis	ASAS 20	ASAS 40	BASDAI 50
ATLAS 2006 Adalimumab (AS)	52 weeks	Observed	193/276 (70%)	138/276 (50%)	167/276 (61%)
	104 weeks	Observed	135/173 (78%)	109/173 (63%)	122/173 (71%)
	5 years	Completer	111/125 (89%)	88/125 (70%)	96/124 (77%)
RAPID-axSpA Certolizumab pegol – all (AS)	96 weeks	Observed	[redacted]	[redacted]	
RAPID-axSpA Certolizumab pegol – all (nr-axSpA)	96 weeks	Observed	[redacted]	[redacted]	

At long-term follow-up mean final values or mean change from baseline for BASDAI, BASFI and BASMI, where reported, were generally maintained at clinically meaningful levels.

For adalimumab, data from the large ATLAS trial showed that mean changes from baseline at 1, 2 and 3 years remain stable and clinically meaningful at around -3.7 for BASDAI and at around -2.9 for BASFI. Similarly, the mean final value for BASMI remains at a level indicative of clinically significant treatment benefit (3.1 to 3.7). At 5 years the mean final values are BASDAI 1.8, BASFI 2.1, and BASMI 3.7. Clearly these results only relate to those patients who have remained on adalimumab in the long-term (40% of those who started adalimumab). They do however demonstrate continued benefit in a significant proportion of patients.

For certolizumab results for these outcomes are only available up to one year (48 weeks). At this time point the mean BASDAI and BASFI are indicative of clinically significant treatment benefit (both around 3 units).

The long-term data from Calin et al 2004 for etanercept, with 81 patients at 2 years and 59 (73%) remaining at 5 years also report mean BASDAI and BASFI scores of around 3.

From GO-RAISE at 2 years for those who took golimumab throughout the trial and follow-up (n=138), median BASDAI was around 3 and median BASFI was around 2. These values are from a LOCF analysis of all patients randomised to golimumab 50 mg.

For infliximab the Braun 2002 study and follow-up found from 1 to 3 years a stable mean BASDAI of around 2.6, a stable mean BASFI of around 3 and a stable mean BASMI of around 2.7.

Overall the reported data (though not particularly robust) do indicate that significant proportions of patients continue to derive real benefit from continued use of anti-TNFs. There is nothing to indicate any difference between them.

Almost no data were available regarding radiographic progression of bony disease in patients with AS. Furthermore it should be noted that radiographic changes and progression of these take many years to appear and x-rays are an insensitive tool by which to evaluate the progression of AS. Therefore evidence, particularly that from relatively short term studies has to be interpreted with caution. The limited evidence includes mSASSS change from baseline, reported for golimumab from the GO-RAISE study at 4 years (208 weeks): 1.3 (SD 4.1) based on the 111of 138 patients randomised to 50 mg. As results from untreated cohorts suggest a progression rate of 2 units/2years, a rate of 1.3 (or even 2) over 4 years seems beneficial. For further discussion of this issue see Section 4.2.4.1. MASES was reported only for adalimumab from ATLAS: in patients remaining on therapy at 2 years the mean change from baseline was 2.2 (n=217).

For nr-axSpA patients long-term data for the continuous outcomes was limited to one year's follow-up. For adalimumab data were available from only one small study (Haibel 2008 n=46): BASDAI change from baseline: 2.8 (95% CI 2.1, 3.6); BASFI change from baseline: 2 (95% CI 1.4, 2.6); BASMI change from baseline: -0.4 (95% CI -0.7 to -0.04); and MASES change from baseline of 0.9 (95% CI -0.02 to 1.9). Also, of 26 patients with MRIs at baseline and 52 weeks follow-up, showed no change in sclerosis or in erosions. For etanercept data were available on 205 patients randomised to etanercept or placebo and then on long-term etanercept (Dougados 2014):

[redacted] For certolizumab LOCF analysis at 48 weeks (n=97) gave a BASDAI final value of around 3, and a BASFI of around 2.5. Overall the one year results in nr-axSpA patients are similar to each other and also reflect those seen in AS patients. Again the short term nature of this follow-up relative to the 8 to 10 years over which radiographic changes develop must be borne in mind.

4.2.4 Findings from anti-TNF patient registry studies

4.2.4.1 Effect of anti-TNFs on radiographic progression

A total of seven studies were identified that provided some comparative results on the effect of anti-TNFs on radiographic progression (Table 18).

Table 18 Effect of anti-TNFs on radiographic progression

Van der Heijde, D. et al. Arthritis Res Ther. 2009; 11:R127.[110]	Study used 2 year data from active treatment arms of two adalimumab trials (total n=397) and compared them with OASIS cohort (186 with radiographs at 2 years). NB primary analysis set = 307 adalimumab (minimum of 1.5 years exposure to drug) and 169 anti-TNF naïve (OASIS).	There were significant differences between adalimumab and OASIS patients at baseline for BASDAI, BASFI and other measures. Increase in mSASSS was very similar in the two groups: adalimumab 0.8 (SD 2.6), OASIS 0.9 (SD 3.3). When only patients who would have qualified for the adalimumab trials were included in the OASIS cohort (n=77) the results were not changed. Note in the light of the van der Heide results above, it would have been good to test effect of baseline BASDAI (mean 6.2 in adalimumab cohort, 3.4 in OASIS) as without treatment progression in adalimumab cohort would have been expected to be higher than in OASIS one, so there might have been some effect of adalimumab.
Van der Heijde D, et al Arth. Rheum 2008; 58: 3063-70[98]	Study compared 2 year data from infliximab trial (ASSERT) (n=201) with that from OASIS (n=192). OASIS patients not treated with any anti-TNF.	There were significant differences between infliximab and OASIS patients at baseline for BASDAI, BASFI and other measures (higher disease activity and worse function in trial patients). Mean increase in mSASSS was very similar in the two groups: infliximab 0.9 (SD 2.6), OASIS 1.0 (SD 3.2). When only patients who would have qualified for the infliximab trials were included in the OASIS cohort (n=70) the results changed very little (mean mSASSS increase 1.2 (SD 3.9).
Van der Heijde D, et al Arth. Rheum 2008; 58: 1324-31[111]	Study compared 2 year data from etanercept trial (Davis et al) (n=257) with that from OASIS (n=175). OASIS patients not treated with any anti-TNF.	There were significant differences between infliximab and OASIS patients at baseline for BASDAI, BASFI and other measures higher disease activity and worse function in trial patients). Increase in MSASSS was very similar in the two groups: etanercept 0.91 (SD 2.5), OASIS 0.95 (SD 3.2). When only patients who would qualified for the etanercept trials were included in the OASIS cohort (n=76) the results changed very little (mean mSASSS increase 1.3 (SD 3.6).
Braun J. et al. Ann Rheum Dis 2014; 73:1107-13[112]	Long-term data on golimumab (2 and 4 year radiographic data) (n= 233). No comparison with OASIS made	Mean Increase in MSASSS to 2 years was 0.9 (SD 2.7) (50 mg) and 0.9 (SD 3.9) (100 mg). Mean Increase in MSASSS to 4 years was 1.3 (SD 4.1) (50 mg) and 2.0 (SD 5.6) (100 mg). Note 2 year results are very similar to those with other anti-TNFs and OASIS. i.e. no benefit of golimumab evident.
Haroon N et al, Arth Rheum 2013;65:2645-54[113]	Cohort study (n= 334 patients with at least two spinal radiographs at 2 year intervals (patients with total spinal fusion at baseline excluded). Logistic regression analysis tested for baseline mSASSS, ESR,BASDAI,Smoking, male vs female, age at onset, disease duration, HLA-B27, anti-TNF use, and NSAID index. Further analysis tested factors that could influence exposure to anti-TNFs using propensity matching.	201/334 patients had received anti-TNFs for a mean of 2.5 years (SD 2.6). No radiographic abnormality of the spine was seen at baseline in 144 patients (43%) and 102 patients (30.5%) showed no progression (>1 mSASSS unit/year). Mulitvariate regression found baseline mSASSS (OR 1.06, 95% CI 1.04-1.08), ESR, and smoking significantly increased and anti-TNF use significantly increased odds of radiographic progression (OR 0.47, 95% CI 0.24-0.94). Further analysis using the 142 that could be included post-propensity matching confirmed these findings except for ESR: baseline mSASSS (OR 1.05, 95% CI 1.02-1.08), anti-TNF (OR 0.30, 95% CI 0.11-0.78). Note the association with anti-TNF use is explained by the more severe patients with radiographic changes at baseline being treated with anti-TNFs.
Barialiakos X. eta l. Ann Rheum Dis 2014; 73: 710-5[114]	Comparison of long-term (8 years) treatment with infliximab with historical cohort (n= 22 infliximab, n=34 Herne cohort).	Progression as assessed by mSASSS increased equally in infliximab treated patients and in the Herne cohort from baseline to 2, 4 and 6 years but then whilst progression increased only slightly in the infliximab group between 6 and 8 years it increased greatly in the Herne cohort so that at 8 years there was a difference in infliximab's favour of 4.5 mSASSS units (p=0.047). Result was adjusted for baseline mSASSS. Other factors (age, symptom duration, BASDAI, BASFI) not significant confounders.
Barialiakos 2007[115]	4 year radiographic progression in AS patients treated with infliximab. Crude comparison made with OASIS cohort results at 4 years	n = 33 Mean (SD) at baseline mSASSS 11.6 (15.3) BASDAI 6.6 (1.4)

		BASFI 3.5 (1.9) Progression assessed by mSASSS. Mean change over 4 years was 1.6 (SD 2.6) mSASSS units. Published results for OASIS are 4.4 units in 4 years

Four studies reported on disease progression over 2 years of follow-up in terms of mSASSS in patients taking adalimumab, [110] infliximab,[98] etanercept,[111] and golimumab.[112] All four open-label, uncontrolled follow-up studies found that mSASSS increased by a mean of around 0.9 over two years. Three of these studies compared their rates with those from the OASIS cohort (of patients not taking an anti-TNF) and found no difference (mean rate over 2 years for OASIS 0.9 units, Table 19). As stated in the previous section radiographic changes and progression of these take many years to appear and therefore the evidence from these relatively short term studies has to be interpreted with caution.

Table 19 Summary of long-term results for mSASSS change

Anti-TNF	Increase in mSASSS over 2 years (mean (SD)(n) – patients on an anti-TNF	Increase in mSASSS over 2 years (mean (SD)) – patients from OASIS Cohort (n)
Adalimumab[110]	0.8 (SD 2.6)(397)	0.9 (SD 3.3) (186)
Etanercept[111]	0.91 (SD 2.45)(257)	0.95 (SD 3.2) (175)
Infliximab[98]	0.9 (SD 2.6) (201)	1.0 (SD 3.2) (192)
Golimumab[112]	0.9 (SD 2.7) (50 mg) (111) 0.9 (SD 3.9) (100 mg)(122)	- -

Comparison of the rates calculated from the OASIS cohort in these studies, with those from the studies by Ramiro highlight a discrepancy: the latter reported rates of 2 mSASSS units every 2 years, rather than the 0.9 units /two years used here to compare with individual anti-TNFs.

Two very small studies of infliximab reported some inhibiting effect on radiographic progression.[114, 115] The first[114] compared findings in 22 infliximab patients with 34 from the HERNE cohort, over 2, 4, 6 and 8 years. Progression as assessed by mSASSS increased equally in infliximab treated patients and in the untreated HERNE cohort from baseline to 2, 4 and 6 years but then whilst progression increased only slightly in the infliximab group between 6 and 8 years it increased greatly in the Herne cohort so that at 8 years there was a difference in infliximab's favour of 4.5 mSASSS units. The result was adjusted for baseline mSASSS (other factors – age, symptom duration, BASDAI, BASFI etc., were not statistically significant confounders). The other study of 33 patients found the mean progression over 4 years was 1.6 (SD 2.6) mSASSS units, lower than the 4.4 units seen in the untreated OASIS cohort at 4 years.[115]

Another study examined a cohort of 334 patients with at least two spinal radiographs at 2 year intervals (patients with total spinal fusion at baseline were excluded).[113] In this study 201/334 patients

had received anti-TNFs for a mean of 2.5 years (SD 2.6) and no radiographic abnormality of the spine was seen at baseline in 144 patients (43%). At follow-up 102 patients (30.5%) showed no progression (≥1 mSASSS unit/year). Mulitvariate regression found baseline mSASSS (OR 1.06, 95% CI 1.04-1.08), ESR, and smoking, significantly increased the odds of radiographic progression, but anti-TNF use was significantly associated with a > 50% reduction in the (adjusted) odds of progression (0.47, 95% CI 0.24-0.94). Further analysis that tested factors that could influence exposure to anti-TNFs using propensity matching confirmed the association with mSASSS and found a stronger association with anti-TNF use (OR 0.30, 95% CI 0.11-0.78).

In conclusion there is evidence of disease progression over time, though the disease course is highly variable. Best estimates of yearly disease progression rates without anti-TNF therapy are around 1.0 mSASSS units and 0.035 to 0.07 BASFI units. Whether there is any impact of anti-TNF treatment is unclear: a beneficial effect cannot be assumed, nor, given the short term nature of the follow-up and the insensitivity of x-rays as a tool for the evaluation of disease progression in AS, can one be discounted.

4.2.4.2 Drug survival and anti-TNF switching

The endnote library generated by the searches for RCTs of all the anti-TNFs were separately screened to identify patient registry studies of any or all of the anti-TNFs. This was possible because the search strategy for RCTs was very sensitive and will have identified any clinical study including any of the named anti-TNFs.

A total of 25 potentially relevant studies were screened fully and 12 publications that reported some data on drug survival or the efficacy of anti-TNFs after switching were identified (see Table 22 for summary details of each). Across the 12 studies, the source of data were either retrospective cohort studies or prospective registers (though analysis plans may have been retrospective), from a range of countries: USA (two studies), Canada (one study), Europe (9 studies). No data from a UK-based cohort were available. Most of the cohorts and registries included experience with the three oldest anti-TNFs: infliximab, etanercept and adalimumab. One study (of the RHAPSODY cohort) included results from 326 patients treated with adalimumab as 2nd anti-TNF after infliximab or etanercept. Small numbers of patients provided data on golimumab (3 studies) and even smaller numbers on certolizumab (2 studies). The population in 10 of the 12 studies was AS, although the diagnostic criteria used to specify AS were rarely given. One study provided results specifically for nr-axSpA, and one study provided results for axial SpA (nr-axSpA or AS).

Drug survival on 1st anti-TNF for all anti-TNFs was around 70- 80% at one year, around 65 - 75% at 2 years, around 70% at 3 years and 55% at 5 years. Little difference between the three older anti-TNFs

was identified, although one analysis using Cox proportional hazard estimates found statistically lower rates of discontinuation with etanercept and adalimumab compared with infliximab.[116]

The median drug survival in AS patients across all anti-TNFs reported varied (Table 20). Based on the largest registry (DANBIO)[117] the median drug survival for a first anti-TNF was 3.1 years (95% CI 2.6, 3.7) (n=1436), with 58% of patients remaining on treatment at 2 years. Median drug survival for a second anti-TNF was 1.6 years (95% CI 1.0-2.2) (n=432), with 47% of patients remaining on treatment at 2 years, and for a 3rd, 1.8 years (95% CI 0.9-2.7) (n=137) (49% on treatment at 2 years).

The efficacy of 2nd or 3rd anti-TNFs after switching in AS patients was reported in only a small number of studies. One analysis based on the NOR-DMARD registry[118] showed how the response rate and BASDAI and BASFI achieved at 3 months in patients who remain on their first therapy is (not surprisingly) better than in patients who switch. Median BASDAI and BASFI achieved with a second anti-TNF were not as low (not as good) as was achieved with a first anti-TNF in non-switchers. An analysis of the DANBIO registry indicated that response (BASDAI 50) at 6 months reduced with subsequent anti-TNFs , as did the median improvement in BASDAI and BASFI achieved (Table 21).[117] These results are supported by the RHAPSODY study that found higher response rates with adalimumab in anti-TNF naïve patients (BASDAI 50 - 63%; ASAS40 – 59%)(n=924) than in anti-TNF exposed (BASDAI 50 – 41%; ASAS40 – 38%) (n=326).[119]

The registries and cohort studies provided no data on the efficacy of anti-TNFs as 2nd or 3rd, after switching in nr-axSpA patients.

Table 20 Drug survival results from analysis of DANBIO registry[117]

Anti-TNF	**Median (95% CI) drug survival (% on treatment after 2yrs) for sequential anti-TNFs:**
1st (n=1436)	3.1 (2.6, 3.7) (58%)
2nd (n=432)	1.6 (1.0-2.2)) (47%)
3rd (n=137)	1.8 (0.9-2.7) (49%)

Table 21 Efficacy results from analysis of DANBIO registry[117]

Anti-TNF	**% BASDAI50/20mm responders at 6 months (at 3 NR):**	**Median (IQR) BASDAI at 0 months for sequential anti-TNFs**	**Median (IQR) BASDAI at 3 months for sequential anti-TNFs:**	**Median (IQR) BASFI at 0 months for sequential anti-TNFs:**	**Median (IQR) BASFI at 3 months for sequential anti-TNFs:**
1st (n=1436)	54%	5.9 (4.5-7.1)	2.8 (1.1-4.8)	5.0 (3.4-6.7)	2.8 (1.1-4.8)
2nd (n=432)	37%	5.6 (3.8-7.3)	(3.6 (1.9-6.4)	5.2 (3.5-7.0)	3.6 (1.7-6.0)
3rd (n=137)	30%	6.4 (4.8-7.9)	(5.1 (3.6-6.7)	6.4 (4.2-7.9)	5.1 (3.0-7.3)

In summary, sequential treatment with anti-TNFs can be worthwhile in patients with AS but the response rates and benefits are reduced with 2nd and 3rd anti-TNFs, with the proportion of BASDAI 50 responders falling approximately 10% with each subsequent anti-TNF and the median BASDAI and BASFIs achieved increasing (worsening). The lower efficacy of a 2nd anti-TNF relative to a first is reflected in lower median drug survival and proportion of patients remaining on therapy at 2 years. Interestingly, despite a further reduction in response and efficacy with a 3rd anti-TNF, drug survival does not fall, suggesting that at this stage in their treatment history patients may continue with a less than optimally effective anti-TNF given any better alternative..

Table 22 Registry studies reporting data on drug survival and anti-TNF switching

Citation	Study/registry and Method	N (duration)	Population	Anti-TNFs included	Drug survival and efficacy on switching
Bonafede 2012 [120]	Market Scan USA (administrative claims data) 2005-2009 Retrospective	308 (360 days)	AS	Etanercept Adalimumab Infliximab	**Drug survival** N (%) stopped treatment and did not switch / switched. Etanercept (n= 149) 42 (28%)/12 (8%) Adalimumab (n= 103) 36 (35%)/11 (11%) Infliximab (n= 46) 14 (30%)/6 (13%) **Efficacy on switching** - NR
Choquette 2012[121] (abstract only)	Rhumadata (Canada)register	119 (5 yrs)	AS, previous NSAIDs and BASDAI ≥4	Etanercept Adalimumab Infliximab	**Drug survival** N who remained on same anti-TNF was 80% at 1 yr; 70% at 2 yrs; and 55% at 5yrs (no difference between anti-TNFs). Efficacy on switching - NR
Gulfe 2014[122]	SSATG registry Prospective, Sweden	112 (2 years)	Nr-axSpA not AS Demographic summary available	Etanercept Adalimumab Infliximab Golimumab Certolizumab	**Drug survival** Kaplan Meier estimates drug survival was 76% at 1 yr and 65% at 2 yrs. **Efficacy on switching** - NR
Nell-Duxneuner 2012[123]	Austrian Drug reimbursement data retrosp	694 (2 yrs)	AS	Etanercept Adalimumab Infliximab	**Drug survival** Starting in 2007 I yr drug survival was: Etanercept 0.83 (1 yr); 0.58 (2 yr) Adalimumab 0.70 (1 yr); 0.55 (2 yr) Infliximab 0.71 (1 yr); 0.54 (2 yr) **Efficacy on switching** - NR
Yeaw 2014[124]	Retrosp use of LifeLink Health Plan Claims database 2004-2010. USA	632	AS patients who had discontinued an anti-TNF	Etanercept Adalimumab Infliximab	**Drug survival** % who restart within 360 days after stopping: Etanercept 59% (n=376) Adalimumab 45% (n=134) Infliximab 39% (n=122) % switch to another anti-TNF or biologic

Citation	Study/registry and Method	N (duration)	Population	Anti-TNFs included	Drug survival and efficacy on switching
					Etanercept 17% (n=376) Adalimumab 13% (n=134) Infliximab 24% (n=122) % switch to non-biologic Etanercept 5% (n=376) Adalimumab 8% (n=134) Infliximab 6% (n=122) % switch to no new treatment Etanercept 18% (n=376) Adalimumab 34% (n=134) Infliximab 30% (n=122) **Efficacy on switching** - NR
Scire et al 2013[116]	MonitorNet database (Italian Soc. Rhuematol) to 2012. Multiple imputation used for missing data	498	AS	Etanercept Adalimumab Infliximab	**Drug survival** Unadjusted K-M estimates of drug survival at 1 yr – 0.87 (95% CI 0.83-0.89) 2 yrs – 0.72 (95% CI 0.67-0.77) 3 years 0.69 (95% CI 0.63-0.74) Adjusted HR discontinuation rate (median follow-up 17 months) 0.59(95% CI 0.46, 0.75) (adjusted for age, gender, no. comorbidities,disease duration, number of previoud DMARDs, concurrent DMARDS, baseline BASDAI and BASFI) **Efficacy on switching** - NR
Zufferey 2014[125]	Single centre in Switzerland (CHUV) 2011-12 Retrospective	112, of whom 77 were AS. Follow-up at 12 and 24 mths	SpA (AxSpA and AS)	Etanercept Adalimumab Infliximab Golimumab	**Drug survival** Median drug survival across all anti-TNFs 12 mths (IR 7-19) for AxSpA and 8 mths (IR 6-13) for AS. Drug survival for AS: 1 yr 49%, 2 yrs 36%. No difference between anti_TNFs. Efficacy on switching - NR

Citation	Study/registry and Method	N (duration)	Population	Anti-TNFs included	Drug survival and efficacy on switching
Pavelka 2009[126]	Czech National registry ATTRA	310 (1 year)	AS (note mean BASDAI 6.4 at baseline)	Etanercept Adalimumab Infliximab	**Drug survival** at 1 year was 84%; at 2 yrs 76%; and at 3 yrs 72%. **Efficacy on switching** - NR
Lie 2010[118]	NOR-DMARD Register (from 2000 to March 2009), Norway	514	AS	Etanercept Adalimumab Infliximab	**Drug survival** 77 patients switched from first anti-TNF; 437 did not. In the 77 switchers median drug survival on first anti-TNF was 266 days *range 1-1392) on the first anti-TNF and the 2nd anti-TNF was started a median of 77 days (Range 0-1608 after the first was stopped). Finding may just be a consequence of the stopping rules in Denmark (patients given around 6 months to achieve a response) % on treatment after 1 and 2 years: 1st anti-TNF: 76% and 65% 2nd anti-TNF: 67% and 60% **Efficacy on switching** Non-Switchers Response to 1st anti-TNF at 3 months (n=362): BASDAI 50 – 105/362 ASAS 20 – 106/202 ASAS 40 – 76/202 Median (IQR) BASFI 2.3 (0.7-4.0) Median (IQR) BASDAI 2.6 (1.3-4.4) Switchers Response to 1st anti-TNF at 3 months: BASDAI 50 – 6/63 ASAS 20 – 11/23 ASAS 40 – 7/23 Median (IQR) BASFI 4.7 (1.5-6.0) (n=63) Median (IQR) BASDAI 4.8 (3.3-7.01) (n=63)

Citation	Study/registry and Method	N (duration)	Population	Anti-TNFs included	Drug survival and efficacy on switching
					Response to 2nd anti-TNF at 3 months: BASDAI 50 – 13/62 ASAS 20 – 18/45 ASAS 40 – 14/45 Median (IQR) BASFI 3.3 (1.6-5.7) (n=62) Median (IQR) BASDAI 4.1 (1.9-6.1) (n=62) Data also available by reason for withdrawal LOE or AE – see publication's web files
Glintborg 2010[108]	DANIBO Registry Denmark	842 (8 years)	AS	Etanercept Adalimumab Infliximab	**Drug survival** Median drug survival was 4.3 years (unadjusted 1 and 2 years retention rates 74% and 63%) – similar across 3 anti-TNFs – only male gender, low baseline VAS fatigue and high CRP (>14mg/l) associated with better drug survival **Efficacy on switching** - NR
Glintborg 2012[117]	DANBIO Registry Denmark	1436 (432 switchers)	AS (Switchers only – had received at least2 anti-TNFs during follow-up)	Etanercept 22% Adalimumab 38% Infliximab 36% Golimumab 3% (certilizumab and other biologics less than 1% between them) and only to 1st treatment course)	Median (95% CI) years of drug survival (n) (% on treatment after 2yrs) for sequential anti-TNFs: 1st anti-TNF3.1 (2.6, 3.7) (n=1436)(58%) 2nd anti-TNF1.6 (1.0-2.2) (n=432)(47%) 3rd anti-TNF1.8 (0.9-2.7) (n=137) (49%) **Efficacy on switching** Median (IQR) BASDAI at 3 months for sequential anti-TNFs: 1st (n=1436) 2.8 (1.1-4.8) 2nd (n=432)3.6 (1.9-6.4) 3rd (n=137) 5.1 (3.6-6.7) Median (IQR) BASFI at 3 months for sequential anti-TNFs: 1st (n=1436) 2.8 (1.1-4.8) 2nd (n=432) 3.6 (1.7-6.0) 3rd (n=137) 5.1 (3.0-7.3) % BASDAI50/20mm responders at 6 months (at 3 NR):

Citation	Study/registry and Method	N (duration)	Population	Anti-TNFs included	Drug survival and efficacy on switching
					1st 54% 2nd 37% 3rd 30%
Rudwaleit 2009[119]	/RHAPSODY – European cohort Prospective uncontrolled cohort of pts treated with adalimumab	1250 (12 week response data only)	AS	Adalimumab	**Drug survival** – NR **Efficacy on switching** 12 week response rates: Anti-TNF naïve (n=924) BASDAI 50 - 63% ASAS40 – 59% Anti-TNF exposed (etanercept and/or infliximab, n=326) BASDAI 50 – 41% ASAS40 – 38% Logistic regression with backward elimination found younger age, higher CRP, HLA-B27+ and anti-TNF naivity all predictive of better response (Table 1 in paper).

4.2.5 Clinical effectiveness results - Adverse events

Randomised trials

We focussed on the following outcomes, known to have possible associations with anti-TNF treatment: serious infections, TB (including TB reactivation), injection/infusion site reactions, congestive heart failure, cancer, non-melanoma skin cancer, serious adverse events, and withdrawals due to serious adverse events. For the randomised phases of the trials included in the review, the reporting of adverse event data was generally limited. For three of the 24 trials no information on adverse events was available.[59, 61, 74] Several trials provided adverse event data only at time points after which placebo patients may have switched to receive an anti-TNF (so true placebo comparisons were not available).

Analysable data on injection/infusion site reactions were available for ten trials, although these studies were only of etanercept or infliximab. The data for certolizumab, golimumab, and adalimumab trials were either not reported, or were only provided at time points after which placebo patients could 'escape' to receive an anti-TNF; these data would not allow for an accurate comparison with placebo. Results for injection/infusion site reactions analyses from this review for etanercept and infliximab showed a statistically significant increase in reactions associated with etanercept (RR 2.69, 95% CrI 1.82 to 3.89) when compared with placebo but no significant difference between infliximab and placebo. When compared with each other, the risk of an injection/infusion site reaction was statistically significantly higher with etanercept than with infliximab (RR 2.27, 95% CrI 1.01 to 5.37). Incidence of serious infections was reported in only eight trials, though such events were rare (9 cases in total). Of the eight trials which reported incidence of tuberculosis, only 4 cases were identified; three cases were reported in the longest study, the 54 week trial which compared infliximab with an inliximab biosimilar (Inflectra).[105] Four trials reported on congestive heart failure (no cases reported), six trials reported on cancer (one case) and three trials reported on non-melanoma skin cancer (2 cases, one in each group of the ABILITY-1 trial). In most trials few SAEs were reported; group rates ranged from 0 to around 9%. Similarly, most trials had few withdrawals due to adverse events; rates ranged from 0 to around 12%. Full results are reported in Appendix 8.

Large systematic reviews

Overall, the number and size of trials, and the short duration of their placebo-controlled phases, were too limited to provide enough data for meaningful analyses of adverse events. This common problem - of having too little data to evaluate adverse events - underpinned the rationale for a Cochrane review (and network meta-analysis) of adverse events of nine biologics in adults with any disease, except HIV/AIDS.[127] In order to provide a better understanding of toxicity, data were pooled across diseases by assuming a similar rate of adverse events (across diseases). For the present assessment, estimates of adverse event rates have therefore been derived from the Cochrane review, which included 160

RCTs (n=48,676) and 46 open-label extension studies (n=11,954). The median durations were 6 months for RCTs, and 13 months for open-label extension studies. The biologics included were abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituzimab and tocilizumab. The anti-TNFs included in the present assessment were studied in 115 (72%) of the RCTs and 40 (87%) of the open-label studies included in the Cochrane review. Most studies assessed etanercept or infliximab, in cancer or rheumatoid arthritis patients; 10 RCTs were of ankylosing spondylitis (fewer than in this assessment, since in the Cochrane review databases were searched up until January 2010). The biologics were evaluated both as a group, and as individual interventions. The results from the RCTs (what the review classified as 'major' outcomes) are in Tables 23 and 24. Biologics as a group were associated with statistically significantly higher rates of total AEs, withdrawals due to AEs, serious infections, and TB reactivation when compared with control treatments. When the individual anti-TNFs were analysed separately, compared with control treatments only infliximab and certolizumab were statistically significantly associated with adverse events: infliximab with higher rates of total adverse events (NNH 13, 95% CrI 8 to 505) and withdrawals due to adverse events (NNH 10, 95% CrI 5 to 30), and certolizumab pegol with higher rates of serious infections (NNH 12, 95% CrI 4 to 79) and serious adverse events (NNH 18, 95% CrI 9 to 162) (Table 24).

Table 23 Cochrane summary of findings Table for biologics as a class (adapted from Singh et al (2011))

Adverse event	Risk with comparator, per 1000 patients unless otherwise stated	Risk with intervention, per 1000 patients, unless otherwise stated (95% CrI)	Odds ratio (95% CrI)	Number of participants (studies)
SAEs	118	127 (115 to 142)	1.09 (0.97 to 1.24)	21,152 (76)
Total AEs	724	770 (741 to 797)	1.28 (1.09 to 1.50)	14,959 (48)
Withdrawal due to AEs	98	137 (115 to 168)	1.47 (1.20 to 1.86)	22,636 (83)
Serious infections	26	35 (27 to 46)	1.37 (1.04 to 1.82)	21,853 (70)
TB reactivation	4 per 10,000	20 per 10,000	4.68 (1.18 to 18.6)	30,671 (71)
Lymphoma	9 per 10,000	1	0.53 (0.17 to 1.66)	21,260 (52)
Congestive heart failure	8	6 (1 to 21)	0.69 (0.18 to 2.69)	8,847 (24)

Table 24 Cochrane summary of findings Table for individual anti-TNFs (adapted from Singh et al (2011))

Anti-TNF	Risk with comparator, per 1000 patients unless otherwise stated	Risk with intervention, per 1000 patients, unless otherwise stated (95% CrI)	Odds ratio (95% CrI)	Number of participants (studies)
SAEs				
Adalimumab	118	114 (90 to 145)	0.96 (0.74 to 1.27)	4662 (15)
Certolizumab	118	174 (124 to 237)	1.57 (1.06 to 2.32)	2421 (6)
Etanercept	118	142 (111 to 184)	1.24 (0.93 to 1.69)	3931 (21)
Golimumab	118	123 (82 to 184)	1.05 (0.67 to 1.69)	1564 (8)
Infliximab	118	133 (102 to 174)	1.15 (0.85 to 1.57)	3403 (14)
Total AEs				
Adalimumab	724	730 (637 to 802)	1.03 (0.67 to 1.54)	3266 (10)
Certolizumab	724	754 (651 to 837)	1.17 (0.71 to 1.95)	1829 (5)
Etanercept	724	784 (677 to 866)	1.38 (0.80 to 2.46)	1600 (7)
Golimumab	724	765 (672 to 839)	1.24 (0.78 to 1.98)	1187 (6)
Infliximab	724	803 (726 to 860	1.55 (1.01 to 2.35)	2330 (9)
Withdrawal due to AEs				
Adalimumab	98	128 (81 to 194)	1.35 (0.82 to 2.22)	5268 (18)
Certolizumab	98	125 (70 to 226	1.32 (0.69 to 2.69)	2421 (6)
Etanercept	98	124 (82 to 191)	1.30 (0.82 to 2.17)	5189 (25)
Golimumab	98	127 (64 to 241)	1.34 (0.63 to 2.92)	1549 (7)
Infliximab	98	203 (132 to 310)	2.34 (1.40 to 4.14)	2973 (15)
Serious infections				
Adalimumab	26	32 (17 to 60)	1.23 (0.65 to 2.40)	4847 (15)
Certolizumab	26	113 (39 to 330)	4.75 (1.52 to 18.45)	1683 (4)
Etanercept	26	33 (19 to 61)	1.29 (0.72 to 2.45)	4630 (19)
Golimumab	26	29 (12 to 65)	1.11 (0.45 to 2.59)	1334 (6)
Infliximab	26	36 (20 to 65)	1.41 (0.75 to 2.62)	2652 (13)
TB reactivation				
All 9 biologics	4 per 10,000	20 per 10,000	4.68 (1.18 to 18.60)	30,671 (71)
Lymphoma				
All 9 biologics	9 per 10,000	1	0.53 (0.17 to 1.66)	21,260 (52)
Congestive heart failure				
All 9 biologics	8	6 (1 to 21)	0.69 (0.18 to 2.69)	8847 (24)

For total adverse events the Cochrane review team judged the strength of evidence to be high; for serious adverse events, withdrawals due to adverse events, and serious infections the strength of evidence was judged to be moderate; for TB reactivation, lymphoma, and congestive heart failure the strength of evidence was judged to be low. For TB reactivation, lymphoma, and congestive heart failure the network meta-analysis statistical models did not converge (due to low numbers of events) so estimates for individual anti-TNFs were not available. Outcomes which were classed in the review as 'minor' were not analysed by the review authors due to low numbers of events and the complexity of the analyses for the major outcomes. The minor outcomes included cardiac adverse events, infusion and injection site reactions, allergic reactions, neurologic outcomes, deaths, all cancers, serious lung infections or pneumonia, fungal infections, and opportunistic infections. For the purposes of the present s assessment further large studies on cancer risk were therefore sought. An individual patient data meta-analysis of 22,904 adults (from 74 RCTs) which assessed the cancer risk of taking adalimumab, etanercept, or infliximab in the short-term (median duration <6 months) was identified.[128]Although funded by manufacturers, this study was requested by the EMA and was planned and conducted by independent researchers working with an independent academic steering committee. For all three anti-TNFs as a group, there was no increase in risk of cancers excluding non-melanoma skin cancer (RR 0.99, 95% CI 0.61 to 1.68), but there was a doubling in the risk of non-melanoma skin cancer associated with taking an anti-TNF (RR 2.02, 95% CI 1.11 to 3.95). Evaluation of drug-specific effects was hampered by statistical precision, and by differences in baseline cancer risk and reporting detail across trials.[128]

Another review of adverse effects of etanercept, adalimumab and infliximab was based on systematic searches for systematic reviews of the safety of biologic agents .[129] Six reviews that were sufficiently rigorous to meet the Database of Abstracts of Reviews of Effects (DARE) inclusion criteria were included in the overview. This review also included large RCTs and non-randomised studies (≥500 patients) and was focused on serious potential adverse events, such as serious infections, reactivation of latent TB, and cancer.[129] Table 25, which summarises the rates of serious adverse events among the included non-randomised studies and large RCTs, indicates that the rates of serious adverse events cover a broadly similar range across the three different biologic agents. However, all estimates were derived from a highly heterogeneous group of studies in terms of participants (e.g. inflammatory condition, disease severity), study design (e.g. length of follow-up) and treatment regimens (e.g. dose and frequency). Consequently, reliable estimates of the relative rate of serious adverse events for each drug could not be made.

Table 25 Prevalence ranges of serious adverse events from non-randomised studies and RCTs (reproduced from Rodgers et al.[129])

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

Withdrawal rates due to adverse events were typically <10% for all drugs, with the highest reported single estimate being 13.6% for one etanercept study. This suggested that the majority of patients can tolerate biologic treatment in the medium term, although again the estimates were derived from a highly heterogeneous group of studies, therefore the possibility of poorer tolerability in specific patient groups was not ruled out.

Open-label extensions of randomised trials

Of the longer-term follow up studies included in our present review we evaluated those reporting adverse events after six months (since the Cochrane review covered events occurring up to six months); 13 trial cohorts had studies which reported data after 6 months. Both the type of adverse events assessed, and the periods over which they were assessed, varied across studies. Table 26 compares results for studies with at least around 2 years of follow up. The ATLAS and GO-RAISE trials both had extension study publications at the 2 year and 5 year time points.[130-133]Both cohorts were analysed using modified intention-to-treat (mITT) data, in which patients had to have received at least one dose of treatment. This amounted to 99% of the randomised patients in both studies (311/315 in ATLAS, and 353/356 in GO-RAISE). Davis reported results for the 257 patients who enrolled in a 168-week open-label study following week 24 of the randomised phase; 277 patients had taken part in the earlier randomised study. All 257 patients in the open-label study had received at least one dose of etanercept.[134, 135] The Calin trial randomised 84 patients, with 81 patients enrolling in the open-label extension study. Results were presented separately for the 12 week to 2 year, and the 2 to 5 year time points.[136, 137] RAPID-axSpA data at 96 weeks were reported in the manufacturer submission. These data related to the mITT population: 315 (97%) of the 325 originally randomised patients.

The 2 year study of the ASSERT (infliximab) cohort allowed dose escalation whereby, from week 36, patients with BASDAI scores of ≥3 could increase their dose to 7.5mg/kg, which is a currently unlicensed dose. Results for the 5mg/kg group (74 patients) between weeks 24 and 102 have therefore been presented in Table 26. The Braun cohort was followed up for eight years, but it was a small study which reported only SAEs and withdrawals due to SAEs.

Table 26 Studies with adverse event data at around 2 years (or later)

Event outcome	Number of events (%) Number per 100 person years (PY)								
	Adalimumab		**Golimumab**		**Etanercept**			**Certolizumab**	**Infliximab**
	ATLAS n=311		GO-RAISE n=353		Davis n=257	Calin n=81	n=59	RAPID-axSpA n=315	ASSERT** n=74
	2 years	5 years	2 years	5 years	24 to 192 weeks*	12 to 108 weeks*	2 to 5 years	96 weeks	24 to 102 weeks
SAEs	48 (15%) 10.5/100 PY	140 (45%) 11.7/100 PY	40 (11%)	72 (20%)	33 (13%) 8/100 PY	19 (23%)	21/100 PY	[redacted]	15 (20%)
Withdrawals due to AEs	24 (8%) 4.5/100 PY	-	19 (5%)	32 (9%) 2.13/100 PY	14 (5%)	15 (19%)	7 (12%)	[redacted]	
Serious infections	6 (2%) 1.1/ 100 PY	17 (5%) 1.4/100 PY	11 (3%)	21 (6%) 2.1/100 PY	6 (2%) 2/100 PY	5 (6%)	3 (5%) 3/100 PY	[redacted]	3 (4%)
Cancer	4 (1%) 0.7/100 PY	3 (1%) 0.2/100 PY	2 (0.6%)	3 (0.8%) 0.21/100 PY	-	4 (5%)	3 (5%)	[redacted]	1 (1%)
NMSC	0.4/100 PY	-	-	-	-	-	-		
Congestive heart failure	0	2 (0.6%) 0.2/100 PY	-	-	-	-	-		
Injection site reactions	42 (14%) 17.6/100 PY	-	38 (11%)	43 (12%)	57 (22%)	30 (37%)	7 (12%)	[redacted]	9 (12%)
TB	0	0	-	-	-	0	0	[redacted]	

* Weeks from randomisation ** 5mg/kg group NMSC Non melanoma skin cancer

Table 26 illustrates that rates of SAEs, cancer, and serious infections were similar across all four anti-TNFs when using incidence per 100 patient years as estimates. At five years SAEs appeared more prevalent with adalimumab (45%) when compared with golimumab (20%), although it is possible this difference is due to the way the data were reported – it was unclear whether the ATLAS data related to the total number of SAEs, or to the number of patients experiencing an SAE. At 2 years, the incidence of injection site reactions was higher in patients taking etanercept than in patients taking adalimumab, golimumab or certolizumab pegol. Withdrawal rates due to AEs were broadly similar across treatments. The reporting of TB and congestive heart failure was limited.

Summary of adverse event data

Data from large systematic reviews, which included patients with a wide range of diseases, suggest that, in the short-term, anti-TNFs as a group are associated with significantly higher rates of serious infections, TB reactivation, non-melanoma skin cancer, total adverse events, and withdrawals due to AEs, when compared with control treatments. Specifically, infliximab is associated with significantly higher rates of total adverse events and withdrawals due to adverse events, and certolizumab pegol is associated with significantly higher rates of serious infections and serious adverse events. Analyses from the present review showed etanercept to be statistically significantly more likely to result in an injection/infusion site reaction when compared with infliximab, although analysable data on such reactions were not reported for the three other anti-TNFs. Evaluations of longer-term data are more scarce though suggest similar safety profiles across anti-TNFs. Data from the open-label studies included in this review also do not suggest that there are important differences between treatments, other than a higher incidence of injection site reactions following treatment with etanercept. These open-label data are however limited by the small sample sizes and non-randomised study designs.

4.2.6 Review of natural history of AS and nr-axSpA

In order to get some understanding of what happens to patients who, although eligible for anti-TNF therapy for their AS or nr-axSpA, do not receive it, we conducted a rapid review of relevant literature. This was not a systematic review but one that started with the library of papers found by the main searches for RCTs of the anti-TNFs and then followed relevant citations to papers on AS and axSpA in patients not receiving an anti-TNF. Potentially relevant papers were those that reported on the pattern of disease - AS or nr-axSpA or axSpA - without treatment with anti-TNFs over time. This process identified a number of relevant registries: OASIS, SIRAS, DESIR, Esperanza, REGISPONSER, GESPIC, and SMART and additional searches of Medline were conducted using these specific registry names. All relevant studies identified through this process are presented in Table 27.

The studies collectively explore the associations between the various components of axSpA: disease activity, structural damage and spinal mobility. The exploration of the ASSERT trial baseline data[25,

[138] reveals that health-related quality of life as determined by SF-36 physical and mental components, is determined by BASFI and BASDAI; BASFI is determined by BASDAI, mSASSS and BASMI (spinal mobility); and BASMI is independently determined both by irreversible (mSASSS) and reversible spinal damage (MRI): the former in late disease, the latter in early disease.

The studies identified that from a clinical practice and patients' point of view disease progression in terms of BASFI, a measure of the patient's functional ability, is very important. A number of studies on the disease progression of AS have been based on the European OASIS cohort (a consecutive cohort, started in 1996, though there were no further specific eligibility criteria); the total cohort numbers 217 patients. One of these, a study by Landewe et al.,[12] demonstrated that physical function impairment (BASFI) is independently affected by both disease activity (BASDAI) and bony progression – usually assessed using mSASSS despite this being a measure of bony growth in the spine only (and not in the sacroiliac joints). Other studies by Ramiro[139, 140] have demonstrated that radiographic progression, increases on average by around 2 mSASSS units every 2 years.[139, 140] However, this progression is highly variable; the average patient with inactive disease (ASDAS 0) would progress by 5 mSASSS units over 12 years compared with a patient with 'very active disease' (ASDAS 4) who would have 19 units of progression.[139] Also, of 68 patients who were followed for 12 years, 18% had no progression on mSASSS.[140] The variability is also demonstrated by the results based on a different cohort: a single German clinic (n=146).[14] Baseline characteristics were similar to those in the OASIS cohort (Table 27). Mean follow-up was 3.8 (SD 1.7) years and mean mSASSS change was 1.3 (SD 2.5) units /year with a range of 0-22.8 mSASSS units. Thirty four (23%) patients showed no progression.

There is evidence that BASDAI is relatively constant over time. A an analysis of data from a UK registry – SIRAS, demonstrated that patients stratified into high or low disease activity (BASDAI) remain in their separate groups over many years (12).[141] Data on the long-term pattern of patient function (BASFI) in patients not being treated with anti-TNFs is more scarce. A cohort study, from a single centre in England, provided data on 69 patients followed over 10 years (two data points: at baseline (1998) and 10 year (2008)).[16] The assessment of BASDAI confirmed that it remains relatively constant (mean at baseline 4.1 (SD 2.5) and after 10 years 4.4 (SD 2.7) (p=0.36). Patient function was assessed using RLQD rather than BASFI, but provided evidence of deteriorating function over time: mean RLDQ at baseline was 10.4 (SD 8.3), and after 10 years was 13.6 (SD 10.9) (p=0.002). Analysis of longitudinal data from the SMART (Bath, UK) data set (n=223) found that BASFI increased over time by 0.035 units/symptom year.[142] In patients with baseline BASDAI of $\geq$4 (those that would be treated with anti-TNFs and 68% of the total cohort) the rate of BASFI increase was 0.039 units/symptom year. Estimates of the rate of change in BASFI over time were also reported in a cost-effectiveness modelling study.[143] The data were from patients who were captured in two

surveys at two time points 1992/1994 and November 2002 approximately 8 years apart (n=1100). The estimate of annual BASFI progression was 0.07 points, but when only patients with BASDAI ≥4 were included in the analysis, BASFI progression was estimated as 0.054. It was reported that data from a cohort of 493 patients who had been followed up for more than 3 years generated similar findings; the number was not actually reported for the whole survey, but was 0.059 for the BASDAI ≥4 subgroup.

Natural history data from patients with nr-axSpA is even more scarce than that for AS patients, with no long-term data identified. A comparison of AS and nr-axSpA patients from a cohort of 100 consecutive patients (Herne clinic, Germany) (Axial SpA n=100, nr-axSpA n=44, AS n=56) found that slightly higher proportions of AS patients met pre-specified cut-offs of disease severity than did nr-axSpA patients, but the differences were statistically significant only for ASDAS, CRP level, mSASSS and the number of inflamed lesions; the proportion of males was also statistically significantly different.[144] The results are given in Table 27. The difference for BASFI was very close to statistical significance.

A larger cross sectional study of the GESPIC cohort (n=462 patients with axial spondyloarthritis (AS or nr-axSpA)) also found differences between AS and nr-axSpA patients.[19] When AS (≤ 5 year) and nr-axSpA were compared there were statistically significant differences in Physicians Global Assessment, BASFI (3.1 in AS vs 2.5 in nr-axSpA), BASMI (1.9 in AS vs 1.1 in nr-axSpA), spinal mobility and lateral spinal flexion, CRP and ESR and all radiographic measures (mSASSS 4.9 in AS vs 1.4 in nr-axSpA). mSASSS was statistically significant worse in males vs females, and between CRP >6 vs <6, though it is unclear whether this is a meaningful cut off for CRP.

In two longitudinal studies of progression in nr-axSpA,[145, 146] also using the GESPIC cohort, progression in terms of sacroiliitis and in terms of radiographic progression in the spine (mSASSS), was slightly more rapid in AS than in nr-axSpA but not statistically significantly so. Raised CRP at baseline was a predictor of both measures of progression in AS but only for sacroiliitis in nr-axSpA. The presence of syndesmophytes was predictive of higher progression rates as assessed by mSASSS in both AS and in nr-axSpA. Of the 95 patients with nr-axSpA, 11 (11.6%) fulfilled the modified New York criteria for AS after two years of follow up. A review of the burden of illness in nr-axSpA[147] cited this (11.6%) progression rate along with a 10% rate over two years and a 24% rate over 10 years. However, the 10 year rate was derived from a broader, more heterogeneous population than the GESPIC cohort: patients had undifferentiated spondyloarthropathies, with over half not having inflammatory low back pain.[148, 149] The GESPIC study recruited only patients with axial spondyloarthritis (AS or nr-axSpA).

Studies of disease progression in nr-axSpA focus on aspects of the disease that can be assessed through imaging techniques: radiographs or MRI scans. This may appear reasonable given the subjective, patient questionnaire basis of the BASFI score.

Finally there is evidence that as well as being progressive, the course of AS includes flares. A study based on the population of a trial comparing probiotic and placebo treatment in AS, found that the overall flare rate was 71.4 per 100 person weeks (pw); the major flare rate was 12/100pw and the minor flare rate 59.4 /100pw.[29] BASDAI and BASFI varied with type of flare: mean BASDAI scores were 5.5 (major flare), 3.1 (minor flare) and 2 – 2.5 (flare free); mean BASFI scores were 5.5 (major flare), 3.1 (minor flare) and 2.5 – 3.5 (flare free). A pilot study used the SMART cohort (Bath, UK) to investigate the pattern of disease and impact of disease flares.[150] Of the 114 patients, 96% patients reported experiencing flares. Flare duration varied by patient: days (40%); weeks (30%); and months (30%). Fifty percent of patients reported flares on a background of symptoms, whilst 26% reported gradually developing and resolving flares, after which symptoms were worse than before the start of the flare. These patterns were associated with higher BASFI scores. Around 20% reported flares with no symptoms between. A small proportion (7%) reported gradually developing and resolving flare with periods of no symptoms.

In summary, the available studies indicate that in AS and nr-axSpA disease activity (BASDAI) is fairly stable over time and does not generally progress, though it can be at a high (severe) level early in the disease. Patients function (as assessed by BASFI) does deteriorate over time, though the course is not constant or predictable. BASFI is determined by both disease activity and bone neo-formation; progression of BASFI over time is driven by progression of bony disease as assessed by imaging scores such as mSASSS, or the presence of syndesmophytes. Best estimates of yearly disease progression rates without anti-TNF therapy are around 1.0 mSASSS units and 0.035 to 0.07 BASFI units. Information on the natural history of nr-axSpA is relatively sparse. Whilst disease progression appears to be faster in AS, patients with nr-axSpA can have severe disease activity and hence poor function.

Table 27 Natural history of axSpA - relevant outcomes and impact of anti-TNFs

Study	Description	Population characteristics	Summary of findings. What it tells us
Landewe 2009 [12]	Examined the relationship between disease activity, radiographic damage and physical function in AS. Based on (European) OASIS cohort – baseline and 2 year data. N=217 consecutive (from	BASFI mean 3.4 (SD 2.6), 41% ≥4. mSASSS median 5, 69% > 0 NB does mSASSS less than 0 mean nr-axSpA? None of the patients in the cohort had used anti-TNFs. Subgroup (n=188) Baseline BASDAI≤6	Univariate correlation between baseline mSASSS and BASFI = 0.45 (Spearman Corr Coef), but this was modified by baseline BASDAI : BASDAI 0-2 (n=68) = 0.68; BASDAI >2-4 (N=60) = 0.58; BASDAI >4-6 n=60 = 0.43; BASDAI >6-8 (n=22) = 0.40; BADDAI >8-10 (n=7) = -0.20. Suggests a ceiling effect of BASFI – because of the high

	1996) patients with AS (no specific criteria. BASDAI mean 3.4 (SD 2,1), 38% ≥4.		level of correlation between BASDAI and BASFI, a correlation between MSASSS and BASFI cannot be demonstrated at the highest level of BASDAI. Multivariate relationship between BASDAI and mSASSS with BASFI using baseline and 2 year data (but not longitudinal?) (n=188, baseline BASDAI≤6 only). Regression coefficients found that both BASDAI and mSASSS are statistically significant (p<0.001) explanatory variables for BASFI (0.73 and 0.057 units respectively)
Ramiro 2014[139]	Analysed long-term relationship between disease activity (ASDAS, BASDAI) and radiographic damage (mSASSS) in AS. Used OASIS cohort over 12 years	Subgroup used (n=184) who had at least 2 sets of x-rays. Baseline characteristics of this subgroup: BASDAI mean 3.4 (SD 2.0) mSASSS mean 10.8 (SD 15.2), 81% >0 None of the patients had used anti-TNFs.	On average patients had a progression of 1.9 mSASSS units/2 years. This varied with baseline ASDAS: ASDAS <1.3 progress=0.7 mSASSS units/2 years; ASDAS >3.5 progress=3.1 mSASSS units/2 years. The relationship with BASDAI was similar: Baseline BASDAI<4: 1.5 mSASSS units/2 years BASDAI ≥4: 2.7 mSASSS units/2 years; BASDAI >6: 2.0 mSASSS units/2 years The analysis found that the average patient with inactive disease (ASDAS 1.0) would progress by 5 MSASSS units over 12 years compared with a patient with 'very active disease' (ASDAS 4) would have 19 units of progression.
Ramiro 2013[140]	Earlier analysis of OASIS cohort 12 year data to describe the evolution of radiographic abnormalities in AS patients.	Subgroup used (n=186) who had at least 2 sets of xrays). Baseline characteristics of this subgroup: BASDAI mean 3.4 (SD 2.0) mSASSS mean 11.6 (SD 16.2) None of the patients had used anti-TNFs.	Long-term radiographic progression in AS highly variable at the patient level, but is more severe in men who are HLA-B27 positive. Over whole follow-up 24% of patients (and 18% of the 68 patients who were followed for 12 years) had no progression on mSASSS. Duration of disease is not relevant. At the group level progress is linear – 2 mSASSS units/2 years.
Baraliakos 2009[14]	Natural course of radiographic progression in AS. Retrospective cohort, single clinic (Herne, Germany), 1993-2005 Mean follow-up 3.8 (SD 1.7) years	N= 146 anti-TNF naïve patients. Baseline mean (SD): mSASSS 20.5 (14,4) BASDAI 4.4 (1.9) (range 0.5-7.3) BASFI 3.8 (2.6) (range 1.0-8.4)	Mean mSASSS change was 1.3 (SD 2.5) units /year NB range was 0-22.8 mSASSS units. 34 (23%) patients showed no progression.
Dean, L et al. 2014 Poster at BSR meeting	Scotland and Ireland Registry for ankylosing Spondylitis (SIRAS) Cohort. Study of BASDAI over time.	BASDAI at diagnosis data available for only 240 patients (out of the 1210 patient cohort). Baseline BASDAI (at diagnosis) 4.9 (SD 2.3). High disease group BASDAI = 6.3 (1.4) and low disease activity group BASDAI 2.5 (1.3)	Baseline BASDAI remained fairly stable over time – across the whole cohort and in the high and low disease activity groups. The subgroup treated with anti-TNFs had higher mean BASDAI (5.7, SD 2.0)) than non-biologicpatients (4.2, SD 2.5) and this remained so until around a year after treatment with anti-TNFs began, when mean BASDAI fell to the level of the non-biologic patients.
Healey, E.L. et	Cohort study, single	At study entry patients were	Only RLDQ changed significantly over time. Mean

al. Clin Rheumatol. 2013; 33:67-72[16]	centre, England. Followed patients over 10 years (n=69 who provided assessments at baseline (1998) and 10 years (2008)). Assessments using RLDQ, BASDAI, AsQoL and EQ-5D (and others)	84% male, mean age 49 years, Disease duration 15.5. years, symptom duration 21.4 years. 1.5% on an anti-TNF at 10 years.	(SD) for assessment 1 (1998) and 2 (2008) for: RLDQ: 10.4 (8.3); 13.6 (10.9) p=0.002; BASDAI: 4.1 (2.5); 4.4 (2.7) p=0.36 AsQoL 6.4 (6.3); 7.5 (6.4) p=0.15 EQ-5D 0.64 (0.28); 0.61 (0.30) p=0.45 However as RLQD (0-48) is a measure of function (comparable with BASFI) it does indicate progression with time even in these AS patients whose disease at study entry was already well established
Stone M. A. Ann Rheum Dis 2007; 66 (suppl II): 410[142]	Analysis of longitudinal data from SMART (Bath, UK) data set. (n=224) Regression analysis of BASDAI on symptom duration and BASFi adjusted for BASDAI >4 at baseline. Duration of follow-up was unclear.	68% had a baseline BASDAI ≥4 Mean symptom duration was 28.8 years.	Only 20% experienced a significant change in BASDAI over time (13% a decrease; 7% an increase). BASFI increases over time by 0.035 units/symptom year. In patients with baseline BASDAI of ≥4 - those that would be treated with anti-TNFs - the increase over time is 0.039 units/symptom year.
Machado 2010[138]	Baseline data from ASSERT. analysis of relation between MsASSS and MRI inflammation and BASMI	N=214 AS patients (mNY criteria) Baseline median (IQR) BASMI 4.6 (3.6, 5.8) BASDAI 6.5 (5.3, 7.0) CRP (mg/dl) 1.5 (0.7, 2.9) mSASSS 13.8 (4.5, 29.1)	Concluded that spinal mobility (BASMI) independently determined both by irreversible (mSASSS) and reversible spinal damage (MRI): the former in late disease, the latter in early disease.
Machado 2011[25]	Baseline data from ASSERT. analysis of relation between SF-36 and BASFI and BASDAI, ASDAS, CRP level, MsASSS, MRI inflammation and BASMI.	N=214 AS patients (mNY criteria)	Regression coeffiicients for associations reported in the publication. Briefly, SF-36 is determined by BASFI and BASDAI; and BASFI is determined by BASDAI, mSASSS and BASMI.
Kobelt 2004; 43:1158-1166[143]	Modelling study of infliximab but refers to large UK observational data set and generates an estimate for BASFI over time. Survey in 2002 (n=1413) Value generated from patients who were captured in two surveys at two time points 1992/1994 and November 2002 approximately 8 years apart (n= 1100) . Data from a cohort of 493 patients who had been followed up for more than 3 years were used as a check for the result based on the survey.		From the whole survey (n=1413) mean BASDAI = 4.2 (2.3) and mean BASFI 4.4 (SD 2.8). The population was broader than that eligible for anti-TNFs, with 47% having a BASDAI < 4. It appears (but is unclear) that this is the BASDAI at the later time (2002) point not the earlier (1992/4) Estimate of annual BASFI progression was 0.07 points. NB progression was faster (0.1 points) in patients with BASFI <4 at baseline, but was stable (0?) in patients with BASFI above 7. (ceiling effect of BASFI?). When only patients with BASDAI ≥4 included BASFI progression was estimated as 0.054. Data from the cohort study generated similar findings – number not actually reported for whole survey. BASFI progression was 0.059 for patients with a BASDAI ≥4.
nr-axSpA			
Kiltz U. eta l. Arth Care Res 2012; 64:1415-	Comparison of characteristics of patients with AS and nr-axSpA.	Consecutive, diagnosed with axial SpA. None of the	Differences were statistically significant for ASDAS, CRP level, mSASSS and number of inflamed lesions.

22[144]	Cohort of 100 patients seen in 2010 inHerne clinic, Germany. Analysis tested if the proportion of patients reaching pre-specified cut-off criteria (markers of disease severity) differed between AS and nr-axSpA.	patients had used anti-TNFs. Axial SpA N=100: nr-axSpA N=44, AS N=56 Median BASDAI 4.3 (AS); 3.6 (nr-axSpA) (p=0.2) Median BASFI 2.9 (AS); 1.5 (nr-axSpA)(p=0.05) Median CRP 8.0 (AS); 3.8 (nr-axSpA)(p<0.001) Median mSASSS 3.0 (AS); 1.1 (nr-axSpA)(p<0.007)	Proportion of males also significantly different. Results: % nr-axSpA; % AS (p value) %male: 31.8%;76.8% (<0.001) BASDAI ≥4: 43%; 53.5% (0.1) BASFI ≥ 3: 34.1%; 46.4% (0.08) ASDAS> 2: 54.5%; 78.6% (0.01) CRP >5 mg/l: 29.5%; 69.1% (<0.001) mSASSS ≥ 3: 27.3%; 51.9% (0.01) Number of inflamed lesions per pt ≥ 3: 9.1%; 46.4% (0.01)
Rudwaleit M. et al. Arth Rheum 2009; 60:717-727[19]	Cross sectional study of GESPIC cohort n=462 patients with axSpA. Divided into AS (n=236) and nr-axSpA (with ≤5 years of symptoms) (n=226).	Baseline mean (SD) – BASDAI 4.0 (2.1) (AS); 3.9 (2.0) (nrAxSpA) BASDAI ≥4 48.7% (AS); 47.7% (nrAxSpA) BASFI 3.1 (2.5) (AS); 2.5 (2.1) (nrAxSpA) NB mean BASFI the same for patients with AS more than or no more than 5 years	When AS patients were divided into those with more than 5 years symptoms and those no more than 5 years, there were no differences in characteristics at baseline. When AS (≤ 5 years) and nr-axSpA were compared there were statistically significant differences (worse for AS) in Physicians Global assessment, Natural History Table id the Table of the disease modification (or not0 studies of anti-TNFsn spinal mobility and lateral spinal flexion, CRP and ESR and all radiographic measures (mSASSS 4.9 in AS vs 1.4 in nr). mSASSS significantly worse in males vs females and CRP>6 vs ≤6 . Note these AS patients are very short duration patients – they must have progressed to AS rapidly. Also nr patients are only a short time from start of symptoms, and may not reflect those who remain nr for many.
Poddubnyy D et al. Ann Rheum Dis 2011;70: 1369-74[145]	Study of radiographic progression of sacroiliitis in AS and nr-axSpA. Radiographic evidence of sacroiliitis is a criterion in the modified NY criteria for AS so useful to see this analysis of progression rather than just mSASSS	German cohort (GESPIC) n= 210 (115 AS; 95 nr), 2 years follow-up. (baseline BASDAI 4 units and BASFI 3 units across AS and nr.) Overall cohort had short symptom duration – 4.2 years (5.2 AS, 3.2 nr). Only 3.5% had had treatment with anti-TNFs (1.1% nr; 3.5% AS).	After 2 years follow-up, 11 of the 95 nr-axSpA patients (11.6% 95% CI 6.6% to 19.6%) fulfilled the modified NY criteria for AS. Also after 2 years approximately 10.5% of patients in the nr cohort had progressed by at least one mNY criteria grade, compared with 8.7% of patients in the AS group (difference not ss). Predictors of sacroiliitis progression – raised CRP for both AS and nrAxSpA. Male sex and HLA-B27+ predicted lower progression in nr, but higher progression in AS.
Poddubnyy D eta l. Arth Rheum 2012:64:1388-98[146]	GESPIC cohort Radiographs of spine and SIJ at baseline and 2 years.	Baseline All patients (n=210) 2.4% of patients treated with anti-TNFs; BASDAI 4, BASFI 3. AS (n=115); 3.5% of patients treated with anti-TNFs; BASDAI 4, BASFI 3. nrAxSpA=95. (nrAxSpA) 1.1% of patients treated with anti-TNFs; BASDAI 4, BASFI 3.	Regresssion analysis found syndemophytes at baseline, elevated ESR and CRP and smoking were significantly associated with spinal progression (≥ mSASS/2 years) in AS but only syndemophytes at baseline in axSpA. In AS patients mSASSS increased significantly from 5.86 (SD 10.30) to 6.81 (SD 11.71) – mean difference 0.95 (SD 2.78). In nr-axSpA patients mSASSS increased significantly from 2.30 (SD 4.24) to 2.76 (SD 5.26) – mean difference 0.46 (SD 1.63). The difference between mean progression in AS and nr-axSpA patients was not statistically significant, nor was the difference between those with symptom duration of ≤ 5 years and > 5 years. % progressed by >2 mSASSS units /2 years: All axSpA 14.3%; AS 20.0% (95% CI 13.7-28.2%); nr-axSpA 7.4% ((%% CI 3.6-14.4%) There was no difference in mSASSS change scores between patients not progressing to AS (0.49 units)

			versus those who progressed to AS (0.27 units), p=0.53.
Flares			
Cooksey R. et al, Rheumatology 2010; 49: 929-32[29]	Cohort derived from full population of a trial comparing probiotic and placebo treatment in AS. followed up for 1216 person weeks and recorded localised/minor flares and generalised/major flares, plus BASDAI, BASFI and pain VAS.	N=134 AS patients. Baseline mean BASDAI 3.7 (SD 2.1); mean BASFI 3.6 (SD 2.8) Mean duration of symptoms 21 years (SD 13) (range 0-58).	Overall flare rate was 71.4 per 100 person weeks (pw); major flare rate of 12/100pw and 59.4 minor flares/100pw. Mean BASDAI scores were 5.5 (major flare), 3.1 (minor flare) and 2 – 2.5 (flare free) Mean BASFI scores were 5.5 (major flare), 3.1 (minor flare) and 2.5 – 3.5 (flare free). Note these means not from whole population but only patients who experienced major flares plus flare free periods (n=27) and minor flares plus flare free periods (n=77).
Stone M.A. et al. Rheumatol 2008;47: 1213-18[150]	A pilot study to investigate pattern of disease and impact of disease flares. It used the SMART cohort (Bath, UK) Patients asked about 4 patterns of disease (see results)	AS patients, though diagnostic criteria not stated. n=114 (though not n=114 for all %). Mean BASDAI 4.2, BASFI 4.0	96% patients reported experiencing flares. Duration varied by patient: days (40%); weeks (30%); and months (30%). 83% reported experiencing symptoms between flares. Percentage of patients for the 4 patterns of disease: a) relapsing/remitting (flares with no symptoms between): around 20%; b) flares on a background of symptoms: around 50%; c) gradually developing and resolving flare with periods of no symptoms: 7%; d) gradually developing and resolving flare after which symptoms worse than before start of flare: 26%. a) and d) associated with higher BASFI.

4.3 Clinical Effectiveness Summary and Conclusions

Summary of RCT results

The quality of the trial evidence was generally high; most studies were unlikely to have produced results which were biased. For both the AS and nr-axSpA populations the results of the meta-analyses demonstrated that anti-TNFs produce statistically significant and clinically relevant benefits to patients in terms of improving function and reducing disease activity. The common class effect model used may have underestimated the uncertainty in the effect estimates. Although there is a possibility that infliximab is more effective than other TNF inhibitors at least at 12 weeks, there is no strong evidence to support this. For the disease activity, function, and responder outcomes, the class efficacy estimates were consistently slightly smaller for nr-axSpA than for AS, most noticeably for BASFI and BASDAI 50. Statistical heterogeneity was more apparent in the nr-axSpA analyses than in the AS analyses. This may be due to both clinical heterogeneity in the nr-axSpA trials (such as variation in CRP levels, or the proportion of MRI positive patients), and the fact that fewer studies were available for analysis. In light of the statistical heterogeneity across the nr-axSpA trials, both the reliability of the nr-axSpA pooled estimates and their true relevance to patients seen in clinical practice is questionable.

FDA re-analyses of two key nr-axSpA trials further emphasised the heterogeneity in the nr-axSpA population. Results for an adalimumab trial in nr-axSpA patients suggested reduced efficacy in a centrally diagnosed nr-axSpA population when compared with a locally diagnosed population and that the treatment benefit in the whole trial population may have been driven by benefit in patients who actually had AS, not nr-axSpA. Conversely, in a certolizumab pegol trial which recruited both populations, the efficacy findings were consistent across the AS and nr-axSpA subpopulations, regardless of the discrepancy in local or central pelvic x-ray readings.

Long-term efficacy

The longest follow-up durations in patients with AS by anti-TNF were: adalimumab 5 years, etanercept 5 years, infliximab 3 years, golimumab around 5 years; and certolizumab pegol nearly 2 years. The results showed that across all the anti-TNFs after approximately two years of treatment, around half of patients still achieved a good level of response to therapy. At five years around 60% of golimumab patients, 50% of etanercept patients and 30% of adalimumab patients still achieved a good treatment response. However, the long-term studies were not as well-reported as the RCTs, and their results were derived from less reliable data; it is therefore unknown if these are true treatment differences or due to differences in follow-up protocols, and/or imputation and analysis methods.

The long-term follow-up for nr-axSpA patients showed a continued high proportion of responders. At one year around half of patients on adalimumab, etanercept or certolizumab still achieved an ASAS

40 or BASDAI 50 level response. With certolizumab this is maintained at two years and with adalimumab at 3 years.

When the long-term data are presented as observed or as completer analyses the long-term results are similarly good: withdrawal rates are not high and those patients who remain on treatment continue to achieve a good response.

For all anti-TNFs, at long-term follow-up mean final values or mean change from baseline for BASDAI, BASFI and BASMI, where reported were generally maintained at levels indicative of clinically significant treatment benefit for those patients with AS and those with nr-axSpA.

Four studies reported on radiographic disease progression over 2 years of follow-up in terms of mSASSS in patients taking adalimumab, infliximab, etanercept, and golimumab. All four open-label, uncontrolled follow-up studies found that mSASSS increased by a mean of around 0.9 over two years. Three of these studies compared their rates with those from the OASIS cohort (of patients not taking an anti-TNF) and found no difference. In conclusion there is no real evidence for the impact of anti-TNF treatment on radiographic disease progression: a beneficial effect cannot be assumed, nor, given the short term nature of the follow-up and the insensitivity of x-rays as a tool for the evaluation of disease progression in AS, can one be discounted. There are some data to suggest an identifiable benefit from around four years, but results from ongoing long-term studies should help to clarify this issue.

Registry data demonstrate that around 60% of patients with AS treated with a first anti-TNF will still be taking their therapy at 2 years, with median drug survival of 3.1 years (based on Danish registry n=1436). Sequential treatment with anti-TNFs can be worthwhile but the drug survival, response rates and benefits are reduced with 2nd and 3rd anti-TNFs, with the proportion of BASDAI 50 responders falling approximately 10% with each subsequent anti-TNF and the median BASDAI and BASFIs achieved increasing (worsening). The lower efficacy of a 2nd anti-TNF relative to a first is reflected in lower median drug survival and proportion of patients remaining on therapy at 2years. Interestingly, despite a further reduction in response and efficacy with a 3rd anti-TNF, drug survival does not fall further, suggesting that patients may be allowed to, and be prepared to continue with a less than optimally effective anti-TNF at this stage in their treatment history.

Adverse effects

Data from large systematic reviews, which included patients with a wide range of diseases, suggest that, in the short-term, anti-TNFs as a group are associated with significantly higher rates of serious infections, TB reactivation, non-melanoma skin cancer, total adverse events, and withdrawals due to AEs, when compared with control treatments. Specifically, infliximab is associated with significantly

higher rates of total adverse events and withdrawals due to adverse events and that certolizumab pegol is associated with significantly higher rates of serious infections and serious adverse events. Analyses from the present review showed etanercept to be statistically significantly more likely to result in an injection/infusion site reaction when compared with infliximab, although analysable data on such reactions were not reported for the three other anti-TNFs. Evaluations of longer-term data are more scarce though suggest similar safety profiles across anti-TNFs. Data from the open-label studies included in this review also do not suggest that there are important differences between treatments, other than a higher the incidence of injection site reactions following treatment with etanercept. These open-label data are however limited by the small sample sizes and non-randomised study designs.

Natural history

The available studies indicate that in AS and nr-AxSpa disease activity (BASDAI) is fairly stable over time and does not generally progress, though it can be at a high (severe) level early in the disease. Patient function (as assessed by BASFI) does deteriorate over time, though the course is not constant or predictable. BASFI is determined by both disease activity and bony disease; progression of BASFI over time is driven by progression of bony disease as assessed by imaging scores such as mSASSS, or the presence of syndesmophytes. Best estimates of yearly disease progression rates without anti-TNF therapy are around 1.0 mSASSS units and 0.035 to 0.07 BASFI units. Information on the natural history of nr-axSpA is relatively sparse. Whilst disease progression appears to be faster in AS, patients with nr-axSpA can have severe disease activity and hence poor function.

Overall conclusions

- For both the AS and nr-axSpA populations the results of the meta-analyses demonstrated that anti-TNFs produce statistically significant and clinically important benefits to patients in terms of improving function and reducing disease activity. The efficacy estimates were consistently slightly smaller for nr-axSpA than for AS.
- In AS, although there is a little variation in treatment effects and it is possible that infliximab may be more effective than other anti-TNFs at 12 weeks, the evidence for this is not strong, and it is plausible that anti-TNFs may have a common class effect, with the treatments being equally effective.
- Statistical heterogeneity was more apparent in the nr-axSpA analyses than in the AS analyses. This may be due to both clinical heterogeneity in the nr-axSpA trials and the fact that fewer studies were available for analysis. In light of this heterogeneity, both the reliability of the nr-axSpA pooled estimates and their true relevance to patients seen in clinical practice is questionable.
- Effectiveness maintained over time; about 50% of patients maintained a benefit at two and five years.

- Evidence for an effect of anti-TNFs on radiographic disease progression was limited: the relatively short-term follow-up available to date and the insensitivity of x-rays as an imaging tool precluded the drawing of firm conclusions regarding the role of anti-TNFs in preventing or delaying the progression of AS; there are some data to suggest an identifiable benefit from around four years, but results from ongoing long-term studies should help to clarify this issue.
- Sequential treatment with anti-TNFs can be worthwhile in patients with AS but the drug survival, response rates and benefits are reduced with second and third anti-TNFs.

5 Assessment of existing cost-effectiveness evidence

5.1 Systematic review of existing cost-effectiveness evidence

The following sections provide an overview of existing cost-effectiveness evidence and an assessment of the relevance of the data from the perspective of the UK NHS. The differences in the approaches and assumptions used across the studies are examined in order to explain any discrepancies in the findings and to identify key areas of remaining uncertainty. The findings from the review provide the basis for the development of a new decision-analytic model reported in Section 7 'Assessment of cost-effectiveness: York Economic Assessment'.

5.1.1 Methods

An initial systematic search was undertaken in the NHS Economic Evaluation Database (NHS EED) using a combination of technology names and disease terms. Further searches were undertaken in MEDLINE and EMBASE for modelling and utility studies using disease terms only (as known references were not identified from the initial search in NHS EED). Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) were included in the review of existing economic literature. No language and date limits were initially applied, although eligibility of studies was subsequently restricted to those reporting results which were specific to the UK. Full details of the search strategies used are reported in Appendix 1.

In addition, as part of the current MTA process, each manufacturer submitted *de-novo* evidence on the cost-effectiveness of the anti-TNFs in line with their respective indications for the treatment of AS and nr-axSpA. These submissions are reviewed and the findings compared with those found in the review of previously published studies.

5.1.2 Results of review of existing cost-effectiveness evidence

The combined searches retrieved 210 citations. A total of six UK studies reporting on the cost-effectiveness of anti-TNFs for the treatment of AS were identified. No previously published studies were identified for patients with nr-axSpA.

Four of these studies were industry funded assessments of the following anti-TNFs: infliximab (Kobelt 2004[143] & Kobelt 2007[151] – both funded via an unrestricted grant by Schering Plough), etanercept (Ara 2007[152] – funded by Wyeth pharmaceutical P.C.) and adalimumab (Botteman 2007[153] – funded by Abbott Laboratories). The three studies published in 2007 are largely based on the economic analyses originally submitted by the manufacturers to NICE as part of the previous MTA (TA143)[1]. Since the earlier publication by Kobelt has been superseded by the 2007 publication, only the latter publication is further considered in this review. The remaining two UK studies were

publications of the assessments and/or critiques undertaken by the independent Assessment Group/Evidence Review Group for infliximab, etanercept and adalimumab for TA143[34] and golimumab for TA233.[154] Therefore, a total of 5 studies met the inclusion criteria and are included in this review.

The following sections provide a narrative discussion of each publication. A single critique section is used to highlight the key issues and potential limitations of existing published cost-effectiveness evidence. These issues are then re-visited with respect to the *de-novo* analyses submitted by the manufacturers considering how these key issues and potential limitations have been addressed in the 2 separate indications. The final section highlights the remaining issues and uncertainties and provides the basis for informing the development of a separate independent analysis of the cost-effectiveness of anti-TNFs for AS and nr-axSpA relevant to informing decisions for the NHS.

5.1.3 Assessment of published cost-effectiveness studies

Kobelt et al (2007)[151]: Comparison of the cost-effectiveness of infliximab in the treatment of ankylosing spondylitis in the United Kingdom based on two different clinical trials.

Kobelt et al, (2007) estimated the cost-effectiveness of infliximab for the treatment of AS compared to standard care over a lifetime horizon (60 years). Results were presented from both societal and NHS/PSS perspectives, although only the latter are reported here in line with the current NICE reference case. Short-term effectiveness data were derived from two separate clinical trials (Braun et al and ASSERT)[94, 97, 155] to inform the proportion and magnitude of initial response to treatment expressed in terms of BASDAI 50 (or a BASDAI<=4) response (12-24 weeks) and changes in BASDAI and BASFI scores. These were combined with longer term observational evidence on disease progression (BASFI only) and other external sources on costs and utilities to estimate cost-effectiveness. Results were reported separately based on each trial. Costs and benefits were discounted at 3.5% and presented at 2005 prices.

Methods

The cost-effectiveness model was based on a short-term decision tree representing the double-blind periods of the trials (12 -24 weeks) and a longer term Markov model to estimate subsequent progression. The Markov model comprised 3 states: 'Off treatment', 'On treatment' and 'Dead'. Only patients responding to treatment as defined by the following criteria (BASDAI<=4 [scale 0-10] or a >=50% improvement in BASDAI) remain on treatment at the end of the double blind periods. Differential BASDAI and BASFI scores (scale 0-10) were derived from Braun ('Off treatment' BASDAI = 6.3 and BASFI = 5.4; 'On treatment' [responders] BASDAI = 1.8 and BASFI = 2.0) and ASSERT ('Off treatment' BASDAI = 6.4 and BASFI = 5.8; 'On treatment' [responders] BASDAI = 1.4 and BASFI = 1.9). Disease progression was expressed in terms of changes in BASFI and was

estimated from two surveys conducted 10 years apart (n=1,110).[143] The mean absolute annual change in BASFI applied was +0.07 (scale 0-10) and this was used to characterise the natural history of progression for patients with AS without infliximab. Three main scenarios were presented reflecting different assumptions concerning the impact of infliximab on disease progression: 1) No progression while on treatment; 2) 50% of natural history (0.035/yr) and 3) Same as natural history (0.07/yr).

15% of patients were assumed to discontinue from infliximab annually based on data specific to responders from the open-label extension period in the Braun trial. Interestingly, the authors noted that the persistence rate was lower in responders compared with the entire sample in the Braun trial and its extension (approximately 10% withdrawal rate per annum). The BASDAI and BASFI scores for patients who withdrew from infliximab were assumed to return to the mean score of the non-treated group. Mortality was modelled from general population life tables applying a standardised mortality rate (SMR) of 1. Hence, no additional mortality was assumed to be related to AS and no direct or indirect benefits for mortality were assumed for infliximab.

Disease costs and HRQoL were derived from a cross-sectional retrospective survey conducted at the University of Bath, with the sample covering the full range of BASDAI and BASFI (1-10). The annual cost of infliximab was based on 5mg/kg body weight (weeks 0, 2, 6 and then every 6 weeks). An initial cost was assigned to all patients starting treatment (£79.25) and an outpatient cost was applied to each infusion.

Results

From an NHS perspective, the cost per QALY gained ranged from £28,332 and £26,751 (no progression while on treatment) to £49,417 and £46,167 (no effect of treatment on progression). The model was also sensitive to the time horizon and the withdrawal rate. Using a 10-year horizon resulted in ICER's between 63-66% higher than the base-case lifetime horizon (60 years) and a withdrawal rate of 5% resulted in ICERs 22-33% higher than the base-case (15%).

Table 28 - Lifetime cost per QALY estimates reported by Kobelt et al (2007) (NHS and PSS perspective)

Scenario	Incremental cost	QALY gain	ICER (£/QALY)
No progression on treatment – BRAUN	36,378	1.28	28,332
50% progression on treatment – BRAUN	35,756	1.01	35,332
Same progression on treatment – BRAUN	39,336	0.80	49,417
No progression on treatment – ASSERT	33,920	1.27	26,751
50% progression on treatment – ASSERT	34,408	1.01	34,067
Same progression on treatment – ASSERT	39,242	0.86	46,167

Ara et al (2007)[152]:The cost-effectiveness of etanercept in patients with severe ankylosing spondylitis in the UK

Ara et al, (2007) estimated the cost-effectiveness of etanercept for the treatment of severe AS in the UK in accordance with BSR guidelines from an NHS/PSS perspective over a 25-year time horizon. Effectiveness data were derived from individual patient data from a large multicentre European RCT to inform the proportion and magnitude of initial response to treatment and associated changes in BASDAI and BASFI scores. These were combined with longer term observational evidence on disease progression (BASFI) and other external sources on costs and utilities to estimate cost-effectiveness. Costs and benefits were discounted at 3.5%. The price year was not formally stated.

Methods

An individual patient model was used to estimate short-term and longer term costs and outcomes. Patients in the model were assumed to have tried and failed at least 2 consecutive NSAIDs and have a BASDAI measurement >= 40 (scale 0-100). Response was defined as a >=50% reduction in BASDAI (or all fall of >= 20 units) and a reduction of the spinal VAS by >= 2 units. Response rates at 12 and 24 weeks were derived from 2 RCTs (67% and 55% for etanercept and 24% and 16% for comparator arm at each respective time point). Individual patient data at 12 and 24 weeks were used to estimate the magnitude of change in BASDAI and BASFI for responders and non-responders. The mean BASDI and BASI scores at week 12 and 24 for responders and non-responders are reported in Table 29 together with observed utility at week 12 and the predicted utility values mapped from BASDAI and BASFI at week 24.

Table 29 - BASDAI, BASFI and EQ-5D measurements at weeks 12 and 24

	Week 12			Week 24		
	BASDAI	**BASFI**	**EQ-5D[£]**	**BASDAI**	**BASFI**	**EQ-5D^**
Treatment non-responder	53.02	54.86	0.48	56.87	56.87	0.46
Treatment responder	19.52	25.39	0.79	18.32	21.41	0.80
Comparator non-responder	55.60	57.55	0.46	47.67	47.78	0.42
Comparator responder	22.97	29.88	0.74	25.11	20.92	0.79

[£] = observed values, ^ = predicted values using a mapping algorithm

For patients who continued responding to treatment it was assumed that BASDAI and BASFI measures remained constant at the levels observed at week 24. For patients who withdrew after week 24, it was assumed patients would immediately revert back to their baseline values of BASDAI and BASFI. After 24 weeks in the model it was also assumed that patients with AS, not receiving anti-TNFs (conventional care and etanercept non-responders), would experience a worsening BASFI. A mean absolute change in BASFI of 0.7 (scale 0-100) was assumed based on a cross-sectional study of over 1000 UK patients.[143]

QALYs were estimated using a relationship derived from BASDAI, BASFI and EQ-5D from a single European RCT (utility = 0.9235-0.004*BASFI-0.004*BASDAI). Disease costs were derived from a separate costing study of 147 patients attending the Staffordshire Rheumatology Centre in Stoke.[156]A relationship between BASDAI and BASFI measurements and costs was used to estimate the disease costs and impact of etanercept (annual costs = 5.862+0.006 *BASDAI+0.016*BASFI). An annual cost of £9,372 was included to reflect the acquisition and monitoring costs associated with etanercept. An initial cost of £71 was also applied to the first 3 month period for etanercept, although no further details were provided by the authors concerning what this cost represented. The costs and/or HRQoL associated with adverse events were not included.

The authors assumed that 10% of patients withdraw from etanercept every year. These data were derived from external sources and no explanation was provided concerning whether these data specifically applied to the post-24 week period or not and/or whether they were derived from responders to treatment or not. Mortality was modelled from general population life tables applying a standardised mortality rate (SMR) of 1.50. No direct or indirect benefits for mortality were assumed for etanercept.

Separate scenarios were presented to explore alternative assumptions related to disease progression, long term annual withdrawal and the model time horizon.

Results

The main results are summarised in Table 30. From an NHS perspective, the base-case cost per QALY gained was £22,704 for etanercept over a 25-year horizon. In contrast to the study by Kobelt et al (2007), the impact of alternative progression assumptions appeared to have limited impact on the ICER, with alternative scenario results ranging from between £23,625 (50% progression on treatment) and £25,679 per QALY (same progression on treatment). The ICERs for alternative annual withdrawal rates ranged from £15,103 (5% withdrawal rate) to £29,428 per QALY (15% withdrawal rate). The ICERs for alternative time horizons ranged between £27,594 (2-years) and £22,704 (25 years).

Table 30 - 25 year cost per QALY estimates reported by Ara et al. (2007) (NHS and PSS perspective)

Scenario	Incremental cost	QALY gain	ICER (£/QALY)
Base-case	35,978	1.59	22,704
No progression for any patient	36,825	1.43	25,679
50% progression on treatment (0.035 BASFI)	36,032	1.56	23,155
Same progression on treatment (0.07 BASFI)	36,088	1.53	23,625
Annual withdrawal rate = 5%	33,976	2.25	15,103
Annual withdrawal rate = 15%	36,968	1.26	29,428

Botteman et al (2007)[153]:Cost-effectiveness of adalimumab for the treatment of ankylosing spondylitis in the United Kingdom

Botteman et al (2007) evaluated the cost-effectiveness of adalimumab versus conventional therapy in patients with active AS from an NHS perspective over a 30-year time horizon. Effectiveness data were derived from pooled data from two Phase III studies in patients with an inadequate response to >=1 NSAID. Micro-simulation methods were subsequently applied to these studies to simulate treatment decisions in accordance with BSR guidelines and associated outcomes. These were combined with author assumptions on disease progression (BASFI only), utility and cost data from the clinical trials and other external sources to estimate cost-effectiveness. Costs and benefits were discounted at 3.5% using a 2004 price year.

Methods

Micro-simulation methods were applied to patients (n=397) recruited into two adalimumab RCTs: ATLAS and M03-606. In the adalimumab clinical trials, patients were kept on active treatment even

when response had not been achieved. Consequently, simulation methods were applied to the patients in the clinical trial to mimic treatment decisions which more closely reflected treatment guidelines and the requirements of the economic model. In accordance with BSR guidelines, a response in the model was defined as a reduction of BASDAI of 50% or a decrease of >=2cm (scale 0-10) accompanied by a reduction of spinal pain VAS of >=2cm. Assessment of initial response was assumed to take place 8 weeks after treatment initiation. If the response criteria were not met at 8 weeks, a second response assessment was assumed at 12 weeks. Failure to achieve response on both occasions was assumed to lead to withdrawal of adalimumab therapy. Therapeutic responses were then assumed to be reviewed every 3 months until the end of the simulation (Year 30). Failure to maintain the original response led to repeat assessments after 6-12 weeks in the first 48 weeks. Failure to maintain response on both occasions led to withdrawal of adalimumab. After week 48, the simulation model defined inadequate response on the basis of BASDAI scores only. In the RCTs, patients were allowed to switch to open-label adalimumab at week 24, for these patients; last observation carried forward at time of switch for BASDAI, BASFI and VAS values were used in the model.

BASDAI, BASFI and spinal pain scores were based on directly observed trial scores (until week 48) and additional assumptions about disease progression (after week 48). BASDAI, BASFI and spinal pain scores were adjusted at each time point by a fixed value equal to the average difference between adalimumab and conventional care patients observed at baseline. BASDAI scores after week 48 were assumed to remain constant at these levels for patients continuing to respond to adalimumab and conventional care patients. BASFI was assumed, for conventional care patients, to worsen after week 48 by 0.05 units (scale 0-10) annually. The estimate applied to the increase in BASFI appears to be based on the authors' own assumption but is argued to be consistent with previous cost-effectiveness/epidemiological studies. In contrast, BASFI scores were assumed to remain stable for adalimumab while patients remained on therapy, which was argued to be consistent with the assumptions applied in previous published cost-effectiveness studies. It was assumed that patients who discontinued would revert back to the BASFI scores of conventional care patients within 12 weeks (i.e. any benefits in BASFI were not maintained over a longer period). This was argued by the authors to be a conservative assumption.

Utilities were derived from the Health Utilities Index 3 (HUI-3) from data at baseline and 24 weeks from both adalimumab trials. A subsequent regression was estimated to predict utilities based on BASDAI, BASFI, gender and race (utility = 0.948857-0.041528*BASDAI-0.034481*BASFI+0.047080*Gender[1=male, 0=female]-0.063801*Race[1=white, 0=other]).

Estimates of disease costs were based on 2-year data from 208 patients in the Outcomes in Ankylosing Spondylitis International Study (OASIS) study, conducted in The Netherlands, Belgium and France.[157] An ordinary least squares (OLS) regression was estimated using only BASDAI (and only BASFI in a sensitivity analysis). The regression utilised in the base-case was £708.45 + £750*BASDAI. Hence each increase in BASDAI of 1 unit (scale 0-10) was assumed to be associated with an increase in costs of £750.

Additional acquisition costs were applied to adalimumab (£357.50 per injection). No additional administration costs were incorporated as patients were assumed to self-administer their injections. All patients, regardless of treatment, were assumed to require at least 2 rheumatologist visits per year. Routine safety monitoring costs were based on national guidance and included the cost of nursing and physician time. The cost of a routine tuberculosis (TB) screening test via chest X-ray was assumed before initiation of therapy and 6 months after and TB skin testing before initiation of therapy. The cost of adverse events was based on data collected from the 2 clinical trials. A cost of £5100 was applied to an active tuberculosis case.

An annual rate of withdrawal of 10% was applied based on an assumption by the authors. The estimate was argued to be consistent with estimates reported in previously published cost-effectiveness analyses.

Results

The main results are summarised in Table 31. From an NHS perspective, the base-case cost per QALY gained was £23,097 for adalimumab over a 30-year horizon. Similar to the study by Ara et al (2007), the impact of alternative progression assumptions appeared to have limited impact on the ICER, with alternative scenario results ranging from between £23,802 (no BASFI progression on any treatment) and £23,812 per QALY (same BASFI progression on treatment). However, in contrast to Ara et al (2007), the ICERs appeared more sensitive to the alternative time horizons with estimates ranging between £47,083 (48 weeks), £26,332 (5-years) and £23,097 (30 years).

Table 31 - 30-year cost per QALY estimates reported by Botteman et al (2007) (NHS and PSS perspective)

Scenario	Incremental cost	QALY gain	ICER (£/QALY)
Base-case	23,857	1.03	23,097
No progression for any patient	NR	NR	23,802
Same progression on treatment (0.05 BASFI)	NR	NR	23,812

McLeod et al (2007)[34]: Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation

Mcleod et al (2007) evaluated the clinical and cost-effectiveness of adalimumab, etanercept and infliximab compared with conventional treatment for AS. The publication is based on the independent assessment undertaken by Liverpool Reviews and Implementation Group (LRiG) for NICE TA143. The cost effectiveness of these interventions over the short term (1 year) and over alternative time horizons of up to 20 years was reported.

Methods

The authors assumed that all three interventions were of equal clinical effectiveness and analysed the anti-TNFs as a class versus placebo. Short-term effectiveness over 1-year was modelled using individual patient data from two RCTs (including an open-label extension from week 24) for adalimumab from 397 patients (246 adalimumab, 151 placebo). 315 of these 397 patients were deemed to meet the BSR guidelines and were included within the Abbott economic model. There is a lack of transparency regarding the values utilised due to the commercial nature of the data used. However, the estimates for response rates were reported to be similar to those reported by LRIG in a separate pooled analysis at weeks 12 and 24; 59% and 49.2% respectively for the TNF alpha inhibitors (vs 22.5% and 14% respectively for placebo). No information is reported on the magnitude of changes assumed. From week 30 onwards it was assumed that spontaneous recovery without treatment (for placebo patients) would occur at a rate of 17.1%, as estimated by LRiG from the patient-level analysis of the two adalimumab RCTs. This assumption was explored in a separate sensitivity analyses.

The Assessment Group model assumed that patients withdraw from TNF-alpha inhibitor treatment at a rate of 15% per year, which was considered to represent the 'central value' of the studies that were identified reporting longer term discontinuation rates. This estimate is also the same as the annual rate reported in the open-label extension study for infliximab (Braun trial) also reported in the review undertaken by LRiG. Rates of 7% and 24% were also explored in separate sensitivity analyses, representing the range of values reported across the studies considered. The annual withdrawal rate (after the first 12 months as observed rates are used in the first 12 months) was applied to the difference in response rate between the two arms of the evaluation, rather than the absolute number of responders. This was to account for a potential anomaly that could arise through the assumption of a constant level (17.1%) of spontaneous recovery without treatment.

The Assessment Group model took into account the cost of drug acquisition, administration, monitoring and adverse events. No administration costs were assumed for etanercept and adalimumab as it was assumed that both would be self-administered at home without supervision. The

authors assumed an additional cost of £267 to administer infliximab infusions based on NHS reference costs estimates for the regular attender cost for chemotherapy with musculoskeletal primary diagnosis. Quarterly monitoring and testing was assumed for all patients receiving long-term treatment with TNF-alpha inhibitor s. However, 2 of these assessments were assumed to take place at the patient's routine follow up outpatient visit, so only the additional costs of tests for monitoring (£25) were applied to these assessments. The remaining 2 assessments were assumed to be undertaken at a GP's surgery and an additional cost of £25 was assumed for nurse/GP time in addition to the costs of tests for monitoring (£25). Adverse events costs were based on estimates reported by one manufacturer (Abbott) of £95.29 in the first year of treatment and £47.65 per patient-year thereafter.

Disease-related costs to the NHS were estimated by fitting an exponential cost model to the weighted aggregate data from the OASIS study; a 2-year prospective study of 208 AS patients from four centres in France, Belgium and The Netherlands (n=208).[157] The exponential model estimated NHS cost = £1585.30 *exp(0.1832*BASFI). The OASIS data were considered by the authors to provide a more reliable source than other published studies from Stoke and Bath, being prospective in design and over a longer period. BASFI was used by the authors as the major predictor of costs because it was considered to better reflect long-term disease progression compared to BASDAI.

Health-related quality of life was estimated using the utility model provided by Schering-Plough developed from the Bath Survey dataset on the grounds that it used a comparatively larger sample of UK ankylosing spondylitis patients (n=1144), and also because it incorporated age and gender variables; utility = 0.8772129-0.0384087*BASDAI-0.0322519*BASFI-0.0278913*Male+0.0016809*Age.

The Assessment Group adopted a long-term increase in BASFI scores of 0.07 units per year for the conventional treatment comparator arm of the model. This progression rate is applied for all periods after week 20 in the model. In the base-case analysis, the same value was used in the intervention arm adjusted pro rata to the proportion remaining of the maximal excess response seen at 12 weeks. In effect, this assumes that patients withdrawn from anti-TNFs are assumed to return to the same trajectory as non-responders, such that there is no ensuring benefit associated with being an initial responder.

Results

Over a 1-year time horizon, base-case ICERs for adalimumab and etanercept versus conventional care were essentially the same (approximately £57,000 per QALY). In contrast, the ICER for infliximab was over £120,000 per QALY. With respect to modelling beyond 12 months, the results for adalimumab were considered as representative of etanercept, and only the former were provided. In contrast with other published models, the ICERs increased steadily from year 2 onwards. At a 20-year

horizon the ICERs for adalimumab/etanercept increased to £98,910 per QALY and to £175,000 per QALY for infliximab.

Additional NICE Decision Support Unit analyses

Given the discrepancy between the results reported by McLeod et al (2007)[34] and the manufacturer submissions (largely reflected in the 3 industry funded publications previously discussed in this section)[151-153] also submitted as part of TA143[1], additional work was undertaken by NICE's Decision Support Unit (DSU) to reconcile the different models and to explore whether differences were due to different parameter inputs or alternative structural assumptions.

A common set of parameter values were applied by the DSU to the 3 manufacturer models and the LRiG model. The purpose of this was to attempt to identify whether differences between the results of the models persisted once this common set of values were used. The specific parameter values which were implemented were:

1. No improvement in BASFI or BASDAI for patients not on anti-TNFs
2. BASFI progression prevented whilst on anti-TNFs
3. BASFI progresses at 0.07 per annum when patients are not on anti-TNFs
4. Annual withdrawal rate of 7% from anti-TNFs
5. Baseline BASDAI/BASFI averages 6.5/5.6
6. Utility model as in the Schering Plough submission
7. Assessment group parameters for cost parameters (drug costs only)
8. 20 year time horizon

These parameter values were reported to have been the values agreed at a separate NICE committee meeting and consequently the rationale for these values and assumptions is not formally stated by the NICE DSU.

The results of the DSU analysis found that the manufacturer models all gave relatively consistent results for each of the drugs. For Schering Plough, the ICERs over 20 years for etanercept/adalimumab were £27k or £24k and for infliximab were £58k and £50k. Two figures were presented because Schering Plough presented two different versions of the model which reflected two different trials. The Wyeth model gave results of £20k for etanercept and £39k for infliximab. Abbott gave results of £17k for adalimumab and £43k for infliximab (over a 30 year time horizon). These ICERs were markedly different from those reported by the independent assessment group. Using a similar set of parameters the results for etanercept/adalimumab using the LRiG model were £42k and for infliximab £82k.

Further work by the DSU revealed that the differences appeared largely driven by 2 key assumptions which differed between the LRiG and industry models relating to:

1. the modelling of a 'placebo' effect
2. the longer term functions fitted to BASDAI and BASFI for responders to anti-TNFs

The LRiG model applied a 17.1% rate of spontaneous recovery without treatment from week 30 onwards (i.e. akin to assuming a long-term 'placebo' response for conventional care) in contrast to the manufacturers who either assumed there would be no response with conventional care or that any response would be transient and dissipate quickly after the 12-week period. .

The LRiG model also applied a quadratic function to the BASDAI and BASFI scores of responders over a longer time horizon, compared to the linear functions used by the manufacturers. The use of a quadratic function assumes that that the difference compared to conventional care was decreasing (initially) with time. That is, over time, the differences in BASDAI/BASFI would slowly reduce in responders and eventually be the same as for conventional care. However, the logical problem of applying a quadratic function is clear. While the scores are reducing for a period, at longer time periods the function starts to increase again. The issues were addressed by LRIG by using various assumptions and logical constraints (i.e. BASDAI/BASFI score not allowed to be higher than conventional care).

To further reconcile the models, the DSU incorporated a series of alternative structural assumptions within the LRiG model. These assumptions included removing the 17.1% rate of spontaneous improvement applied to conventional care and assuming constant BASDAI/BASFI scores after 1-year for responders. Applying these assumptions resulted in an ICER for etanercept/adalimumab of £30,100 per QALY (estimates for infliximab not reported) which were considered to be more consistent with the manufacturer results.

Importantly the DSU highlighted that, although these analyses helped to reconcile the different model results, any progression in terms of BASDAI or BASFI over time while on treatment would cause the ICER to increase beyond £30,100. Similarly, the DSU concluded that the exclusion of the 17.1% spontaneous recovery, without a comparable adjustment made to the intervention group was favourable towards the cost-effectiveness of TNF alpha-inhibitors and any adjustment for this issue would similarly lead to a higher ICER.

Armstrong et al (2013)[154]: Golimumab for the treatment of ankylosing spondylitis: A NICE Single Technology Appraisal.

Armstrong et al (2013) summarises the report undertaken by the Evidence Review Group (ERG) on the clinical and cost-effectiveness of golimumab for AS for a NICE STA (TA233)[2]. The ERG provided a critique of the manufacturer submission (Merck Sharpe & Dohme) and undertook additional exploratory analyses. The manufacturer's model applied a 20 year time horizon in the base case and a separate lifetime analysis (60.1 years) was presented in a separate sensitivity analysis. The discount rate applied was 3.5% for utilities and costs and costs are considered from an NHS and PSS perspective.

Methods

The manufacturer submission for golimumab was based on a single trial versus placebo (GO-RAISE). A total of 7 additional placebo controlled trials were included of other anti-TNFs; 5 RCTs for etanercept and 2 for adalimumab. In the absence of head-to-head studies directly comparing the relative effectiveness of the alternative anti-TNFs, the manufacturer undertook a Bayesian random-effects MTC including BASDAI 50 response, discontinuations and serious AEs. All treatments were reported by the manufacturer to be statistically significantly more effective than placebo in terms of BASDAI 50 response. No statistically significant differences were reported between each of the alternative anti-TNFs in terms of discontinuations and serious AEs. When the alternative anti-TNFs were compared with each other, no significant differences between golimumab, adalimumab and etanercept were identified for BASDAI 50. A higher risk of discontinuation was reported for golimumab vs etanercept (relative risk 4.30; 95% credible interval 1.01-18.50), although golimumab was associated with significant improvements in BASDAI vs etanercept (mean difference -0.88, 95% credible interval -1.58 to -0.14) and BASMI vs adalimumab (mean difference 0.52, 95% credible interval 0.23-0.80).

The manufacturer cost-effectiveness model was based on a short-term decision tree (12 weeks) and a longer term Markov model. The short-term tree was used to characterise response to each TNF-alpha inhibitor treatment based on the MTC results for BASDAI 50. After the short-term tree, patients entered a separate Markov model with a cycle length of 12 weeks and time horizon of 20 years. If patients were already receiving a TNF-alpha inhibitor, they either stayed on therapy ('on TNF inhibitor' state) or discontinued therapy because of lack of efficacy or adverse effects ('not on TNF-inhibitor' state). It was assumed that discontinuations occurred at a rate of 15% per year in line with NICE TA143. To model the lower disease activity just after discontinuation of TNF-alpha inhibitor therapy, two 12-week tunnel states ('just discontinued' and 'discontinued') were also incorporated into the model. Patients who are in the health state 'on TNF-alpha inhibitor' are assumed to have at least a 50% improvement in BASDAI (BASDAI 50) during the first 12 weeks of treatment and do not discontinue. Treatment is discontinued in patients whose condition does not respond to treatment and

they are switched to conventional therapy. Patients in the conventional care arm enter the Markov model in the 'not on TNF-alpha inhibitor' state. Patients could die at any point in the model.

Disease progression was incorporated in the model using BASDAI and BASFI scores. Data from the GO-RAISE trial and the open-label extension period were used to develop predictive equations of mean change from baseline in BASDAI and BASFI scores over time. Two separate equations were developed based on the 24 week data for all patients and post-24 week data from GO-RAISE for responders only. These equations were used for all anti-TNFs and the manufacturer assumed that the scores followed the GO-RAISE data for 2 years before they either levelled off (BASDAI) or started to deteriorate (BASFI at 50% of the rate of conventional care, equivalent to an increase of 0.035 [scale 0-10] units per year).

Although the equations are critical to the model structure and parameter estimates, these are not reported in the paper by Armstrong et al (2013). A separate examination of the full ERG report[2] revealed that these were reported as commercial-in-confidence (CIC) by the manufacturer and hence it is not possible to report the assumptions made in relation to the magnitude of change in BASDAI and BASFI over the initial 24 week period and subsequent post 24 week period for the anti-TNFs (responders, non-responders) and conventional care. BASFI scores for conventional care were reported to deteriorate according to the GO-RAISE trial (short term equations were available only) after which they were assumed to deteriorate at a rate of 0.07 units per year. The assumptions related to the impact of discontinuation of anti-TNFs are not formally stated in the paper by Armstrong et al (2013). However, the structure of the model implies that patients will revert back to the subsequent trajectories of conventional care for both BASDAI and BASFI after 2 cycles (24 weeks).

Utilities were derived from the previous NICE technology appraisal (TA 143) and incorporated age, sex, BASFI and BASDAI. Costs included in the model comprised drug acquisition, short-term (12 week) costs, longer term disease costs and adverse events. Longer term disease costs were based on BASFI scores from the GO-RAISE trial using the same regression equation used for NICE technology appraisal guidance 143. Mortality was included in the model and was considered to be a constant across the comparator treatments at a relative risk of 1.47.

Results

The main base-case results from the manufacturer are summarised in Table 32. From an NHS perspective, the base-case cost per QALY gained was £26,597 for golimumab compared to conventional care over a 20-year horizon. Both etanercept and adalimumab were reported to be extendedly dominated by golimumab.

Table 32 - Manufacturer cost-effectiveness results – 20 year horizon

Technology	Costs (£)	QALYs	Incremental Costs	Incremental QALYs	ICER (£)
Conventional care	88,667	6.6581	-	-	-
Adalimumab	93,601	6.8426	4,934	0.1845	NA (Extendedly Dominated)
Etanercept	93,782	6.8504	5,115	0.1923	NA (Extendedly Dominated)
Golimumab	93,786	6.8506	5,119	0.1925	26,597

The ERG undertook a limited validation of the model and reported various errors which were corrected. However, they concluded that questions remained concerning the integrity of the manufacturer model. The ERG subsequently presented results based on an exploratory re-analysis of the manufacturer submission, using results from a separate MTC analysis and employing a lifetime horizon. The results of the ERG re-analysis are reported in in Table 33. The results of this re-analysis resulted in golimumab being extendedly dominated by the other two anti-TNFs.

Table 33 - ERG exploratory cost-effectiveness results – lifetime horizon

Technology	Costs (£)	QALYs	Incremental Costs	Incremental QALYs	ICER (£)
Conventional care	95,227	7.8762	-	-	-
Golimumab	99,361	8.0296	4,134	0.1534	NA (Extendedly Dominated)
Adalimumab	108295	8.3683	8,934	0.3387	NA (Extendedly Dominated)
Etanercept	108,347	8.3712	52	0.0029	26,505

There is no discussion by Armstrong et al (2013) of the appropriateness of the assumptions applied to BASFI progression, despite this being a critical structural assumption. However, a separate sensitivity analysis was presented in the full ERG report which uses the same rate of disease progression for BASFI (0.07 units per year) for all patients after 2 years. As part of this analysis, the ERG corrected errors identified in the way the BASFI regression equations were incorporated by the manufacturer.

Table 34 reports the ERG results based only on correcting the error identified and Table 35 reports the results of also applying a common rate of disease progression for all patients after 2 years as well as correcting for the error. Golimumab was reported to be extendedly dominated by the other two anti-TNFs in both scenarios. It is also worth noting that the ICER for etanercept vs conventional care exceeded £30,000 per QALY in both scenarios.

Table 34 - ERG exploratory cost-effectiveness results –correction for BASFI error (from TA233)

Technology	Costs (£)	QALYs	Incremental Costs	Incremental QALYs	ICER (£)
Conventional care	77,505	6.7336	-	-	-
Golimumab	81,849	6.8746	4,334	0.1410	NA (Extendedly Dominated)
Adalimumab	91,340	7.1703	9,491	0.2937	NA (Extendedly Dominated)
Etanercept	91,408	7.1734	68	0.0031	31,612

Table 35 - ERG exploratory cost-effectiveness results –correction for BASFI error and common BASFI progression after 2 years (from TA233)

Technology	Costs (£)	QALYs	Incremental Costs	Incremental QALYs	ICER (£)
Conventional care	74,980	6.8267	-	-	-
Golimumab	79,330	6.9675	4,350	0.1408	NA (Extendedly Dominated)
Adalimumab	88,994	7.2567	9,664	0.2892	NA (Extendedly Dominated)
Etanercept	89,055	7.2600	61	0.0033	32,483

5.1.4 Summary and critique of published cost-effectiveness studies

No previously published studies were identified which assessed the cost-effectiveness of anti-TNFs for nr-axSpA. Consequently, the *de-novo* submissions provided by the manufacturers provide the only existing evidence which can be considered to inform decisions for the NHS. Of the previously published UK cost-effectiveness study identified, there appear marked differences between the results of the industry funded assessments and the results from the independent assessment by LRiG. Importantly, the results of the independent critique and exploratory re-analysis by the ERG for TA 233 also appear potentially less favourable than the industry funded published assessments. Although the DSU review of models submitted as part of TA143 has reconciled many of the key differences and highlighted the key assumptions, a number of key uncertainties remain. The remainder of this section provides an overview of the issues and uncertainties identified based on existing published studies and the DSU reports. This summary provides an important basis for considering the extent to which the *de-novo* submissions provided by the manufacturers for this appraisal have adequately addressed these.

All existing models are based on similar 2 part structures:

- Initial-response period (short term model used to determine initial response rate);

- post-response period (longer term model used to characterise natural history of disease (i.e. without anti-TNFs) and impact of anti-TNFs (while on therapy and when therapy is stopped)

All models employ changes in BASDAI and/or BASFI to quantitatively model the short and longer-term costs and quality of life implications (using QALYs) of the use of anti-TNFs s vs conventional care alone.

Although there are differences between the modelling of the initial response period, existing models are broadly comparable being based on an assessment around 12-weeks (and potentially at 24-weeks as well) using a particular variant of existing BSR guidelines. Patients receiving anti-TNFs who meet the response criteria at the 12/24 week assessment are continued on anti-TNFs. Anti-TNFs are withdrawn in non-responders at the 12/24 week assessment point and patients subsequently receive conventional care alone.

However, there are marked differences between existing studies in relation to the modelling of the post-response period and the assumptions employed. This period is often separated into different time intervals allowing different assumptions to be made regarding the effect of anti-TNFs (i.e. initially improving with time in responders but then later 'levelling off' or even deteriorating over a longer term time horizon relative to conventional care). An important difference between existing models is the timing of this 'levelling off' period and assumptions employed over a longer time horizon. The differences in approaches and the timing of this 'flattening off' period are also closely linked to the data used. That is, whether the changes in BASDAI/BASFI used in the model are restricted to the 12-24 week data from RCT evidence reported during the double-blind phase (Kobelt et al [2007], Ara et al [2007]) or also incorporate longer-term data from the open-label extensions. Studies which use change in BASDAI/BASFI data directly in the model, from the double-blind phase, appear to employ shorter 'levelling off' periods compared to studies using data from the open-label extension phase (Botteman [2007], McLeod [2007], Armstrong [2007]).

Those studies incorporating an open-label extension typically assume continuing changes in BASDAI/BASFI for responders to anti-TNFs versus non-responders/conventional care beyond the initial 12/24 week period. Importantly, none of the studies using open-label extension data appear to provide any discussion of the potential for selection bias (e.g. related to the initial consent for patients to participate and/or agree to switch treatments as well as ongoing selection issues concerning retention over a longer period) and how these should be considered and/or adjusted for in the economic model. However, the implication of this is important since the assumption being made by several models appears to incorporate an assumption of an increasing effect of anti-TNFs in responders over time (i.e. in terms of continuing improvements in BASDAI/BASFI), which does not

appear to be adequately justified or related to any underlying clinical/pharmacological mechanism. In the absence of the counter-factual (i.e. comparable data in patients who did not participate or were subsequently withdrawn from the open-label study) it is unclear whether the apparent increasing effect is simply a function of the selection issue or is a real effect of the anti-TNFs. Importantly, those studies which only use data from the double-blind periods of RCTs often cite the open-label data as providing supportive evidence regarding the maintenance of the effects observed at 12/24 weeks but not use it to support an assumption of an increasing effect over time.

The longer-term impact on costs and utilities beyond the initial response period are subsequently quantified by estimating separate BASDAI/BASFI 'trajectories' for different patient categories. The 3 main categories are:

1. Conventional care
2. Non-responder to anti-TNFs at 12/24 week assessment
3. Initial responder to anti-TNFs at 12/24 week assessment

The 'trajectory' for patients who are responders to anti-TNFs at the initial 12/24 week assessment are further separated into; (i) the period up to the point that anti-TNFs are subsequently withdrawn (i.e. due to loss of efficacy, AEs) and the period post TNF-alpha inhibitor withdrawal.

After the 'levelling off' period for BASDAI, the majority of existing studies assume BASDAI is constant over the longer term. That is, the BASDAI of responders to anti-TNFs is assumed to be lower than the equivalent BASDAI value (lower disease activity) applied to conventional care/non-responders and a constant difference is assumed to be retained until patients discontinue. At the point of discontinuation of anti-TNFs, patients subsequently revert back to the same value assumed for conventional care/placebo and non-responders to anti-TNFs at 12/24 weeks. Hence, any improvement in BASDAI is assumed to dissipate immediately or within a short-period (3-6 months) after discontinuation of anti-TNFs.

All existing studies model BASFI as a linearly increasing function over the longer term for non-responders/conventional care. That is, a constant rate of change is subsequently applied which is used to characterise the impact of disease progression on functional ability – typically a worsening of 0.07 (0-10 scale) units per annum. Again, the same assumptions applied to BASDAI for non-responders to anti-TNFs are applied to BASFI. That is, beyond 12/24 weeks, non-responders are assumed to follow an identical BASFI 'trajectory' as conventional care/placebo patients. By contrast, patients who respond to anti-TNFs are typically assumed not to 'progress' further in terms of functional disability, or progress at a lower rate than conventional care patients, whilst continuing to receive anti-TNFs. Hence the difference in individual mean BASFI scores increases over time in existing economic models between patients who continue to receive anti-TNFs and non-responders/conventional care.

The only study which employs a markedly different approach to the modelling of BASDAI and BASFI for responders is the study undertaken by the previous independent assessment group (LRiG) for TA 143. Instead, LRiG applied a quadratic function to the BASDAI and BASFI scores of responders. This approach assumed that the difference compared to conventional care was decreasing (initially) with time. That is, over time, the differences in BASDAI/BASFI would slowly reduce in responders and eventually be the same as for conventional care. While the logical problems of applying a quadratic function over a longer period were recognised by the authors (i.e. function begins to increase after a particular period) and was addressed using a series of logical restrictions (i.e. BASDAI/BASFI score constrained to be the same or better than conventional care), the clinical 'face' validity of this approach also appears questionable in the context of longer term projections which are required for appropriate assessments of cost-effectiveness.

Another key difference between existing studies relates to the assumptions made concerning the subsequent trajectory of BASFI for patients who withdraw from active treatment. Given that BASFI is linearly increasing with time for conventional care, the assumption of the subsequent BASFI trajectory is potentially an important driver of cost-effectiveness. This is often referred to as 'rebound'. Typically two scenarios are used:

1. *Rebound equal to gain.* When patients fail therapy (after initially responding), their BASFI deteriorates by the same amount by which it improves when they responded to therapy.
2. *Rebound back to natural history/conventional care*. When patients fail therapy (after initially responding), their BASFI deteriorates to the level and subsequent trajectory it would have been had they not initially responded to therapy.

In the absence of evidence on the magnitude of any rebound, these alternative scenarios represent the 'best-case' and 'worst-case' scenarios possible. In other words, the reality regarding rebound is likely to be somewhere between these two scenarios which should, therefore, be seen as the limits.

The implications of the different rebound scenarios are clearly illustrated in Figures 2 and 3. Studies which are based on assumptions of rebound equal to gain incorporate an ongoing benefit of anti-TNFs in patients in whom therapy is subsequently withdrawn after an initial response. Hence, such an assumption is more optimistic than assuming no continuing benefit at the point treatment is withdrawn.

Figure 2 - Illustration of the scenario of rebound equal to gain

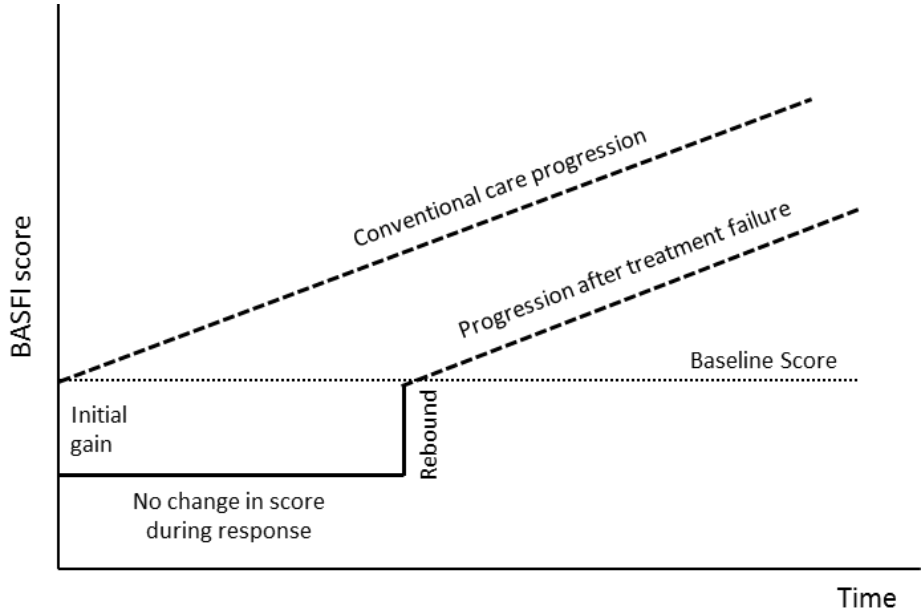
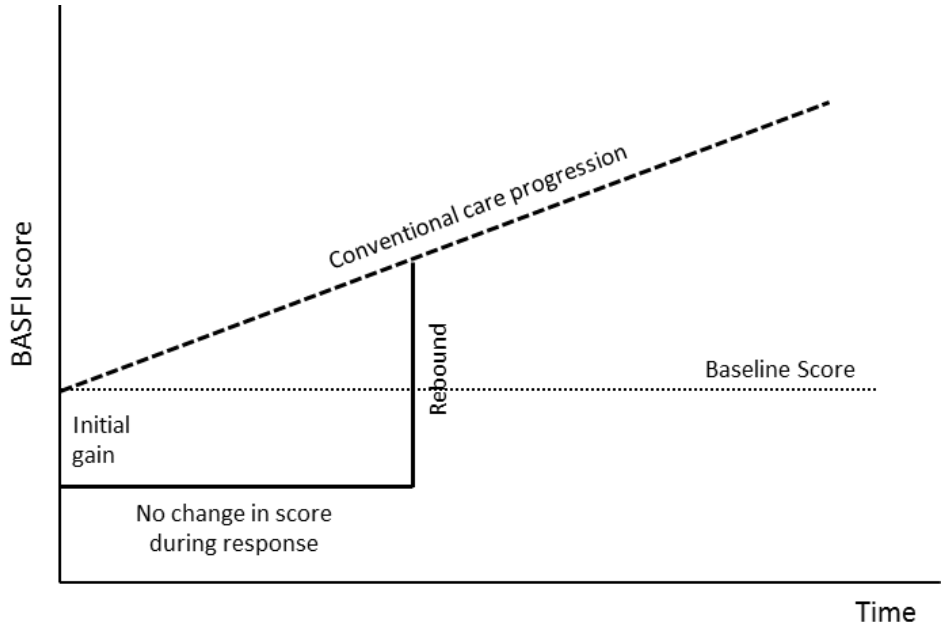


Figure 3 - Illustration of the scenario of rebound to conventional care



Although the impact of discontinuation in patients who initially respond is clearly an important issue, the assumptions underpinning the subsequent trajectories of patients who are non-responders at 12/24 weeks to anti-TNFs are rarely explicitly justified. The most common assumption applied is that non-responders during the initial period follow the same subsequent trajectory for BASDAI/BASFI as conventional care/placebo patients beyond the 12/24 week assessment point. However, the appropriateness of this assumption does not appear to have been discussed in existing studied. Essentially, for this assumption to hold, the initial response to anti-TNFs has to be independent of baseline patient characteristics, such that response to treatment is effectively a random process.

However, if response is not independent of patient characteristics, the implication is that responders/non-responders to TNFs-alpha inhibitors may be systematically different from each other. This has implications for the appropriateness of current assumptions being applied to non-responders at 12/24 weeks and subsequent responders who later withdraw. For example, all other things being equal, if patients with more severe disease (high BASDAI/high BASFI) were more likely not to respond, then assuming that the non-responders at 12/24 weeks follow the same trajectory as the 'average' conventional care/placebo patient is likely to be optimistic towards the anti-TNFs (and vice-versa for if less severe patients are more likely to respond). Hence, rather than following the trajectory of an 'average' placebo/conventional care patient, a non-responder may actually follow a different trajectory i.e. that of an equivalent more/less severe conventional care patient. Inevitably, the impact of different patient characteristics is likely to be more complex than the simplistic scenarios presented above.

As previously noted, all models employ changes in BASDAI and/or BASFI to quantitatively model the short and longer-term costs and quality of life implications (using QALYs) of the use of anti-TNFs s vs conventional care. The justification for using these measures appears largely driven by the existence of external sources of costs and health utility estimates which can be directly linked to these measures and not to others (e.g. BASMI, ASDAS, mSASSS etc). Hence, current models appear more of a function of the data which is available to link to costs and utilities rather than being based on a clear underlying biological or clinical process. This raises more general conceptual concerns regarding existing models and also regarding the generalisability of findings in an AS population to the separate nr-axSpA population.

The use of BASDAI/BASFI per se is perhaps not the most significant issue, since in the absence of alternative mapping functions to costs and/or utilities it's unclear how to estimate longer term costs and QALYs without ultimately linking to these measures. However, it is concerning that the majority of existing studies do not appear to link the data and assumptions applied to these measures to any coherent clinical underpinning regarding differences between population characteristics and the effect of anti-TNFs. Consequently, 'progression' over time is currently modelled entirely via changes in BASFI, since BASDAI is assumed to remain constant. However, no attempt is made to justify why BASFI increases, the rate at which it increases and how this rate might differ across different groups as well as the impact that anti-TNFs might have (i.e. any effect on BASFI which may be independent of the effect on BASDAI).

Modelling 'progression' implicitly (i.e. employing natural history estimates of the rate of change of BASFI from external studies) rather than explicitly (i.e. attempting to explain how BASFI evolves over time in relation to inflammatory and other processes and how these may differ within

populations and across the AS and nr-axSpA groups) has led to a series of implicit/evidence free assumptions. These include:

- No change in BASFI while receiving anti-TNFs (i.e. assuming implicitly that these act as disease modifiers and that while patients respond and continue to receive them, further deterioration in functional progression is completely prevented).
- Lower BASFI changes while receiving anti-TNFs (i.e. assuming that anti-TNFs do not completely halt further deterioration in functional progression but that the rate of progression is reduced relative to progression on conventional care).
- Similar natural history rates of change in BASFI across different subgroups and populations (i.e. assuming that rate of change in BASFI is independent of time and/or patient characteristics).

Similar conceptual concerns were also highlighted by the NICE DSU in their work to support TA143, noting that in inflammatory arthritis a clearer conceptual relationship is assumed between disease activity, radiographic progression and physical functioning. Such that changes in physical functioning can be more clearly related to different processes and evidence for the anti-TNFs on each separate process. In highlighting these issues the DSU cited emerging longer-term data reported for anti-TNFs based on measures of radiographic progression (mSASSS) in AS. Although this evidence was not formally included in their analyses, the evidence was cited to indicate that an assumption of no further progression while on anti-TNFs for AS was potentially optimistic based on emerging longer-term radiographic progression data.

Importantly, the only UK study published since the NICE DSU review did subsequently employ a less favourable assumption concerning the impact of anti-TNFs on functional progression (BASFI). The assumption employed by the manufacturer for golimumab assumed that the longer term rate of change in BASFI for responders who continued on treatment would be 50% of that assumed for conventional care/non-responders. Although this assumption is a significant departure from the base-case assumptions applied within previous industry funded studies, no justification appeared to be identified by Armstrong et al (2013) in the review of the manufacturer submission to support this.

In summary, there appear significant differences between the cost-effectiveness results reported in existing UK published studies. Many of these differences appear largely due to differences in data sources (i.e. double-blind period vs open-label extensions), subsequent assumptions and estimates related to the magnitude and duration of the differences in BASDAI and BASFI measurements between responders and non-responders in the short to medium term (i.e. the ‘levelling off’ period) and then longer term in relation to assumptions concerning BASFI progression and issues around ‘placebo’ effect and the withdrawal of anti-TNFs. Some of the main differences between existing

studies have been highlighted in a separate review by the NICE DSU. However, while this review is helpful in identifying the impact of parameter and structural assumptions, it does not provide a basis for informing which assumptions appear most justified based on existing data and clinical understanding of the progression of AS and the impact of anti-TNFs. It is also concerning that many of the existing studies are based on CIC data and hence lack transparency regarding specific inputs and assumptions.

To date only two UK studies have attempted to assess the cost-effectiveness of the alternative anti-TNFs. One of these studies, McLeod et al (2007), assumed that the alternative treatments were identical in terms of clinical effectiveness and hence only considered differences in the acquisition, administration and monitoring cost. The justification provided by the authors was based on the lack of statistically significant differences across key outcome measures based on indirect comparisons. The other study, Armstrong et al (2013), assumed differences in the clinical effectiveness of the alternative anti-TNFs based on a separate MTC. However, differences between the anti-TNFs appeared sensitive to the studies included and the specific outcomes considered. Hence, different conclusions could be drawn concerning the most 'efficient' intervention depending on the analysis considered. However, the magnitude of differences in clinical effect and QALYs remained small and the clinical and economic value of this might appear questionable.

There are conceptual concerns surrounding all existing models relating to the subsequent projection of BASDAI and BASFI over a longer time-horizon which are required in order to generate more appropriate lifetime estimates of costs and QALYs required for cost-effectiveness assessments. The speculative nature of these projections was highlighted as a significant concern by the previous independent assessment group (LRiG) and hence their longer-term results were presented as exploratory scenarios. However, it appears that all existing models are largely based on implicit approaches and assumptions and lack a clearer conceptual basis which might help to more appropriately inform parameter estimates and structural assumptions and facilitate a more evidence based assessment of the potential longer term impact of anti-TNFs.

The following sections present a summary of the *de-novo* submissions provided by the manufacturers for the separate AS and nr-axSpA indications. Brief overviews of the manufacturers' submissions for AS and nr-axSpA are provided alongside a summary of the base-case cost-effectiveness results. This is followed by a more in-depth comparison of key parameter and structural assumptions across the manufacturers and the separate indications. The issues and concerns regarding existing published studies are used as the basis for a more critical assessment of these submissions; investigating the extent to which these concerns have been adequately addressed and highlighting key uncertainties which still remain.

Note: Although fully incremental results were routinely presented by each manufacturer, there were differences between manufacturers in terms of how the results were presented and also whether the correct calculations based on dominance and extended dominance were included. Consequently the fully incremental ICER tables reported are based on our own calculations to ensure accuracy and consistency between the various manufacturer results tables.

5.2 Summary of manufacturers' *de-novo* submissions

Manufacturers submitted *de-novo* analyses for both AS (AbbVie, UCB, Pfizer, MSD) and nr-axSpA (AbbVie, UCB, Pfizer) populations.

5.2.1 Overview of AbbVie (adalimumab) model

The economic model presented by AbbVie compared the cost-effectiveness of adalimumab vs. conventional therapy and other licensed anti-TNFs for nr-axSpA and AS. Separate state-transition models were developed for the two indications separately based on the ASAS guidelines for the use of anti-TNFs. All patients were assumed to take conventional therapy/background therapy (e.g. NSAIDs) during the modelled horizon and also receive one of the licensed anti-TNFs or placebo (conventional therapy only). Specifically, patients were assumed to stay on therapy as long as they had an adequate therapeutic response (i.e., ASAS40 for nr-axSpA and ASAS20 for AS) and patients were assumed to discontinue therapy when insufficient response occurred. Discontinuations due to adverse events (AEs) or reasons other than therapeutic failures were also included.

The model consists of a short-term component (first 12 weeks) and a longer term component to estimate lifetime costs-effectiveness (40 years). In common with previously published models, the model was based on the estimation of BASDAI and BASFI scores over time. The model used the available long-term open-label extension data of trials of adalimumab (up to 156 weeks in ABILITY-1 for nr-axSpA and 260 weeks in ATLAS for AS – see Figures 4 and 5) as well as including assumptions beyond these study durations to inform the life-time cost-effectiveness results. To avoid extrapolating life-time improvement by applying a functional form to the BASDAI/BASFI data, the manufacturer applied the mean observed BASDAI and BASFI scores until the last available data point and carried forward the last observed values to the end of horizon.

Figure 4 - Observed mean BASDAI and BASFI scores for adalimumab ASAS20 responders in the licensed population from ATLAS (AS)

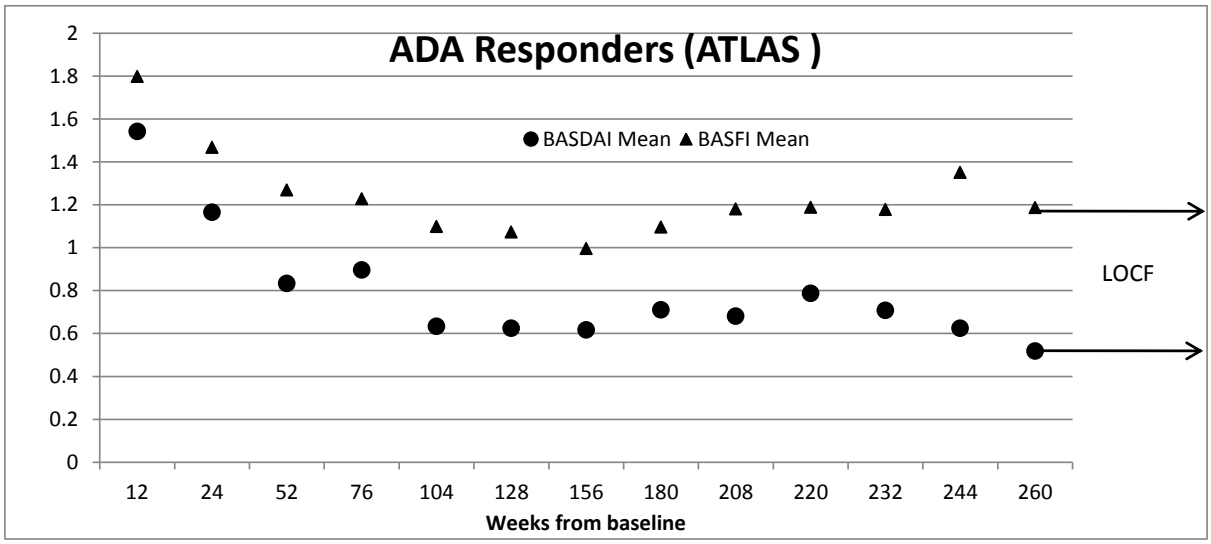
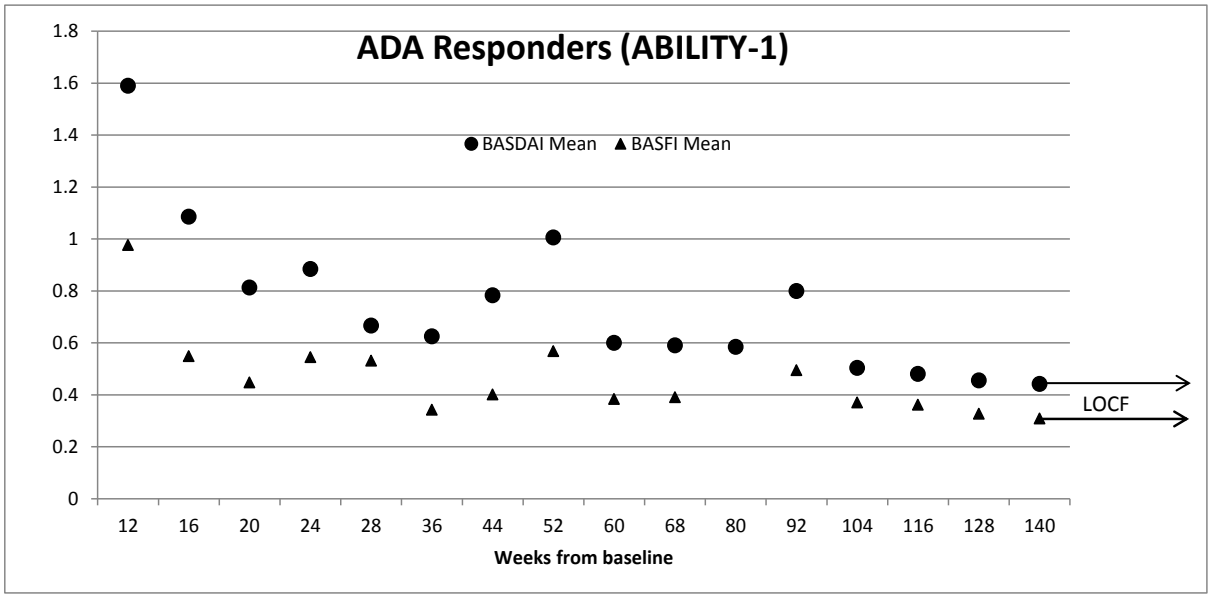


Figure 5 - Observed mean BASDAI and BASFI scores for adalimumab ASAS40 responders in the licensed population from ABILITY-1 (nr-axSpA)



Response rates and other select treatment efficacy endpoints were based on a separate systematic review and network meta-analysis. In the base-case, ASAS40 for nr-axSpA and ASAS20 for AS were used to define clinical response at week 12, based on the primary outcome measures from the clinical trials of adalimumab. In the base-case analysis, placebo responders at week 12 were assumed to lose response and return to baseline disease severity. Patients who subsequently withdrew from TNF-alpha treatment at any time point were also assumed to return to baseline disease severity (rebound equal to gain). Longer term discontinuation was assumed to be time-dependent and was based on a log-normal parametric distribution from the separate open-label RCTs adjusting for subsequent loss of response.

In the base case model, the BASFI score for all patients not on TNF-alpha inhibitor treatment increases in a linear fashion by 0.084 (scale 0-10) per year in patients with nr-axSpA, in line with the

evidence from the ABILITY-1 trial, where each additional year of baseline symptom duration was reported to be associated with a significant (+0.084, p=0.0005) increase in baseline BASFI score, adjusting for the age of onset (age at first reported axial SpA symptom) to control for the age effect on functional damage. An estimate of +0.056 was applied to patients with AS based on applying a similar approach to the ATLAS trial, adjusting for age at disease diagnosis. Hence, a higher BASFI progression was applied to patients not on anti-TNFs in the nr-axSpA population compared to the AS population.

BASDAI and BASFI scores were used jointly to estimate quality of life associated with AS, using the relationship observed between the utility scores (measured in HUI3) and the BASDAI and BASFI scores in ATLAS trial. Observed EQ-5D scores were mapped to BASDAI and BASFI for the relationship in the base case for nr-axSpA from ABILITY-1.

The relationship between BASDAI and costs, derived from a re-analysis of the OASIS data, was applied in the base-case. Costs of drug, administration, initiation and monitoring, and adverse events were also included. Discounting was applied at 3.5% for both costs and outcomes. . Standardised mortality ratios of 1 and 1.5 were assumed for nr-axSpA and AS, respectively. Uncertainty surrounding results was addressed using probabilistic sensitivity analyses (PSA).

Base-case results from AbbVie (adalimumab) model

The main base-case ICER results from the manufacturer are summarised in Table 36 for the AS population. From an NHS perspective, the base-case cost per QALY gained versus conventional care ranged from £16,391 per QALY (adalimumab) and £44,448 per QALY (infliximab).

Table 36 - TNF -alpha inhibitors compared to conventional care for AS - AbbVie (base-case)

	Total costs (£)	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£)**
Conventional care	112,762	8.62	-	-	-
Adalimumab	139,860	10.28	27,098	1.65	16,391
Certolizumab	133,273	9.82	20,511	1.20	17,067
Etanercept	139,574	10.21	26,812	1.59	16,897
Golimumab	138,385	10.17	25,624	1.55	16,535
Infliximab	197,100	10.52	84,339	1.90	44,448

Table 37 reports the results based on the fully incremental analysis. In the manufacturer base-case analysis, certolizumab and etanercept were ruled out by extended dominance. The ICER of adalimumab was £16,391 per QALY compared to conventional care. The ICER of the next more

costly (and non-dominated) TNF-alpha inhibitor was £238,500 per QALY for the comparison between infliximab and adalimumab.

Table 37 - Fully incremental comparison of anti-TNFs for AS – Assessment Group analysis based on AbbVie (base-case)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Conventional care	112,762	8.62	-	-	-
Certolizumab	133,273	9.82	-	-	Extendedly dominated
Golimumab	138,385	10.17	-	-	Extendedly dominated
Etanercept	139,574	10.21	-	-	Extendedly dominated
Adalimumab	139,860	10.28	27,098	1.66	16,391
Infliximab	197,100	10.52	57,240	0.24	238,500

The main base-case ICER results from the manufacturer and fully incremental analysis are summarised in Tables 38 and 39 for the nr-axSpA population. The ICERs versus conventional care ranged from £12,866 (certolizumab) to £13,288 per QALY (adalimumab). In the fully incremental comparison, adalimumab was extendedly dominated and hence the ICER for certolizumab vs conventional care is the only ICER reported (£12,866).

Table 38 – Anti-TNFs compared to conventional care for nr-axSpA – AbbVie (base-case)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Conventional care	126,075	8.88	-	-	-
Adalimumab	142,218	10.10	16,143	1.22	13,228
Certolizumab	142,608	10.16	16,532	1.28	12,866
Etanercept	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed

Table 39 - Fully incremental comparison of anti-TNFs for nr-axSpA – Assessment Group analysis based on AbbVie (base-case)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Conventional care	126,075	8.88	-	-	-
Adalimumab	142,218	10.10	-	-	Extendedly dominated
Certolizumab	142,608	10.16	390	0.06	12,866
Etanercept	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed

The manufacturer reported more favourable ICERs vs conventional care in the nr-axSpA population compared to the AS population. This appears largely driven by 2 inputs: (1) the lower

BASDAI/BASFI scores assumed for responders based on ABILITY-1 (compared to ATLAS) and (2) the higher annual BASFI progression rate assumed for non-responders/conventional care in the nr-axSpA population (0.084 vs 0.056).

5.2.2 Overview of UCB (certolizumab) model

The economic model presented by UCB compared the cost-effectiveness of certolizumab vs. conventional therapy and other licensed anti-TNFs for nr-axSpA and AS. Separate Markov cohort models were developed for the two indications separately based on the subpopulations of the RAPID-axSpA trial. Separate analyses were argued to be necessary given that the comparators differed for each subpopulation. Analyses performed for the AS subpopulation consisted of all patients with AS from the RAPID-axSpA study, including those who were anti-TNF therapy-experienced or naïve. The nr-axSpA subpopulation consisted of anti-TNF therapy-naïve patients only, as there were no anti-TNF therapy-experienced patients in this subpopulation.

The analyses used a lifetime time horizon in the base case. An alternative time horizon of 20 years was tested in a scenario analysis. An NHS & PSS perspective was used and an annual discount rate of 3.5% was applied to costs and outcomes. All costs are reported at 2013 values.

The model consists of a short-term component and a longer term component to estimate lifetime costs-effectiveness. The duration of the short-term component varied between the models used for the AS and the nr-axSpA subpopulations based on the response endpoint assumed. Response was assessed at 24 weeks in the AS subpopulation which was argued by the manufacturer to be in accordance with clinical practice as indicated key British opinion leaders. For the nr-axSpA subpopulation, response assessment was assumed at 12 weeks since comparator data were only available at that time point. In their base-case, the manufacturer used ASAS20 to determine response in line with the primary outcome measure in the RAPID-axSpA. However, it should be noted that ASAS 20 response at week 12 was the primary outcome in the RAPID-axSpa trial. Hence, while the measure of response used is in accordance with the primary outcome of the RAPID-axSpA trial, the differential timing of this applied across the separate populations clearly deviates from this. This has potential issues since at week 16, patients were allowed an ‘early escape’ from placebo and hence results at week 24 used for the AS subpopulation are no longer based on the original randomised population.

ASAS 20 response rates for certolizumab and relative treatment effects for the other anti-TNFs were derived based on a separate systematic review and MTC. The base-case model inputs applied in the manufacturer submission are replicated (and associated footnotes) in Tables 40 and 41 below.

Table 40 - Base case model inputs: ASAS20 response at Week 24 (AS subpopulation, CZP pooled dosing§)

Treatment	ASAS20 Response (%)	SE	RR†	CI	Source
CZP	[redacted]	[redacted]	-	-	MTC
Adalimumab†	-	-	[redacted]	[redacted]	MTC
Etanercept†	-	-	[redacted]	[redacted]	MTC
Golimumab†	-	-	[redacted]	[redacted]	MTC
Infliximab†	-	-	[redacted]	[redacted]	MTC

ASAS: Assessment in SpondyloArthritis international Society (criteria); **CC**: Conventional care; **CI**: Confidence interval; **CZP**: Certolizumab pegol; **MTC**: Mixed treatment comparison; **RR**: Relative risk; **SE**: Standard error
* proportion responding
§ Based upon pooled CZP 200 mg Q2W and 400 mg Q4W arms from RAPID-axSpA
†CZP versus comparator

Table 41 - Base case model inputs: ASAS20 response at Week 12 (nr-axSpA subpopulation, CZP pooled dosing§)

Treatment†	ASAS20 Response (%)	SE	RR†	CI	Source
CZP	[redacted]	[redacted]	-	-	MTC
Adalimumab†	-	-	[redacted]	[redacted]	MTC
Etanercept†	-	-	[redacted]	[redacted]	MTC

ASAS: Assessment in SpondyloArthritis international Society (criteria); **CC**: Conventional care; **CI**: Confidence interval; **CZP**: Certolizumab pegol; **MTC**: Mixed treatment comparison; **RR**: Relative risk; **SE**: Standard error
* proportion responding
§ Based upon pooled CZP 200 mg Q2W and 400 mg Q4W arms from RAPID-axSpA
†CZP versus comparator

The MTC was also used to determine change in baseline BASFI and BASDAI scores. The base-case inputs for change from baseline in BASFI and BASDAI at Week 24 for the AS subpopulation reported by the manufacturer are replicated in Tables 42 and 43. The manufacturer noted that the mean change from baseline reported in the tables is that observed per trial arm, which includes both the ASAS20 responders and non-responders in each arm. In order to determine the change in BASFI and BASDAI for responders alone, the manufacturer used the equation below:

> Mean change in BASFI = (change in BASFI amongst ASAS20 responders * proportion ASAS20 responders) + (change in BASFI amongst ASAS20 non-responders * proportion ASAS20 non-responders)

This approach assumed that the change in BASFI (and BASDAI) amongst ASAS20 non-responders is equal to that of the conventional care (CC) arm. Thus, the equation is used to algebraically solve for change in BASFI (and BASDAI) amongst ASAS20 responders. The manufacture stated that "*As an example for the AS subpopulation base case, the change in BASFI amongst ASAS20 responders for CZP is:* [redacted]*. Thus, in this example, the actual change from baseline in AS responders to CZP is* [redacted]*. The same approach was used for change from baseline for BASDAI. This approach, where the change from baseline for BASDAI and BASFI is*

calculated amongst responders only, is consistent with previous evaluations pharmaco-economic evaluations conducted for AS." (p69-70, manufacturer submission)

Table 42 - Base case model inputs: Change from baseline in BASFI score at Week 24 (AS subpopulation, CZP pooled dosing§)

Treatment	Change from Baseline in BASFI Score at Week 24: Initial Response Assessment Period		Source
	Mean	SD	
CZP	[redacted]	[redacted]	MTC
Adalimumab	[redacted]	[redacted]	MTC
Etanercept	[redacted]	[redacted]	MTC
Golimumab*	[redacted]	[redacted]	MTC*
Infliximab	[redacted]	[redacted]	MTC
Conventional care**	[redacted]	[redacted]	Assumed zero in base case**

BASFI: Bath Ankylosing Spondylitis Functional Index; **CZP**: Certolizumab pegol; **MTC**: Mixed treatment comparison; **SD**: Standard deviation
§ Based upon pooled CZP 200 mg Q2W and 400 mg Q4W arms from RAPID-axSpA
* GOL assumed same values as ADA, given that specific input values for BASFI at 24 weeks were not available from MTC.
** Conventional care assumed to produce no change in BASFI score initially in the base case. As noted in main text, it is reasonable to assume patients receiving CC do not achieve a change from baseline (worsening or improvement) in BASDAI or BASFI as evidence from RAPID-axSpA, ATLAS and ABILITY-1 demonstrate that in the PBO arms of these studies where patients were essentially maintained on CC, patients did not achieve MCID for BASDAI or BASFI.[46, 52, 63] Furthermore, Dougados and colleagues describe CC regimens as "palliative at best, providing no alteration of the disease process". This assumption is consistent with previous manufacturers' submissions to NICE in AS. However, a mean change in BASFI of [redacted] estimated from the MTC was used in the sensitivity analysis.

Table 43 - Base case model inputs: Change from baseline in BASDAI score at Week 24 (AS subpopulation, CZP pooled dosing§)

Treatment	Change from Baseline in BASDAI Score at Week 24: Initial Response Assessment Period		Source
	Mean	SD	
CZP	[redacted]	[redacted]	MTC
Adalimumab	[redacted]	[redacted]	MTC
Etanercept	[redacted]	[redacted]	MTC
Golimumab	[redacted]	[redacted]	MTC
Infliximab	[redacted]	[redacted]	MTC
Conventional care*	[redacted]	[redacted]	Assumed zero in base case*

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; **CZP**: Certolizumab pegol; **MTC**: Mixed treatment comparison; **SD**: Standard deviation
§ Based upon pooled CZP 200 mg Q2W and 400 mg Q4W arms from RAPID-axSpA
* Conventional care assumed to produce no change in BASDAI score initially in the base case. As noted in main text, it is reasonable to assume patients receiving CC do not achieve a change from baseline (worsening or improvement) in BASDAI or BASFI as evidence from RAPID-axSpA, ATLAS and ABILITY-1 demonstrate that in the PBO arms of these studies where patients were essentially maintained on CC, patients did not achieve MCID for BASDAI or BASFI. Furthermore, Dougados and colleagues describe CC regimens as "palliative at best, providing no alteration of the disease process". This assumption is consistent with previous manufacturers' submissions to NICE in AS.[2] However, a mean change in BASDAI of [redacted] estimated from the MTC was used in the sensitivity analysis.

The manufacturer base case inputs for change from baseline in BASFI and BASDAI at Week 12 for the nr-axSpA subpopulation are replicated in Tables 44 and 45 – all footnotes supplied by the manufacturers are reported in their entirety for further clarification, although supporting references have been removed here.

Table 44 - Base case model inputs: Change from baseline in BASFI score at Week 12 (nr-axSpA subpopulation, CZP pooled dosing§)

Treatment	Change from Baseline in BASFI Score at Week 12:Initial Response Assessment Period		Source
	Mean	SD	
CZP	[redacted]	[redacted]	MTC
Adalimumab	[redacted]	[redacted]	MTC
Etanercept	[redacted]	[redacted]	MTC
Conventional care*	[redacted]	[redacted]	Assumed zero in base case*

BASFI: Bath Ankylosing Spondylitis Functional Index; **CZP**: Certolizumab pegol; **MTC**: Mixed treatment comparison; **SD**: Standard deviation

§ Based upon pooled CZP 200 mg Q2W and 400 mg Q4W arms from RAPID-axSpA

* Conventional care assumed to produce no change in BASFI score initially in the base case. As noted in main text, it is reasonable to assume patients receiving CC do not achieve a change from baseline (worsening or improvement) in BASDAI or BASFI as evidence from RAPID-axSpA, ATLAS and ABILITY-1 demonstrate that in the PBO arms of these studies where patients were essentially maintained on CC, patients did not achieve MCID for BASDAI or BASFI. Furthermore, Dougados and colleagues describe CC regimens as "palliative at best, providing no alteration of the disease process" This assumption is consistent with previous manufacturers' submissions to NICE in AS. However, a mean change in BASFI of [redacted] estimated from the MTC was used in the sensitivity analysis.

Table 45 - Base case model inputs: Change from baseline in BASDAI score at Week 12 (nr-axSpA subpopulation, CZP pooled dosing§)

Treatment	Change from Baseline in BASDAI Score at Week 12: Initial Response Assessment Period		Source
	Mean	SD	
CZP	[redacted]	[redacted]	MTC
Adalimumab	[redacted]	[redacted]	MTC
Etanercept	[redacted]	[redacted]	MTC
Conventional care*	[redacted]	[redacted]	Assumed zero in base case*

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; **CZP**: Certolizumab pegol; **MTC**: Mixed treatment comparison; **SD**: Standard deviation

§ Based upon pooled CZP 200 mg Q2W and 400 mg Q4W arms from RAPID-axSpA

* Conventional care assumed to produce no change in BASDAI score initially in the base case. As noted in main text, it is reasonable to assume patients receiving CC do not achieve a change from baseline (worsening or improvement) in BASDAI or BASFI as evidence from RAPID-axSpA, ATLAS and ABILITY-1 demonstrate that in the PBO arms of these studies where patients were essentially maintained on CC, patients did not achieve MCID for BASDAI or BASFI. Furthermore, Dougados and colleagues describe CC regimens as "palliative at best, providing no alteration of the disease process". This assumption is consistent with previous manufacturers' submissions to NICE in AS. However, a mean change in BASDAI of [redacted] estimated from the MTC was used in the sensitivity analysis.

The manufacturer submission assumed no change in BASDAI and BASFI for conventional care during the response period. The manufacturer justified this assumption with reference to evidence from RAPID-axSpA, ATLAS and ABILITY-1 studies, although no specific data were reported to support this. In addition, we requested additional data from the manufacturer on change scores conditional on response for certolizumab and placebo from the RAPID-axSpA trial but this was not provided. Hence, it is not possible to adequately assess the appropriateness of the method of adjustment used by the manufacturer to estimate change scores or the assumption applied to conventional care. However, it might be reasonable to assume that the actual conditional scores from RAPID-axSpa are unlikely to be higher than those reported here for certolizumab, since the manufacturer would presumably have responded to the request for the additional data if this had been the case.

These change scores are assumed to be maintained for BASDAI as long as a patient continues to receive an anti-TNF. For AS patients on conventional care, an additional annual increase of 0.07

points (scale 0-10) in BASFI is assumed and justified by the manufacturer according to the assumptions deemed reasonable by a previous NICE committee. Hence, while the change scores are assumed constant, the absolute difference between patients receiving anti-TNFs and conventional care is increasing over time given the underlying progression assumed for BASFI for patients receiving conventional care. The assumption of no progression in BASFI for patients receiving anti-TNFs is not explicitly discussed within the manufacturer's submission, nor are separate results provided for alternative assumptions.

The same annual rate (0.07) in BASFI progression for conventional care is also applied to the nr-axSpA subpopulation. In addition, it is assumed that some nr-axSpA patients may progress to AS during their course of treatment. The manufacturer's model adopts an estimate for disease progression for the nr-axSpA subpopulation based on a German cohort of axSpA patients, the German Spondyloarthritis Inception Cohort (GESPIC). In this cohort, the rates and predictors of radiographic spinal progression over two years were estimated based on mSASSS. 7.4% of the 95 nr-axSpA patients were reported to show spinal radiographic progression, which was defined as a worsening of mSASSS by ≥2 units over two years. As this 7.4% progression represents a proportion it was converted to a rate for use in the economic model, assuming an exponential distribution through the following formula:

$$1-0.074 = \exp(-\text{rate}*2 \text{ years}); \text{ rate} = 0.0384 \text{ or } 3.84 \text{ per } 100 \text{ pt-year}$$

The manufacturer's submission is not explicit about how this additional aspect of progression subsequently alters the BASDAI/BASFI trajectories within the nr-axSpA model. However, examination of the electronic model submitted by the manufacturer reveals that once patients are assumed to show spinal radiographic progression, they effectively become AS patients by picking up the same absolute values of BASDAI and BASFI (on and off treatment) applied in their AS subpopulation model. The justification for this approach and the values subsequently assigned are not formally discussed by the manufacturer and the validity of the approach appears questionable (i.e. given other differences e.g. disease duration, severity of radiographic disease etc, that may differ between the two populations even after radiographic progression has occurred in the nr-axSpA subpopulation)..

Patients who subsequently withdrew from TNF-alpha treatment at any time point were assumed to revert back to the same trajectory as conventional care over a 6-month period (i.e. rebound back to conventional care/natural history). A constant annual rate of discontinuation of 7% was assumed for all Anti-TNFs over the longer-term period in both the AS and nr-axSpA populations. The estimate of 7% applied to the AS subpopulation was justified by citing the rate apparently assumed by the NICE committee for TA143 and the lack of long-term evidence more generally. This estimate was referred

to earlier in the review section of our report when the additional analyses undertaken by the NICE DSU were considered. Identical assumptions for discontinuation rates were assumed for the nr-axSpA subpopulations, although no justification was provided by the manufacturer.

BASDAI and BASFI scores were used jointly to estimate quality of life in both subpopulations based on EQ-5D data collected in the RAPID-axSpA study. Data from subjects having EQ-5D, BASDAI and BASFI scores available at baseline, Week 12 and Week 24 were used to estimate a relationship between utility and BASDAI and BASFI. Utilities were subsequently converted using a logistic transformation with the justification based on possible floor and ceiling effects since they are bounded by 0 and 1. Without access to the original data to it is not possible to determine the impact of this transformation, although it should be noted that EQ-5D is not bounded by 0 (i.e. negative values are possible). The manufacturer used a repeated-measures logistic regression to model the relationship between utility and BASDAI, and BASFI scores.

The relationship between BASFI and costs, derived from the OASIS study and used by the previous independent assessment group in TA143, was applied in the base-case. Costs of drug, administration, initiation and monitoring were included. The costs and or HRQoL of adverse events were not included. Discounting was applied at 3.5% for both costs and outcomes. Uncertainty surrounding outcomes was addressed using PSA.

Base-case results from UCB (certolizumab) model

The main base-case ICER results from the manufacturer are summarised in Table 46 for the AS population, together will a fully-incremental comparison of ICERs (Table 47). The ICERs vs conventional care ranged from £16,647 per QALY (certolizumab) and £42,671 per QALY (infliximab). In the fully incremental analysis, certolizumab dominated (i.e. less costly and more expensive) all other TNF-alpha treatments apart from infliximab. However, it should be noted that the costs of certolizumab are based on a PAS which has been proposed but is not yet formally agreed with the Department of Health and NICE. Results without the PAS were not reported by the manufacturer. UCB will make Cimzia available free of charge to all NHS patients for the first three months of therapy, at which point clinical response should be clear. Only after this three month stage will the NHS be charged for continuing to use this therapy.

The ICER of certolizumab was £16,647 per QALY vs conventional care and the ICER for infliximab was £113,871 (vs certolizumab).

Table 46 - TNF -alpha inhibitors compared to conventional care for AS - UCB (base-case)

	Total costs (£)	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£)**
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]	-

Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	19,932
Certolizumab	[redacted]	[redacted]	[redacted]	[redacted]	16,647
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	19,272
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	19,049
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	42,671

Table 47 - Fully incremental comparison of anti-TNFs for AS – Assessment Group analysis based on UCB (base-case)

	Total costs (£)	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£)**
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]	-
Certolizumab	[redacted]	[redacted]	[redacted]	[redacted]	16,647
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	113,871

The main base-case ICER results from the manufacturer are summarised in Table 48 for the nr-axSpA population, together will a fully-incremental comparison of ICERs (Table 49). In contrast to the results for AS, there was a more marked difference between the ICERs of the alternative anti-TNFs and conventional care. The ICERs vs conventional care ranged from £15,615 (certolizumab) to £50,692 per QALY (etanercept). The higher differential ICERs appears to be largely due to the more heterogeneous trials included in the MTC for the nr-axSpA populations and a higher differential effect assumed for certolizumab vis-à-vis the other alternative anti-TNFs compared with the AS population. Importantly, other manufacturers (Pfizer) argue that the results for certolizumab in this population maybe confounded by population characteristics which could invalidate the indirect comparison of certolizumab versus the other comparator treatments in the current nr-axSpA MTC. In the fully incremental analysis, certolizumab dominated adalimumab and etanercept.

Table 48 - TNF -alpha inhibitors compared to conventional care for nr-axSpA - UCB (base-case)

	Total costs (£)	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£)**
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]	-
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	30,370
Certolizumab	[redacted]	[redacted]	[redacted]	[redacted]	15,615
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	50,692

Table 49 - Fully incremental comparison of anti-TNFs for nr-axSpA – Assessment Group analysis based on UCB (base-case)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]	-
Certolizumab	[redacted]	[redacted]	[redacted]	[redacted]	15,615
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

5.2.3 Overview of Pfizer (etanercept) model

The economic model submitted by Pfizer compared the cost-effectiveness of etanercept vs. conventional therapy and other licensed anti-TNFs for AS, nr-axSpA and a combined population (axSpA). The results for the combined population are not summarised in this review but are reported separately in the manufacturer submission. The model is based on a lifetime time-horizon and costs and benefits are discounted at an annual rate of 3.5%. The reference year for costs was reported to be 2014.

The model was based on a patient-level simulation model based on a discrete event simulation (DES). The analysis was conducted from an NHS/PSS perspective. Data to populate the model were derived from key clinical trials for etanercept and results of a clinical systematic review, MTC and in a separate analysis presented for the nr-axSpA population, a match adjusted indirect comparison (MAIC). The model structure was reported to be developed in accordance with current OMERACT (Outcome Measures in Rheumatology) guidance and was constructed around BASDAI and BASFI in line with other published studies.

The AS population was defined based on current NICE guidance in TA143 and TA233. The nr-axSpA population was defined based on the scope issued by NICE and was defined by the manufacturer as people with severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation, whose disease has responded inadequately to, or who are intolerant to, NSAIDs.

An important aspect of the submission for the nr-axSpA population was an attempt to adjust analyses for differences in the baseline patient characteristics between the trials included. The manufacturer reported that:

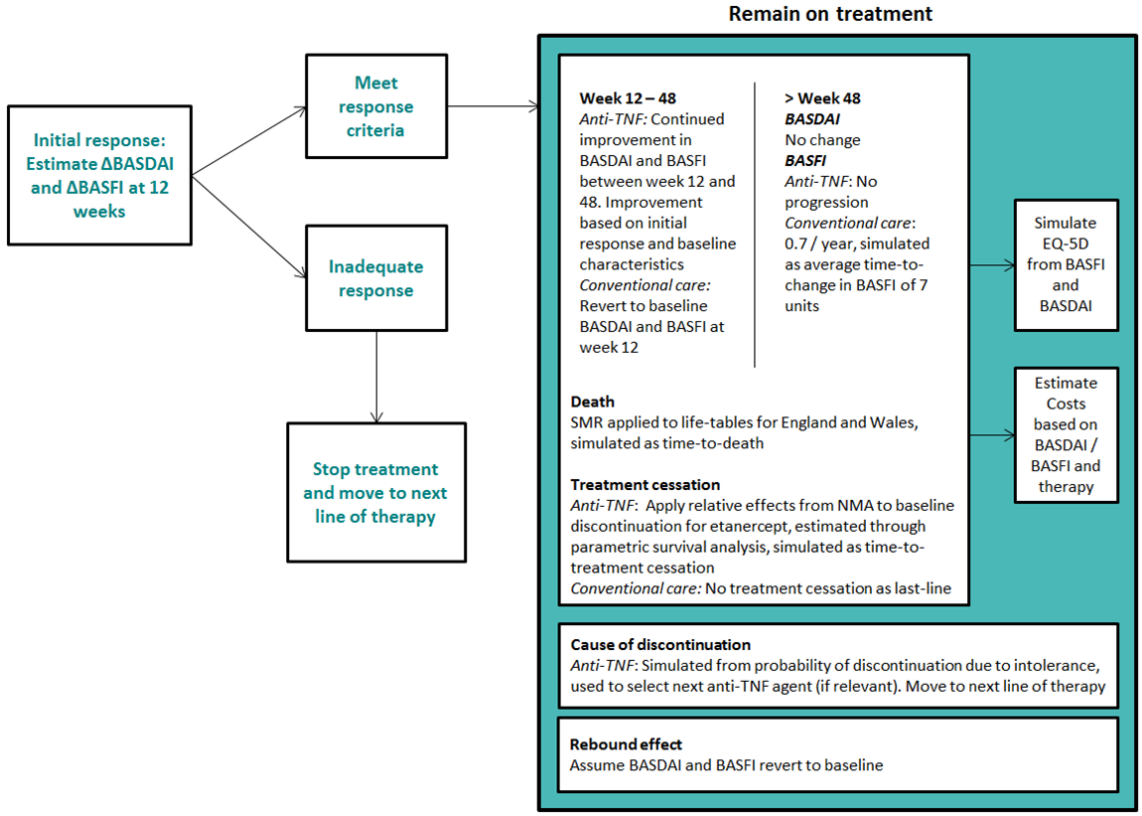
"The clinical systematic review identified that the baseline characteristics of nr-axSpA patients within the randomised controlled trials of certolizumab pegol and adalimumab were heterogeneous, and potentially differed in characteristics that could act as treatment effect modifiers. Furthermore, the populations of these trials also included sizable proportions of AS patients who were originally

classified as nr-axSpA on the basis of a difference between centralised and localised readings of x-rays

To address the differences in the proportions of AS patents in the trials due to reclassification upon central assessment, analyses were conducted using match adjusted indirect comparison (MAIC) and simulated treatment comparison (STC) techniques that incorporated AS patients from the etanercept 314-EU trial. These analyses are referred to collectively as "analyses adjusting for differences in study baseline characteristics". A comparison of the results from the MAIC and STC approaches show that while the results of the two analyses are similar, when considering comparisons between etanercept and both adalimumab and certolizumab, the MAIC analysis provides a lower overall comparative estimate of the benefit of etanercept, and is therefore considered overall to be the more conservative of the two approaches. To maintain consistency in the analysis utilised in the economic section, the MAIC was used throughout as the adjusted comparative efficacy measure between etanercept versus adalimumab and etanercept versus certolizumab. For the analysis comparing etanercept against certolizumab pegol, it was possible to address the issue of patient reclassification and differences in baseline characteristics by utilising the RAPID-axSpA trial results that were also available at the level of AxSpA patients, an approach not possible in the comparison of etanercept versus adalimumab. We note that although not explicitly detailed within the scope, the AxSpA population encompasses both nr-axSpA and AS patients, thus making it a relevant comparison to the decision problem outlined in the scope." (p226-227, manufacturer submission)

The manufacturer argued that the use of DES conferred potential advantages in relation to modelling non-linearity due to heterogeneous patient characteristics and in relation to modelling time dependency. The latter was also argued as an advantage to considering the impact of sequential therapy which was argued to be complex within a more conventional Markov type structure. Pfizer's model was the only model which explicitly explored issues of treatment sequences. However, in the base-case the use of second-line TNF-alpha inhibitor treatment was restricted to those patients who withdrew due to adverse events and assumed equal efficacy to 1st line usage. The schematic of the model provided by the manufacturer is replicated in Figure 6:

Figure 6 – Pfizer DES model schematic



Etanercept RCT data were used to predict an initial 12-week response (in terms of reduction in BASDAI and BASFI) for etanercept for both nr-axSpA and AS populations. Separate multivariate regressions were used to account for correlation between BASDAI and BASFI. A range of variables were initially included in the regression models based on potential predictors of response identified from their review of economic studies. The statistical significance and direction of effect were evaluated before final models were specified. The 12-week models of BASDAI and BASFI for the nr-axSpA had R-squared values of [redacted], respectively. For the AS population, the equivalent R-squared values were [redacted]. The regressions were used to estimate mean change in BASDAI and BASFI which through the patient level simulation were used to assign patients into BASDAI50 responder/non-responder categories and to assess the associated magnitude of change at 12 weeks for these categories.

Relative effects from the MTC (or MAIC in the analyses adjusting for differences in study baseline characteristics), in terms of mean differences in BASDAI and BASFI, were applied in order to predict equivalent response and change scores for the other anti-TNFs agents and conventional care at 12 weeks

From week 12, the BASFI scores for conventional care were assumed to increase at a rate of 0.7 units per annum (0-100 scale). The modelling of change in BASDAI and BASFI at Week 48 for responders to etanercept was conducted using the same approach used for the Week 12 treatment response. However, change in BASDAI and BASFI from baseline at Week 12 were included as additional covariates within the resulting models in order to ensure that an individual's response at Week 48 was dependent on their response at Week 12. The 48-week models of BASDAI and BASFI for the nr-axSpA had R-squared values of [redacted], respectively. For the AS population, the equivalent R-squared values were [redacted]. In the absence of relative effect estimates at Week 48 for other therapies, it was assumed that patients who remained on TNF-alpha inhibitor treatment beyond week 12 (i.e. responders) would converge at the BASDAI and BASFI levels predicted for etanercept by week 48. Constant BASDAI and BASFI scores for TNF-alpha inhibitor responders were assumed at the level observed at Week 48 for subsequent periods.

Treatment discontinuation was modelled by fitting separate parametric survival curves to long-term open-label study data from etanercept for the AS and nr-axSpA populations. In order to predict treatment cessation in the population likely to continue treatment after 12 weeks, parametric curves were fitted only to subjects who achieved a BASDAI 50 response at Week 12. Only subjects who were randomised to etanercept at baseline were retained within these survival analyses and subjects who began etanercept during open-label phases of studies were excluded. The distributions that provided the best fit were exponential ([redacted]) and log-normal ([redacted]), based on the minimisation of the AIC and the BIC. The exponential model was chosen based, in part, on the goodness of fit but also because the use of hazard ratios which were applied to estimate the effect of other anti-TNFs on the rate of discontinuation, required the use of a proportional hazard survival model (to avoid making further assumptions when applying the hazard ratio to the log-normal [accelerated failure time] model).

The same risk of discontinuation was applied to all individuals in the model. The models of discontinuation translate into annual probabilities of discontinuation for etanercept, for patients who achieve a BASDAI 50 response, of 5% and 11% for nr-axSpA and AS populations, respectively. Based on data from the DANBIO registry, it was assumed that other anti-TNFs have an increased risk of discontinuation compared with etanercept; a hazard ratio of 1.3 is applied for infliximab and 1.12 for adalimumab. In the absence of evidence for golimumab and certolizumab, it was assumed that the relative effect is the same as for adalimumab on the basis that these have common molecular structure and belong to monoclonal antibodies.

After discontinuation of the first treatment, an alternative TNF-alpha inhibitor was modelled as second-line treatment for patients who discontinued due to adverse events ([redacted]% for AS and [redacted]%

for nr-axSpA). The same efficacy as applied for first-line treatments was assumed for second-line treatments for patients switching due to adverse events. For patients who discontinued due to loss of efficacy, no further TNF-alpha treatment was modelled. These assumptions were considered by the manufacturer to be consistent with current NICE guidance. For the base case model, it was assumed that following discontinuation from anti-TNFs, patients would rebound back to their baseline BASDAI and BASFI scores and that the rebound takes 6 months based on the approach used within the TA233 submission to NICE.

In the absence of previously published studies reporting the relationship between BASDAI/BASFI and EQ-5D utility scores in the nr-axSpA population, a *de-novo* relationship was estimated from study 1031; variables included age, gender, baseline BASDAI and BASFI. OLS regression models were used, with standard errors clustered around each subject to account for repeated observations. For consistency a similar relationship was estimated for the AS population using study 314-EU. Alternative linear and non-linear relationships were evaluated and final model selection based on AIC statistics. In the nr-axSpA population, the final model included squared terms for BASDAI and BASFI and an interaction between BASDAI and BASFI, while in the AS population, the covariates for the interaction term, age and male were not included. Scenario analyses considered using alternative model specifications for mapping. The manufacturer reported that according to visual inspection, the estimated models were very similar between populations and reported a high degree of similarity between the results of the *de-novo* estimated models and those published previously.

Figures 7 and 8 replicate the relationships reported by the manufacturer between EQ-5D, BASDAI and BASFI in the nr-axSpA and AS populations, respectively. Additional figures were also presented by the manufacturer for predicted versus observed EQ-5D in each of the populations. The manufacturer concluded that the models over-predicted EQ-5D at low observed EQ-5D and under-predicted at higher observed EQ-5D values. The manufacturer argued that this was a common feature of mapping algorithms and argued that the approach would be conservative towards the use of anti-TNFs.

Figure 7 - Relationships between EQ-5D, BASDAI and BASFI from study 1031 (nr-axSpA population)

[redacted]

Figure 8 - Relationships between EQ-5D, BASDAI and BASFI from study 314-EU (AS population)

[redacted]

The manufacturer included the acquisition, administration and pre-treatment monitoring costs of TNF alpha-inhibitors. Subsequent monitoring costs were not included in order to avoid potential double counting of the costs which were estimated as a function of BASDAI and BASFI. In the base-case analysis the manufacturer used data from Rafia et al, 2012[158] based on BASDAI scores only. A categorical approach was applied to BASDAI scores based on the following annual costs: BASDAI<40=£151.96; 40<=BASDAI<60=£311.08; BASDAI>=60= £1039.16. The manufacturer justified the use of this source as it provides the most recent UK specific data reported and permitted separation of particular cost items. The costs and HRQoL of adverse events (serious infections only) were included in the base-case analysis (none observed in the nr-axSpA trial 1031, however, serious infections were observed in the AS trial 314-EU). A separate sensitivity analysis included the costs of serious infections.

An SMR of 1 for the nr-axSpA population and 1.5 for the AS population were applied to general population life-tables.

Results of Pfizer (etanercept) model

The main base-case ICER results from the manufacturer are summarised in Table 50 for the AS population, together will a fully-incremental comparison of ICERs (Table 51). The ICERs vs conventional care ranged from £19, 586 per QALY (certolizumab) and £37,741 per QALY (infliximab). In common with the UCB model, it should be noted that the costs of certolizumab assumed within Pfizer's model were also based on the PAS for certolizumab which has been proposed

but is not yet formally agreed with the Department of Health and NICE. Hence the ICER for certolizumab vs conventional care without the PAS will be higher than the estimates reported here.

Table 50 - TNF -alpha inhibitors compared to conventional care for AS – Pfizer (base-case)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Conventional care	18,122	7.318	-	-	-
Adalimumab	57,535	9.203	39,413	1.885	20,909
Certolizumab	51,843	9.040	33,721	1.722	19,586
Etanercept	60,338	9.334	42,216	2.016	20,938
Golimumab	62,698	9.412	44,576	2.094	21,288
Infliximab	98,340	9.443	80,218	2.125	37,741

In the fully incremental analysis, adalimumab was extendedly dominated. Of the remaining non-dominated treatments, the ICER of the next most costly intervention compared with the previous non-dominated alternative was: £19,586 (certolizumab vs conventional care), £28,834 (etanercept vs certolizumab), £30,376 (golimumab vs etanercept) and £1,131,181 (infliximab vs golimumab).

Table 51 - Fully incremental comparison of anti-TNFs for AS – Assessment Group analysis based on Pfizer (base-case)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Conventional care	18,122	7.318	-	-	-
Certolizumab	51,843	9.040	33,721	1.722	19,586
Adalimumab	57,535	9.203	-	-	Extendedly dominated
Etanercept	60,338	9.334	8,495	0..294	28,834
Golimumab	62,698	9.412	2,360	0.078	30,376
Infliximab	98,340	9.443	35,642	0.031	1,131,181

The main base-case ICER results from the manufacturer are summarised in Table 52 for the nr-axSpA population, together will a fully-incremental comparison of ICERs (Table 53). The ICERs vs conventional care ranged from £23,195 (etanercept) and £23,575 (certolizumab). In contrast to the UCB analysis, the ICERs for the nr-axSpA population were marginally less favourable than the results for the AS population. There was also less of a marked difference between the ICERs for each of the anti-TNFs and conventional care compared to the UCB results, although a large difference was evident relating to the magnitude of the incremental QALY estimates for certolizumab vis-à-vis the other anti-TNFs. Table 54 reports the results of the fully incremental analysis. None of the anti-TNFs were ruled out via dominance or extended dominance and the ICER of each comparison remained below £30k per QALY for each successively more expensive and effective treatment.

Table 52 - Anti-TNFs compared to conventional care for nr-axSpA - Pfizer (base-case)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Conventional care	20,609	10.221	-	-	-
Adalimumab	62,667	12.030	42,058	1.809	23,242
Certolizumab	74,282	12.497	53,673	2.276	23,575
Etanercept	59,635	11.903	39,026	1.682	23,195

Table 53 - Fully incremental comparison of for nr-axSpA – Assessment Group analysis based on Pfizer (base-case)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Conventional care	20,609	10.221	-	-	-
Etanercept	59,635	11.903	39,026	1.683	23,195
Adalimumab	62,667	12.030	3,033	0.127	23,871
Certolizumab	74,282	12.497	11,615	0.467	24,864

To address the concerns noted by Pfizer relating to the heterogeneity across the different trials in the nr-axSpA population, a separate matched indirect comparison was presented for etanercept vs adalimumab. A separate comparison was also presented vs certolizumab for the combined axSpA population in the manufacturer submission. Using the MAIC approach, the ICER for etanercept vs adalimumab was £23,195 per QALY. Total cost and QALYs estimates were reversed in the MAIC approach when compared to the base-case analysis (adalimumab generated greater QALYs at increased cost), demonstrating the potential impact of trying to minimise observable sources of possible confounding.

Table 54 - Incremental results of etanercept vs adalimumab in nr-axSpA (using MAIC data) - Pfizer

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Adalimumab	48,494	11.473	-	-	-
Etanercept	60,404	11.928	11,910	0.455	26,176

MAIC = matching adjusted indirect comparison

5.2.4 Overview of MSD (golimumab, infliximab) model

The economic models submitted by MSD compared the cost-effectiveness of golimumab and infliximab vs. conventional therapy and other licensed anti-TNFs for AS. Although the manufacturer made separate submissions for golimumab and infliximab, the model structures and data sources used to inform the economic models are identical across the submissions. Hence, this review focuses on the specific submission for golimumab but also considers key data sources and assumptions specific to infliximab. The model base-case is based on a lifetime time-horizon (approximately 60 years) and costs and benefits are discounted at an annual rate of 3.5%. An NHS & PSS perspective is used for costs. The reference year for costs was reported to be 2012/13.

The economic model submitted by the manufacturer for golimumab is based on the same model structure submitted as part of NICE TA233 and summarised previously in the review section (Armstrong et al, 2013)[154]. Hence, a description of the structure of the model is not repeated in this section. In summary, the manufacturer's cost-effectiveness model was based on a short-term decision tree (based on an assessment of BASDAI 50 response at 12 weeks in the base-case) and a longer term Markov model.

The proportion of patients achieving BASDAI50 at week 12 (+/-2 weeks) for each TNF-alpha inhibitor was obtained from a systematic review and MTC undertaken by the manufacturer. Their results are summarised in Table 55.

Table 55 – ORs and probability of BASDAI50 response to anti-TNFs and conventional therapy (MSD)

Treatment	BASDAI50	
	OR (95% CrI)	**Probability**
Golimumab	5.54 (2.12-12.13)	0.49
Infliximab	22.44 (2.78-89.05)	0.79
Adalimumab	5.20 (2.14-10.62)	0.47
Etanercept	5.46 (2.03-11.74)	0.60
Certolizumab pegol	6.62 (1.66-17.59)	0.53
Conventional therapy	-	0.15

OR = odds ratio, CrI = credible interval

Data from the GO-RAISE trial and the open-label extension period (up to week 108) were used to develop predictive equations of mean change from baseline in BASDAI and BASFI scores over time. 2 separate equations were developed based on the 24 week data (0-24 weeks) for all patients and post-24 week (week 24 to 108) data from GO-RAISE for patients who remained on treatment. The variables applied in each equation are summarised below in Tables 56 and 57.

Table 56 - Short-term regression equations used by MSD for BASDAI/BASFI (0-24 weeks) – all patients

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$^{\wedge(-2)}$	5.226	0.2767
Treatment × week$^{\wedge(-2)}$	-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$^{\wedge(-2)}$	-3.4664	2.1365
Treatment × week$^{\wedge(-2)}$	-7.1029	2.6887

Table 57 - Long-term regression equations used by MSD for BASDAI/BASFI (24-108 weeks) – responders only

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

The treatment coefficient (and interaction term) in the short-term regression equation is used to estimate separate BASDAI/BASFI scores for anti-TNFs and conventional care. Hence, up week to week 24, the same estimate of BASDAI/BASFI appears to be applied to all-TNFs (i.e. regardless of the differential response rates assumed). Beyond week 24, the same BASDAI/BASFI score is applied to a responder to any of the TNFs, although a different response rate for each TNF-alpha inhibitor is assumed based on the MTC. The BASDAI/BASFI regressions are applied to responders who continue on TNF-alpha inhibitor therapy up to week 108 for BASDAI and up to week 108 for BASFI.

BASDAI and BASFI scores beyond week 108 for responders who continue to receive anti-TNFs beyond this period in the model are assumed to remain constant (at the week 108 value). BASFI scores beyond week 256 for responder who continue to receive anti-TNFs beyond this period in the model are assumed to remain constant (at the week 108 value) but are also subject to an annual progression rate of BASFI at this point which is set to half the rate of conventional care in the baseline (0.035 units per annum – 0-10 scale). The justification for this is not explicitly made by the manufacturer. For the base case model, BASFI scores for conventional care patients on conventional therapy are assumed to progress at a rate of 0.07 units per year after week 24.

An annual discontinuation rate of 6.1% is applied for the entire time horizon after week 12 in the base case analysis. This estimate is derived from data reported between weeks 24 to week 256 in the 50mg arm of golimumab from the GO-RAISE extension period. The manufacturer does not formally state whether this is specific to those patients who were identified to be responders at 12 weeks or not. However, it appears to be based on all patients who continued to receive golimumab beyond 24 weeks regardless of their response status. The same discontinuation rate is applied to all TNF-alpha inhibitor. Following discontinuation from anti-TNFs, the BASFI and BASDAI scores are assumed to deteriorate/rebound over a 24-week period back to their baseline BASFI and BASDAI score (i.e. rebound equal to gain). Therefore, in common with other models which apply this rebound assumption, patients are assumed to achieve a lifetime benefit from treatment with anti-TNFs for BASFI.

Utilities were derived from a NICE technology appraisal (TA 143) and incorporated age, sex, BASFI and BASDAI. Costs included in the model comprised drug acquisition, short-term (12 week) costs, longer term disease costs and adverse events. Longer term disease costs were based on BASFI scores from the GO-RAISE trial using the same regression equation used for NICE TA143.

The proportion of males and females recruited in the GO-RAISE trial is used to estimate a weighted average mortality risk by gender. The gender-specific SMR for AS from a study by Bakland et al (2011)[18] is applied to the mortality rates from the general population to calculate adjusted mortality rates for AS patients in the model. The study by Bakland reported an SMR of 1.63 (95% CI: 1.29-1.97) for males and 1.38 (95% CI: 0.48-2.28) females.

Results of MSD (golimumab, infliximab) model

The main base-case ICER results from the manufacturer are summarised in Table 58 for the AS population, together will a fully-incremental comparison of ICERs (Table 59). The ICERs vs conventional care ranged from £19,070 (golimumab) to £42,532 (infliximab). In the fully incremental analysis, golimumab and certolizumab were the non-dominated anti-TNFs. The ICER for golimumab vs conventional care was £19,070 and for certolizumab vs golimumab was £21,441 per QALY.

Table 58 Anti-TNFs compared to conventional care for AS – MSD (base-case)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Conventional care	160,837	10.5529	-	-	-
Adalimumab	181,589	11.6296	20,752	1.0766	19,275
Certolizumab	183,017	11.6962	22,180	1.1432	19,401
Etanercept	183,540	11.5862	22,703	1.0332	21,972
Golimumab	181,427	11.6326	20,590	1.0797	19,070
Infliximab	208,856	11.6819	48,019	1.1290	42,532

Table 59 - Fully incremental comparison of anti-TNFs for AS – Assessment Group analysis based on Pfizer (base-case)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Conventional care	160,837	10.5529	-	-	-
Golimumab	181,427	11.6326	20,590	1.0797	19,070
Adalimumab	181,589	11.6296	-	-	Dominated
Certolizumab	183,017	11.6962	1590	0.0636	21,441
Etanercept	183,540	11.5862	-	-	Dominated
Infliximab	208,856	11.6819	-	-	Dominated

5.2.5 Summary and critique of *de-novo* cost-effectiveness submissions

In general the manufacturer models appeared to be constructed to a high-standard and it is evident that significant work had been undertaken by each to identify and utilise previously published studies and to exploit existing individual patient data from their own RCTs and open-label extension periods to generate estimates which were appropriate for the requirements of the model.

Despite the different model structures and assumptions applied across the various manufacturer submissions, the ICERs reported for the anti-TNFs vs conventional care were remarkably consistent in the AS population. Table 60 presents a summary of the ICER reported by each manufacturer for each of the anti-TNFs vs conventional care. The figures reported in bold indicate which specific TNF-alpha inhibitor has the lowest ICER vs conventional care in each of the manufacturer submissions. It is perhaps expected that the majority of manufacturer's reported the lowest ICER vs conventional care for their own products. The only exception to this is Pfizer, whose model estimated the lowest ICER vs conventional care for certolizumab in this population (etanercept was the next lowest). Although it should be noted that Pfizer included the proposed PAS costs for certolizumab which was not universally applied across the different manufacturer submissions. Hence, although differences between the ICER vs conventional care were quite similar, the variation in approaches employed by each manufacturer appears partially driven by maximising any potential comparative advantage considered vis-à-vis other manufacturer products (i.e. in terms of assumptions made about similarities and differences for response rates, magnitude of changes in BASDAI and BASFI and withdrawal rates). However, it should be noted that no manufacturer makes a strong claim regarding differential efficacy between the alternative anti-TNFs which is borne out in the relatively small differentials reported between the different products in each of the submissions.

Table 60 - Comparison of manufacturer ICER estimates vs conventional care (AS population)

	AbbVie (Adalimumab)	**UCB (Certolizumab)**	**Pfizer (Etanercept)**	**MSD (Golimumab, Infliximab)**
	ICER (£)	**ICER (£)**	**ICER (£)**	**ICER (£)**
Conventional care	-	-	-	-
Adalimumab	**16,391**	19,932	20,909	19,275
Certolizumab	17,067	**16,647**	**19,586**	19,401
Etanercept	16,897	19,272	20,938	21,972
Golimumab	16,535	19,049	21,288	**19,070**
Infliximab	44,448	42,671	37,741	42,532

Table 61 presents a summary of the ICERs reported by each manufacturer for each of the anti-TNFs vs conventional care for the nr-axSpA population. There appears much more heterogeneity across the

manufacturer submissions compared to the AS population. Again, the figures reported in bold indicate which specific TNF-alpha inhibitor has the lowest ICER vs conventional care in each of the manufacturer submissions. There appears an almost two-fold difference in the ICERs reported across the submissions for each of the anti-TNFs. Importantly, there also appears variation across the populations with more favourable ICERs reported vs conventional care for the nr-axSpA population vis-à-vis the estimates by AbbVie (both adalimumab and certolizumab) and UCB (certolizumab only). Hence, the differences in structural and parameter assumptions appear more evident in the results for the nr-axSpA population compared to results for the AS population.

Table 61 - Comparison of manufacturer ICER estimates vs conventional care (nr-axSpA population)

	AbbVie (Adalimumab)	**UCB (Certolizumab)**	**Pfizer (Etanercept)**
	ICER (£)	**ICER (£)**	**ICER (£)**
Conventional care	-	-	-
Adalimumab	13,228	30,370	23,242
Certolizumab	**12,866**	**15,615**	23,575
Etanercept	Not Assessed	50,692	**23,195**

To assist in identifying possible reasons for the differences between populations, a summary of the key structural assumptions used by each manufacturer are provided in Tables 62 and 63. A more micro-level of comparison of specific parameter estimates is reported separately in Appendix 14.

Table 62 - Model structure and key structural assumptions - AS population

Parameter	**MSD economic model (Infliximab, Golimumab)**	**AbbVie economic model (Adalimumab)**	**UCB economic model (Certolizumab)**	**Pfizer economic model (Etanercept)**
Model type	Decision tree followed by Markov model	Markov model	Markov model	Patient-level simulation model (discrete event simulation [DES])
Time horizon	Lifetime	40 years	Lifetime	Lifetime
Response criteria	BASDAI50 response at week 12	ASAS20 response at week 12	ASAS20 response at week 24	BASDAI50 response at week 12
Response criteria justification	Efficacy outcome in GO-RAISE study; recommended by the ASAS Working Group (Keat 2005)[159]	Primary endpoint of ATLAS study	ASAS20 is the primary endpoint of RAPID-axSpA study	Based on the current NICE definition of treatment response (TA143)

Progression assumption BASDAI				
Anti-TNFs responders	Constant after week 108	Constant after week 260	Constant after week 24	Constant after week 48
Anti-TNFs non-responders	Constant	Constant	Constant	Constant
Conventional care	Constant after week 24	Constant	Constant	Constant after week 12
Progression assumption BASFI				
Anti-TNFs responders	Constant after week 108; 0.035 after week 256	Constant after week 260	Constant after week 24	Constant after week 48
Anti-TNFs non-responders	0.07	0.056	0.07	0.07
Conventional care	0.07 after week 24	0.056	0.07	0.07 after week 12
Rebound assumption	Rebound to baseline	Rebound to baseline	Rebound to conventional therapy	Rebound to baseline
Rebound assumption duration	Over a 6 month period	Immediately	Over a 6 month period	Over a 6 month period
Placebo response	14.5% at week 12; Loss or maintenance of placebo response not reported.	BASDAI and BASFI return to baseline at week 12	No placebo response	BASDAI and BASFI return to baseline at 12 weeks

Table 63 - Model structure and key structural assumptions – nr-axSpA population

Parameter	AbbVie economic model (Adalimumab)	UCB economic model (Certolizumab)	Pfizer economic model (Etanercept)
Model type	Markov model	Markov model	Patient-level simulation model (discrete event simulation [DES])
Time horizon	40 years	Lifetime	Lifetime
Response criteria	ASAS40 response at week 12	ASAS20 response at week 12	BASDAI50 response at week 12
Response criteria justification	Primary endpoint of ABILITY-1 study	Primary endpoint of RAPID-axSpA study	Based on the current NICE definition of treatment response (TA143)
Progression assumption BASDAI			
Anti-TNFs responders	Constant after week 140	Constant after week 12	Constant after week 48
Anti-TNFs non-responders	Constant	Constant	Constant

Conventional care	Constant	Constant	Constant after week 12
Progression assumption BASFI			
Anti-TNFs responders	Constant after week 140	Constant after week 12	Constant after week 48
Anti-TNFs non-responders	0.084	0.07	Constant/0.07
Conventional care	0.084	0.07	0.07 after week 12
Rebound assumption	Rebound to baseline	Rebound to conventional therapy	Rebound to baseline
Rebound assumption duration	Immediately	Over a 6 month period	Over a 6 month period
Placebo response	BASDAI and BASFI return to baseline at week 12	No placebo response	BASDAI and BASFI return to baseline at 12 weeks

In general it is difficult to identify the specific factors which can easily explain differences within and between the 2 populations across the manufacturer submissions. In general, similar model structures were applied by each manufacturer across the separate populations. However, it is evident that there are important differences based on a number of key structural issues: (i) the response criteria and timing applied; (ii) the magnitude of change scores and particularly the assumption concerning the time at which these were assumed to 'level off' (generally longer in the AS populations due to the longer open-label extension periods); (iii) the underlying rate of progression of BASFI with conventional care and the impact of anti-TNFs on this rate and (iv) the rebound assumption and timing of this.

Given the complex inter-relationship between these structural assumptions and subsequent parameter estimates, it is difficult to identify single specific reasons for differences. However, the structural differences clearly lead to marked differences in the BASDAI and BASFI scores estimated over time by each manufacturer for each population. Figures 9 to 11 provide a graphical summary of the cohort BASDAI and BASFI score, for the AS population, from three of the manufacturers. These highlight the significant differences in subsequent parameter estimates applied at a cohort level. Equivalent estimates are not presented for the Pfizer model due to the complexities of generating this data from the DES model. BASDAI and BASFI scores are only presented here for the case made by each manufacturer for their own product.

Figure 9 - Comparison of cohort BASDAI/BASFI scores for AS population from AbbVie model (adalimumab)

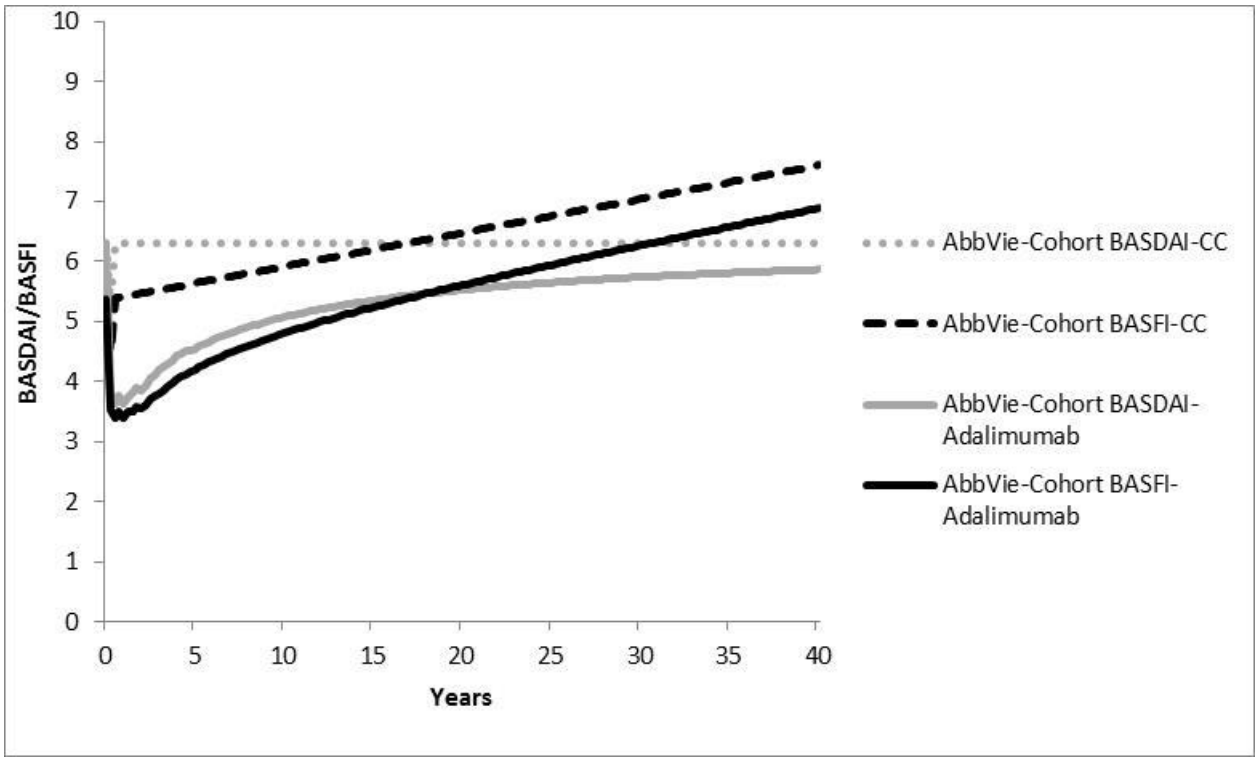


Figure 10 - Comparison of cohort BASDAI/BASFI scores for AS population from UCB model (certolizumab)

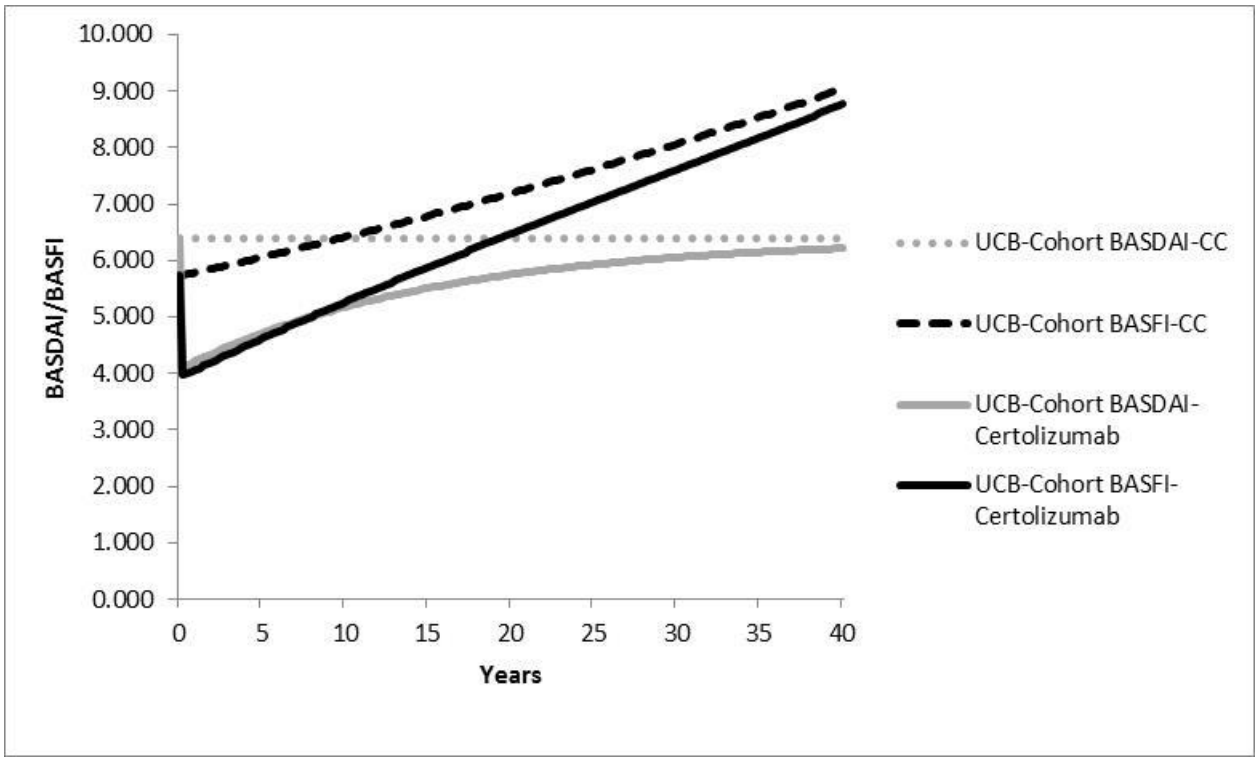
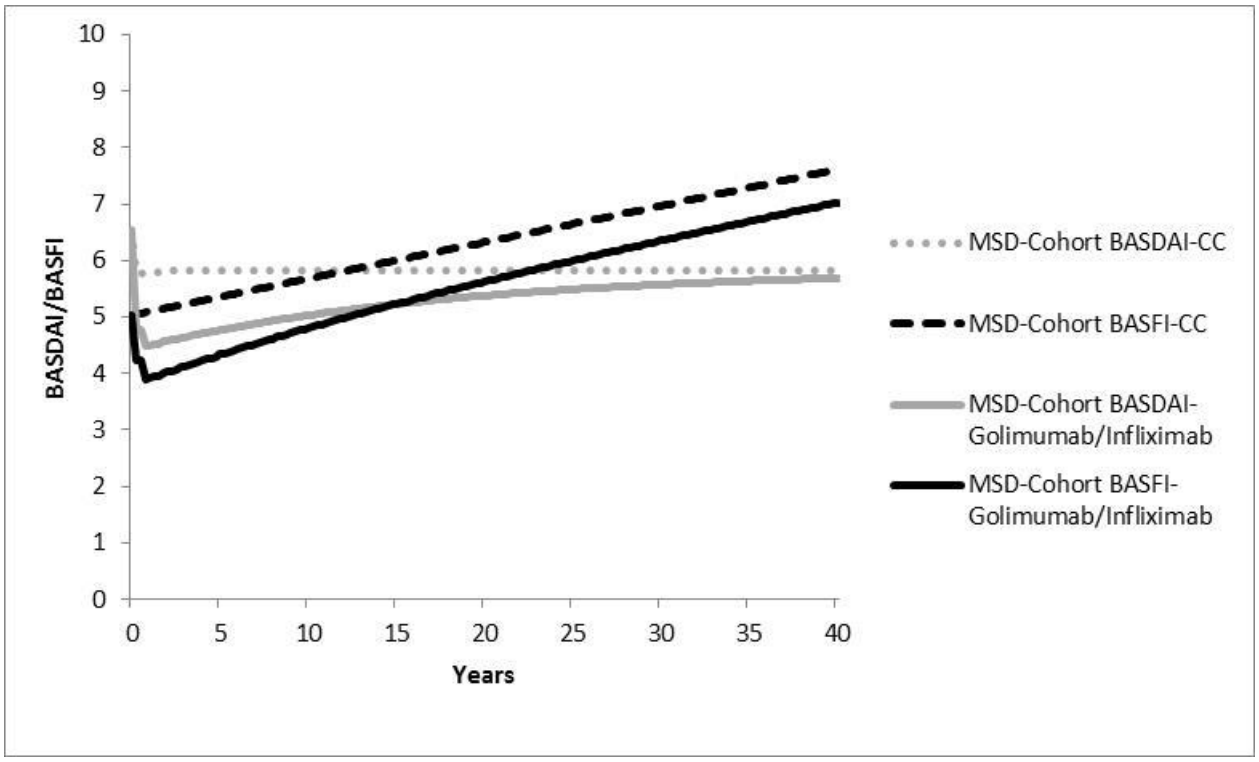


Figure 11 - Comparison of cohort BASDAI/BASFI scores for AS population from MSD model (golimumab/infliximab)



Tables 64 and 65 summarise the mean difference in BASDAI and BASFI scores applied to responders to anti-TNFs and those applied to conventional care at various time points in each model. The table clearly highlights the range of different values applied across the separate manufacturers. This further emphasises the variation in approaches, sources and assumptions.

Table 64 - BASDAI score difference for treatment responders vs conventional care - AS Population

Time	Adalimumab vs CC	Certolizumab vs CC	Infliximab/Golimumab vs CC
12 weeks	-2.98	[redacted]	-2.01
24 weeks	-4.42	[redacted]	-2.05
1 year	-4.9	[redacted]	-2.77
3 years	-5.23	[redacted]	-2.83
5 years	-5.31	[redacted]	-2.83
10 years	-5.31	[redacted]	-2.83
20 years	-5.31	[redacted]	-2.83
40 years	-5.31	[redacted]	-2.83

Table 65 - BASFI score difference for responders vs conventional care - AS Population

Time	Adalimumab vs CC	Certolizumab vs CC	Infliximab/Golimumab vs CC
12 weeks	-2.03	[redacted]	-1.68
24 weeks	-3.28	[redacted]	-1.74
1 year	-3.71	[redacted]	-2.49
3 years	-4.25	[redacted]	-2.59
5 years	-4.25	[redacted]	-2.66
10 years	-4.53	[redacted]	-2.85
20 years	-5.09	[redacted]	-3.18
40 years	-6.21	[redacted]	-3.75

The equivalent figures and tables are reported below for the nr-axSpA population.

Figure 12 - Comparison of cohort BASDAI/BASFI scores for nr-axSpA population from AbbVie model (adalimumab)

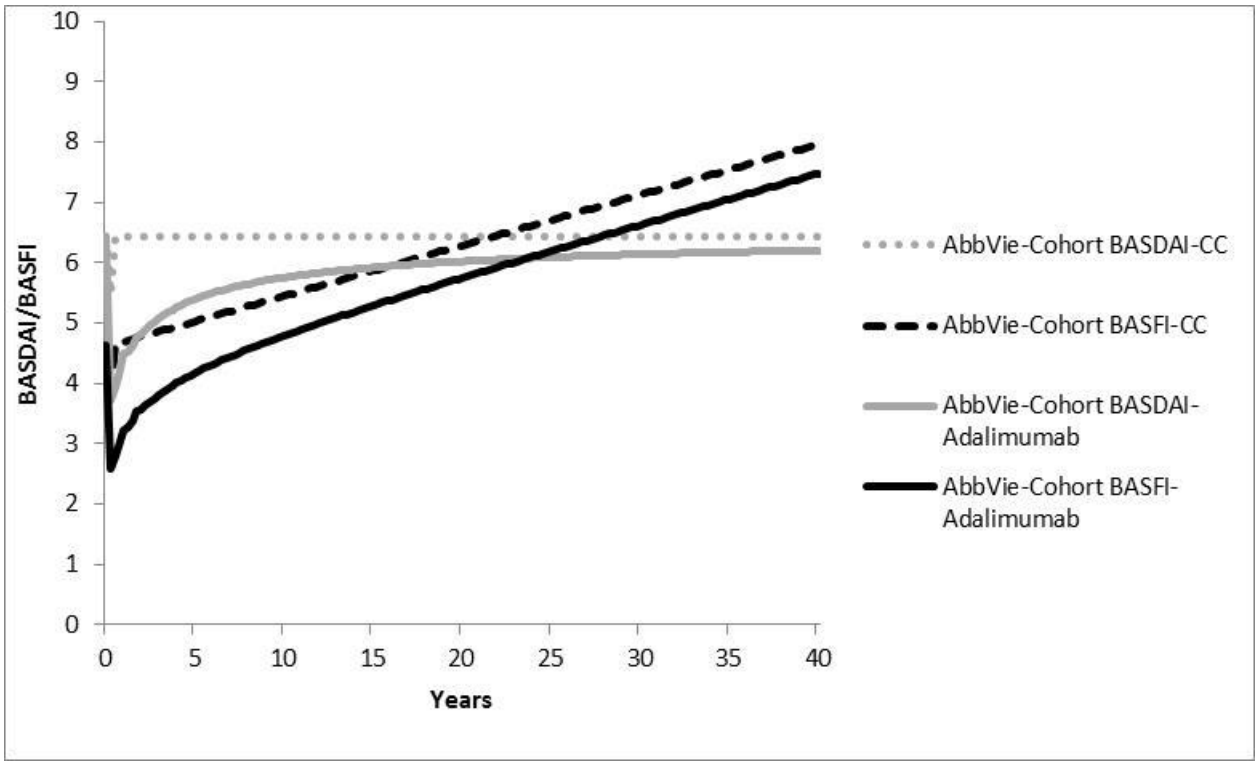


Figure 13 - Comparison of cohort BASDAI/BASFI scores for nr-axSpA population from UCB model (certolizumab)

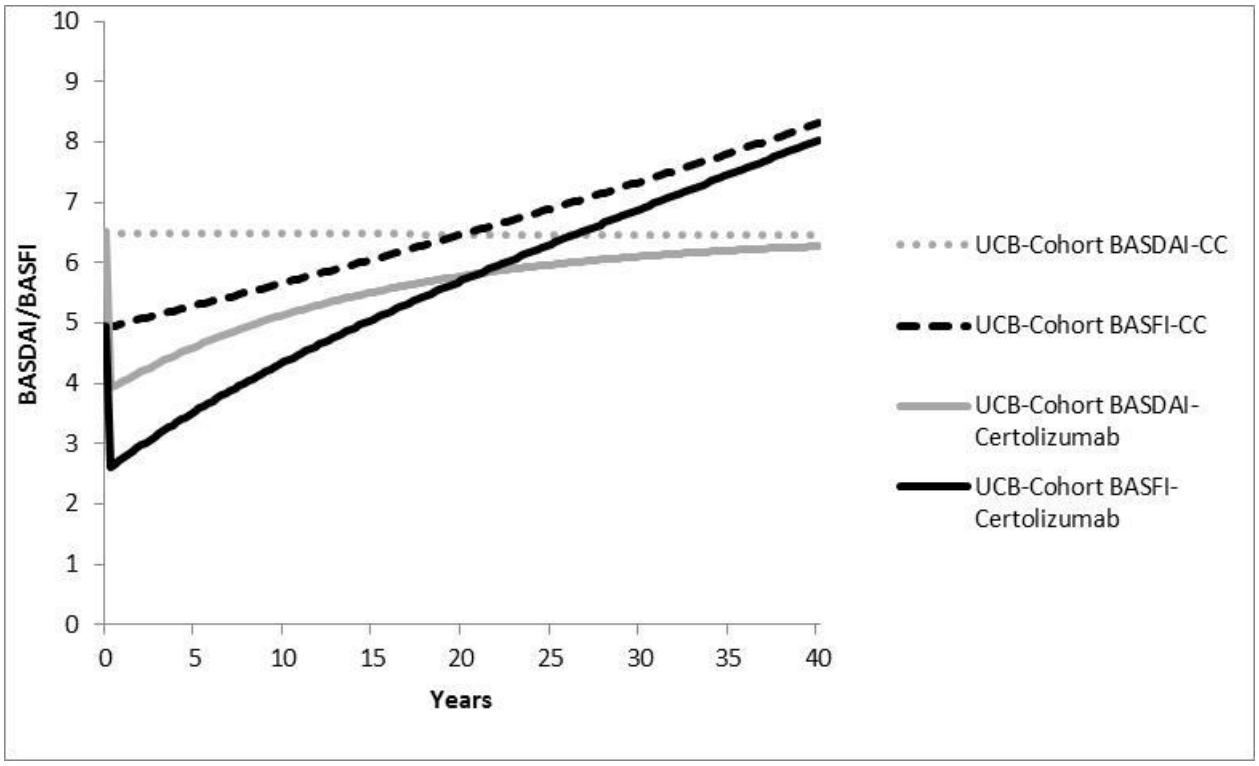


Table 66 - BASDAI score difference for responders vs conventional care - nr-axSpA Population

Time	Adalimumab vs CC	Certolizumab* vs CC
12 weeks	-3.89	[redacted]
24 weeks	-5.54	[redacted]
1 year	-5.42	[redacted]
3 years	-5.99	[redacted]
5 years	-5.99	[redacted]
10 years	-5.99	[redacted]
20 years	-5.99	[redacted]
40 years	-5.99	[redacted]

* = certolizumab patients who remain nr-axSpA and do not transition to AS

Table 67 - BASFI score difference for responders vs conventional care - nr-axSpA Population

Time	Adalimumab vs CC	Certolizumab* vs CC
12 wk	-2.95	[redacted]
24 wk	-4.11	[redacted]
1 year	-4.12	[redacted]
3 years	-4.55	[redacted]
5 years	-4.72	[redacted]
10 years	-5.14	[redacted]
20 years	-5.98	[redacted]
40 years	-7.66	[redacted]

* = certolizumab patients who remain nr-axSpA and do not transition to AS

The differences across manufacturers and between the populations are further illustrated by the summary of key parameter inputs reported in Appendix 14. As well as reporting the main parameter inputs, the appendix also explores differences in approaches at a parameter level for key inputs (e.g. withdrawal, costs etc).

It is evident from these comparisons that there are significant differences across the manufacturers in terms of key structural and parameter estimates. While it might appear reassuring that these differences do not appear to lead to significant differences across the ICER estimates reported for the AS population, the greater heterogeneity reported in the ICER estimates for the nr-axSpA is clearly an issue. However, even within the AS population, any reassurance that one might have in relation to the robustness and appropriateness that these estimates have for informing NHS practice needs to be carefully considered in relation to the key conceptual issues and concerns highlighted in Section 5.1.4 described in relation to previously published cost-effectiveness studies. Despite significant work undertaken by each manufacturer in support of existing and new indications for their products, it is particularly concerning that many of the key conceptual issues and concerns appear not to have been fully addressed. Indeed many of these issue seem not to have been addressed at all, such that many models still seem reliant on the use of open-label extension data (and even more so with the extended follow-up reported in the AS population) without any formal consideration of the potential issues with selection that the use of these studies inevitably are subject to. Consequently, the benefits of anti-TNFs are being projected over significant periods of time without any evidence on the counterfactual (i.e. what happens to patients who don't enter into the open-label extension periods? What happens to patients who subsequently withdraw from anti-TNFs? And what would have happened to patients over a longer-time horizon who didn't receive anti-TNFs?).

It appears that much of the case being made concerning the cost-effectiveness of the anti-TNFs rests on comparison of single arm studies (the subject of open-label data) and retrospective comparisons

against historical cohorts (as the counterfactual, for patients not on treatment, is unknown). While such a comparison may be necessitated by the short-term nature of the double-blind periods, the lack of a more detailed consideration of the appropriateness of the comparisons being made in relation to sources of natural history data (and subsequent assumptions made concerning the BASDAI/BASFI trajectories of the different patient categories) is concerning and, hence, current ICER estimates reported by the manufacturers must be considered to be both speculative and highly uncertain.

Many of these problems can be related to whether BASDAI and BASFI scores provide an appropriate conceptual basis for modelling the chronic and progressive nature of AS and nr-axSpA. Hence, current models appear largely driven by data availability (i.e. the extensive evidence which has been generated and continues to be generated investigating the relationship between BASDAI/BASFI and costs/utilities) rather than trying to develop a clearer underlying biological or clinical process which may better characterise the disease and subsequent progression across the separate populations.

Until such time that sufficient data linking costs and utilities to other measures are reported, it seems inevitable that models will continue to be driven largely by BASDAI and BASFI scores over time together with assumptions concerning the longer-term effect of anti-TNFs. However, given the nature of existing models and the reliance on uncontrolled longer-term follow-up of anti-TNFs and comparison with historical 'controls' (particularly in relation to BASFI progression over time and the assumptions being made concerning the potential disease modification properties of anti-TNFs in both AS and nr-axSpA populations), it is surprising that greater efforts have not been made by the manufacturers to try to more formally link to the increasing evidence base being generated in relation to radiographic progression in the AS population.

It is also surprising that more thought has also not been given to characterising the potential difference in BASFI progression across the separate populations and how generalisable assumptions maybe between these. The result is that many of the key assumptions concerning whether the anti-TNFs are primarily symptom control treatments or whether they are also potential disease modifiers remains implicitly dealt with within existing submissions. The result is that several manufacturers employ identical assumptions across populations with respect to BASFI progression and the effect of the anti-TNFs. Interestingly, only one manufacturer appears to employ differential rates of BASFI progression across the populations (AbbVie), although the same structural assumption concerning the effect of anti-TNFs is still made. Interestingly, this manufacturer applies a higher rate of change in BASFI for patients receiving conventional care in the nr-axSpA population vis-à-vis the AS population. However, while such a difference is interesting, the basis of and implication for this differential is not fully explained or justified by the manufacturer.

The issue of intermittent and sequential use of anti-TNFs remain important clinical questions but the existing models do not provide a robust basis for informing these decisions. The cost-effectiveness of intermittent therapy vs continuous therapy was not formally considered in any model identified. However, it could be argued that such a comparison might be deemed outside the scope of a NICE appraisal. Although one manufacturer (Pfizer) explored the potential cost-effectiveness of sequential therapy, much of this has been done via assumptions (e.g. assuming equal efficacy 2nd line in patients who discontinue 1st line due to an AE) or via adjustments applied to 1st line efficacy estimates based on 'real-world' evidence reported from large scale registries (which typically show anti-TNFs to be clinically effective but with lower response rates than reported in naïve patients). Consequently, existing attempts to model sequential therapy are largely based on applying adjustments to 1st line efficacy data using observational evidence which are clearly subject to potential confounding. In large part, the limitations of existing cost-effectiveness models for informing these clinical questions appears less a function of the models themselves but rather that robust clinical data to date has not been generated to inform unbiased estimates of relative efficacy of alternative strategies for using the anti-TNFs.

The following sections report the development of a *de-novo* model to address some of the key issues and uncertainties which have been identified in this review. Section 6 reports the results of an extended synthesis which has been developed to provide a more generalizable framework for synthesising clinical efficacy data ensuring that appropriate estimates are generated for the model which make use of all relevant and available evidence. This is followed in Section 7 by a description of the *de-novo* model (York model) which attempts to link this framework to a more coherent conceptual model of the chronic and progressive nature of AS and nr-axSpA.

6 Independent economic assessment: Extended synthesis

Existing evidence on the short term clinical effectiveness of anti-TNF drugs has been presented and discussed in Section 4. The methods of evidence synthesis are extended in this section to more directly address the decision problem and the parameter inputs required for the economic model. There were two specific aims to these analyses. Firstly we aimed to more formally explore the differences between individual anti-TNF treatments to inform the most appropriate assumption for the economic model (i.e. equivalence or drug specific differences). Within Section 4 of this report, the assumption of independent treatment effects was evaluated alongside the assumption of a common (equal) treatment effect across anti-TNFs, for every outcome of interest. Whilst there is no evidence that supports differences in the effectiveness of these drugs, assuming equal effectiveness means that the trials are pooled as if the same drug had been trialled – this leads to an arguably overly precise estimate of effect for the class of drugs. For this reason, we explore an additional scenario where treatments are assumed to have a similar, but not equal, effectiveness. That is, there are differences between the effectiveness of treatments that we may not be able to explain but that we should consider.

The second aim was to generate appropriate effect size estimates and their associated uncertainty to inform the main input parameters of the economic model by synthesising together evidence on BASDAI and BASFI outcomes jointly. Initially, we considered the two related BASDAI outcomes relevant to the decision model reported in the effectiveness evidence available – changes in BASDAI scores over a certain period of time and a probability of response to BADSDAI50 (that is, a 50% change in the BASDAI score in relation to baseline). BASDAI50 is important as patients are expected to discontinue anti-TNFs if, at 12 weeks, they have not been able to achieve response to this criterion (according to NICE guidance).[1, 2] Changes in BASDAI scores observed at this same time point determine the magnitude of initial response to treatment, and have often been used in economic modelling as the basis for extrapolating treatment effects. Given these outcomes are both central to informing effect parameters in the decision model, a synthesis model that considers the relation between these two outcomes provides a more consistent and coherent basis for informing these parameters.

We developed a synthesis model that pools evidence on the change in BASDAI by considering both those studies that report this measure directly and also those that report the proportion of patients achieving a BASDAI50 response. We expressed BASDAI50 as a function of the absolute change in BASDAI and we use this relationship in the extended synthesis. We also aim to simultaneously synthesise information on BASFI score, a measure that is used together with BASDAI score to determine the long term QALY and cost burden of the disease in the economic model. Treatments improving AS symptoms are expected to affect both disease activity and function, and thus we expect

a reduction in both BASDAI and BASFI scores – this mean we expect changes to these two measures to be correlated. Extending the synthesis modelling to consider BASFI scores not only allows all relevant evidence to contribute to the synthesis, but also ensures that all measures are synthesised together to reflect the expected correlations between the two outcomes. Uncertainty is also more appropriately quantified than synthesising each outcome separately.

In the decision model, prognosis, costs and QALY are determined by absolute BASDAI and BASFI scores. Given that treatment continuation is determined by response to BASDAI50 at 12 weeks, it is important for the economic model to estimate the absolute change in BASDAI and BASFI separately for responders and non-responders, i.e. the conditional scores. However, the published clinical effectiveness evidence does not report the conditional scores. Consequently, we requested the conditional data from the pivotal trials in both the AS and nr-axSpA indications from each manufacturer. These data were subsequently provided by AbbVie, Pfizer, and MSD for their pivotal trials but not UCB. Hence information on the conditional scores was only available for select trials and not for all drugs. In view of the limited data available on the conditional scores, another important extension of the synthesis approach was the evaluation of these. We used the results from the extended synthesis model to evaluate the conditional scores by simulating BASDAI and BASFI scores for two equivalent cohorts of patients the only difference being that one cohort was treated and the other was not.

This section provides only a summary of these analyses; full details are in Appendices 9, 10 and 11. We will describe first the approach for the synthesis of evidence on the AS population, followed by the approaches and results for the nr-axSpA population.

6.1 AS population

6.1.1 Brief description of the data

Based on study population and follow-up (i.e. around 12-week in duration), 16 of the RCTs are considered directly relevant to the decision problem for the AS population (studies 1 to 16 in Table 68). One of these studies did not report BASDAI or BASFI outcomes (study 3) and thus could not be included in the analyses. The 15 remaining studies reported at least one outcome measure – BASDAI50 and/or change from baseline on BASDAI and BASFI scores.

Table 68: Evidence on BASDAI and BASFI related outcomes for the AS population

	Trial name	treat	N treat	N PLA	BASDAI50	change BASDAI	change BASFI
1	Hu (2012)	1	26	20		X	X
2	Huang (2014)	1	229	115	X	X	X
3	Lambert (2007)	1	38	44			
4	ATLAS (2006)	1	208	107	X	X	
5	RAPID-axSpA (2014)	2	121	57	X	X	X
6	Barkham (2010)	3	20	20	X	X*	X*
7	Davis (2003)	3	138	139		X	X
8	Dougados (2011)	3	39	43	X	X	X
9	Gorman (2002)	3	20	20			X
10	Calin (2004)	3	45	39		X	X
11	Van der Heijde (2006)	3	305	51	X		
12	GO-RAISE (2008)	4	138	78	X		X
13	Bao (2012)	4	108	105	X		X
14	Braun (2002)	5	34	35	X	X*	X*
15	Marzo-Ortega (2005)	5	28	14		X	X*
16	Van den Bosch (2002)	5	9	12		X*	X*

* Do not report any measure of dispersion (such as standard deviations)
treat: 1 =ADA, 2=CER (CER200 and/or CER400), 3=ETA (ETA25 and/or ETA50), 4=GOL50 , 5=INF

Note that some studies only report one of the BASDAI measures. For example, the golimumab trials (studies 12 and 13) only report BASDAI 50 and not the absolute change in this score.

6.1.2 General aspects of implementation and software

The synthesis was conducted from a Bayesian perspective, using WinBUGS (a Markov Chain Monte Carlo simulation based software for Bayesian inference). For burn-in, we ran 100,000 simulations and another 100,000 were used in inferences. Convergence was assessed by running two chains and convergence was assumed if the Gelman Rubin statistic was equal to 1. Goodness of fit was assessed using the Deviance Information Criterion (DIC), a criterion developed by Spiegelhalter et al (2002) based on the trade-off between the fit of the data to the model and the complexity of the model.[160] Fit is measured using the deviance, and complexity is included using a measure of the 'effective number of parameters' (i.e. posterior mean deviance minus deviance evaluated at the posterior mean of the parameters). Models with smaller DIC are better supported by the data, that is, the lower the DIC the better the data fits the model. In the presence of autocorrelation, the MCMC simulation for inference was increased to 200,000 and a thin of 20 was applied (yielding a sample for inference of 10000 for each chain).

The main synthesis models (approaches B and C described next) pooled differences between treatment and control in change scores from baseline (BASDAI and BASFI). The treatment associated with the lowest (most negative) mean change score is expected to be best. However, it is important to quantify the uncertainty around the estimates and for this reason standard deviations were reported alongside expected values. Where averaged odds ratios are presented, median values instead of means were used as odds ratios tend to follow a skewed distribution.

Relative effectiveness estimates for models assuming exchangeability across treatments are based on the predictive distribution, representing the distribution of the data averaged over all possible parameter values. This summary statistic best reflects the impact of uncertainty in the parameters of the model and is here judged as a more appropriate basis to be used in the decision model.[161]

Where possible, meta-regression analyses were conducted to evaluate potential treatment effect modifiers. Meta-regression is a tool aimed at examining the impact of variables on effect size using regression-based techniques. In these explorations, the following baseline characteristics were considered: BASDAI score, BASFI score, age, gender, duration of symptoms (years) and C-reactive protein (CRP).

6.1.3 Exploring assumptions for the relative effectiveness of individual anti-TNF treatments (modelling approach A)

In AS, pivotal trials for the licensed anti-TNFs do not perform head-to-head comparisons with other agents, but compare the effect of treatments against standard care. These trials show anti-TNFs to be effective in relation to standard care. In view of the available evidence, previous NICE guidance (TA143[1] and TA233[2]) concluded that there was no compelling evidence on which it could reliably distinguish between the anti-TNFs on the basis of clinical effectiveness when making recommendations.

Our analysis, based on the most up to date evidence-base, aimed to evaluate anti-TNF drugs using indirect comparisons across trials. Within this sub-section, alternative assumptions of equivalence in the effectiveness of anti-TNF treatments will be more formally assessed. Note that at this stage each outcome was synthesised independently.

Brief description of synthesis methods

In brief, the synthesis model directly aggregates relative treatment effects – i.e. log OR for BASDAI50 response and the difference between treatment and placebo in change in BASDAI from baseline (the dataset analysed is shown in Appendix 9). In common with the approach implemented in Section 4, all outcomes are here assumed normally distributed. We implemented alternative models that differ in the way treatment effects are considered; a summary of each is presented below.

Model A1 (treatments: independent, studies: FE) – This model considers treatments to be independent, i.e. assumes the effects to differ between treatments. This is a fixed effect model in that multiple studies evaluating the same treatment are considered to measure the same treatment effect.

Model A2 (treatments: independent, studies: RE) – This model differs from A1 in that a random effect is assumed to describe the findings of multiple studies evaluating the same treatment.

Model A3 (treatments: equal, studies: FE) – This model differs from A1 in that treatments are not assumed to differ. The model thus evaluates a common relative effectiveness for all anti-TNFs.

Model A4 (treatments: equal, studies: RE) – This model differs from A3 in that a random effect is assumed to describe the findings of multiple studies evaluating the same treatment.

Model A5 (treatments: exchangeable, studies: FE) – This model differs from A1 in that a random effect is used to describe any differences between treatments (exchangeability is assumed). This model thus assumes the treatments to have a similar, but not equal, effectiveness – there are differences between the effectiveness of treatments that we may not be able to explain but that we should consider.

There is some evidence that health outcomes may depend on patients' characteristics such as age, BASFI score, enthesitis, therapy, CRP and HLA-B27 genotype [162]. There is, however, no evidence on which factors may modify the effects of treatment with anti-TNFs (note that Lord [2010][163] studied predictors of BASDAI50 response in patients receiving anti-TNFs, but by not including a placebo arm this study was not able to evaluate treatment effect modifiers). To our knowledge, previous meta-analysis of studies in AS have not explored how the effect of treatment may depend on characteristics of the patients or of their disease. Within this modelling approach we explored potential heterogeneity in treatment effects using meta-regression (i.e. potential treatment effect modifiers). We did so by extending the modelling approach in A1 to include treatment effect interactions with baseline characteristics (centered on their means where relevant). We have explored the inclusion of alternative covariates by evaluating the DIC associated with alternative models.

Results of modelling approach A

All models implemented synthesise results on each of the outcomes separately. The results of each modelling approach are shown in Table 69.

Models A1 and A2 consider that anti-TNF have distinct relative effects. Applying the assumptions of model A1, adalimumab is expected to be the least effective of the set of treatments analysed in terms of BASDAI50 (the expected OR is 4.71), but in terms of the differences in change scores, it is certolizumab that is expected to be the least effective, with differences of -1.45 and -1.10 in BASDAI and BASFI scores respectively. It should be noted that studies on golimumab (studies 12 and 13 in Table 68) do not report absolute changes in BASDAI scores, and thus using this modelling approach we were unable to estimate a treatment effect for this outcome measure. Model A2 reports similar results to model A1, but the standard error of the estimates is slightly higher, reflecting increased uncertainty due to the use of the random effects to characterise between study results. The DIC is lower in model A1 (52 vs 57), indicating that model A1 is preferable to A2.

Table 69: assumptions over the relative effectiveness of anti-TNF treatments – results

	A1. Treat: indep Studies: FE (median, SD)	**A2. Treat: indep Studies: RE** (median, SD)	**A3. Treat: common Studies: FE** (median, SD)	**A4. Treat: common Studies: RE** (median, SD)	**A5. Treat: exchang Studies: FE** (median, SD)
Outcome 1: OR on BASDAI50					
Adalimumab	4.71 (1.00)	4.69 (6.11)			
Certolizumab	6.02 (3.33)	6.04 (22.87)			
Etanercept	4.73 (1.43)	4.72 (3.32)	5.21 (0.72)	5.30 (0.98)	5.34 (9.79)
Golimumab	5.86 (1.81)	6.10 (7.45)			
Infliximab	11.9 (11.94)	12.10 (44.00)			
Outcome 2: change in BASDAI	(mean, SD)	(mean, SD)	(mean, SD)	(mean, SD)	(mean, SD)
Adalimumab	-1.56 (0.16)	-1.57 (0.27)			
Certolizumab	-1.45 (0.37)	-1.46 (0.51)			
Etanercept	-1.76 (0.20)	-1.73 (0.28)	-1.66 (0.11)	-1.67 (0.15)	-1.70 (0.87)
Golimumab	NA	NA			
Infliximab	-2.28 (0.46)	-2.27 (-2.28)			
Outcome 3: change in BASFI	(mean, SD)	(mean, SD)	(mean, SD)	(mean, SD)	(mean, SD)
Adalimumab	-1.22 (0.18)	-1.18 (0.29)			
Certolizumab	-1.10 (0.37)	-1.11 (0.47)			
Etanercept	-1.48 (0.19)	-1.50 (0.24)	-1.38 (0.11)	-1.39 (0.13)	-1.41 (0.49)
Golimumab	-1.45 (0.20)	-1.44 (0.29)			
Infliximab	-2.16 (0.53)	-2.17 (0.56)			
DIC	52.4	57.0	39.1	44.3	43.6

outcome: 1 OR for BASDAI50, 2 difference between treatment and placebo on change in BASDAI from baseline, 3 difference between treatment and placebo on change in BASFI from baseline

Models A3 and A4 consider the treatments as equal in terms of their effectiveness in each of the 3 outcomes. This means drugs are assumed equally effective and results from trials are pooled together as if these trials evaluated the same drug, which will return more precise estimates (i.e. less uncertainty) and interpretations of this evidence may thus be overly confident. The DIC of these models is substantially lower than that of model A1 and A2, indicating that the data supports the assumption of equivalence, rather than one of independence. As with models A1 and A2, the random effect assumption was also not deemed worthwhile.

Model A5 assumes the treatments to have a similar, but not equal, effectiveness – this model introduces more flexibility than assuming treatment effects to be equal (model A3), but does not fully assume treatments to differ as in model A1. It does imply that there are differences between the effectiveness of treatments that we may not be able to explain but that we should consider. These may be due to differences between the treatments themselves, or because of differences in the design of the trials used to evaluate each treatment. Ignoring such difference could lead to misrepresenting uncertainty, with over-precise results. Model A5 shows a slightly higher DIC than model A3, but this difference is not significant (i.e. lower than 5 units) which means both models represent equally well the existing data. Given the underlying assumptions, results differ to those of model A3 particularly in relation to the measures of uncertainty. As expected, results from model A3 are more precise than the

results of model A5. The results from model A5 in Table 69 relate to the predictive distribution which reflects uncertainty in all model parameters; in this case, such uncertainty explicitly accounts for the observed differences in the effects treatments.

Despite our preferred summary from model A5 in this evaluation being the common effect for the 'class of drugs' (Table 69), the assumption of treatment effects being drug specific may still retain some plausibility. From model A5, drug specific estimates can be retrieved (Table 70). Within this model drug specific inferences will borrow strength from the common class effect and estimates are thus shrunken towards the mean of this class effect (that is, estimates are closer to the value reported for the class in Table 2).

Table 70: Shrunken estimates of treatment effect from model A5.

Shrunken estimates of treatment effect for model A5	**Model A5**		
	Outcome 1: OR on BASDAI50 (median, SD)	**Outcome 2: change in BASDAI** (mean, SD)	**Outcome 3: change in BASFI** (mean, SD)
Adalimumab	5.05 (0.87)	-1.60 (0.15)	-1.31 (0.16)
Certolizumab	5.42 (1.71)	-1.59 (0.26)	-1.31 (0.23)
Etanercept	5.13 (1.08)	-1.72 (0.17)	-1.43 (0.15)
Golimumab	5.47 (1.25)	-1.69 (0.84)	-1.42 (0.16)
Infliximab	5.70 (3.30)	-1.88 (0.34)	-1.55 (0.33)

Explorations of heterogeneity suggested only gender to potentially modify the effect of anti-TNF treatment, specifically for change in BASDAI as outcome; however, when gender is used together with all covariates, such evidence on effect modification disappears.

Interpretation/discussion

The models implemented above show that there is no significant heterogeneity across trials evaluating each treatment– i.e. the DIC of model A2 is higher than that of model A1, indicating the use of a random effect across studies to be unnecessary.

The statistical analysis has also shown the effectiveness of the different treatments to be similar. This is in line with the published evidence that, in AS, does not demonstrate one anti-TNF treatment to be significantly more effective than another. Specifically, we implemented a model considering a common effect for all anti-TNFs when compared to placebo (model A3). This model shows a better fit than the one estimating a different effect for each anti-TNFs (model A1). However, unless we believe this assumption to hold AND the trials to be homogeneous in design and in the populations included, we believe adopting model A3 would misrepresent uncertainty in the estimates.

For this reason, we evaluated an alternative model (model A5) that assumes treatments to have a similar (but not equal) effect. In this model, the treatment effects for the anti-TNFs are assumed to come from a 'common' distribution, assumed Normal with a common mean, i.e. a 'class effect'. This is an assumption of exchangeability across treatments within the class, which we also refer to as a random-effect distribution. The DIC for this model is not significantly different to that of model A3, and allows a more appropriate description of the uncertainty over the effects of anti-TNFs. However, it should be noted that this model is not explicit about the source of the differences in the effects of treatments.

The evidence available does not appear to suggest obvious treatment effect modifiers. However, because only aggregate data were available, the results may be prone to ecological fallacy – where statistical associations between variables present or absent at the group-level may not be reflective of associations at the individual level.[164]

6.1.4 Extending the modelling approach to jointly relate outcomes (modelling approach B)

In the previous section the two outcomes based on BASDAI scores were synthesised separately; however, BASDAI50 is the probability of having a reduction in BASDAI score of 50%, and thus it should be possible to relate the proportion of BASDAI50 responders to the change in absolute BASDAI scores from baseline observed in each study. Such structural constraints should be incorporated into the synthesis, where possible, by expressing it algebraically.[164] Within this section, we use this structural relation within the synthesis, allowing change scores from baseline to be informed not only from direct data on this quantity but also from data on BASDAI50 (subsection 1.4.1). We then extend the modelling framework further to consider BASFI outcomes (subsection 1.4.2).

6.1.4.1 Joint synthesis of BASDAI outcomes

The model implemented here pools the change in BASDAI score from baseline to evaluate the difference between treatment and placebo, using evidence reported in trials directly on the change scores for each arm and also data on BASDAI50.

The following description briefly explains the approach used to model these data.

Brief description of synthesis methods

Data on the mean change in BASDAI score from baseline, alongside the standard error for this measure, were assumed normally distributed (likelihood). The mean of this distribution was the treatment effect, defined as the sum of the change score for the placebo arm plus the difference in change score for the treatments. Some studies also reported the number of responders to BASDAI 50 (a 50% reduction in BASDAI score), out of the total individuals in the study. The likelihood for the

BASDAI50 data was expressed as a binomial distribution. The probability parameter of this distribution was then related to the change score as follows. The BASDAI score at baseline and the change score were assumed correlated using a bivariate normal distribution. To define the bivariate distribution a number of quantities were needed. Firstly, the mean score at baseline; this was reported in the data and was thus assumed known. Secondly, the variability on BASDAI score at baseline was assumed equal to that of the change score. This was also reported in the data and was thus assumed known. Finally, the unknown correlation between baseline and change score was estimated within the model by assuming this quantity was independent of study. The correlation parameter was estimated separately for placebo and anti-TNF treatment. Under these assumptions, the probability parameter from BASDAI50 data was expressed algebraically as a function of the change score. For treatment effects, our preferred approach was to assume a common class effect (i.e. exchangeable effects across treatments, analogous assumption to model A5 above). See Appendix 9 for a fuller description of the methods used in analyses.

Results of modelling approach B

The summary results regarding relative treatment effects from this modelling approach are reported in Table 71 for model B. The treatment effect reported here represents difference between treatment and placebo on BASDAI score changes from baseline.

Table 71: Modelling approach B: results

	estimated Difference in change score from baseline	**assumed* Probability of having a BASDAI50 response, placebo**	**Predicted Probability of having a BASDAI50 response, anti-TNF**	**OR for BASDAI50 response, anti-TNF vs. placebo**
	(mean, SD)	(mean, SD)	(mean, SD)	(median, SD)
Anti-TNFs	-1.91 (0.48)	0.10 (--)	0.40 (0.08)	5.94 (4.06)

* This figure is based on a BASDAI baseline score of 6.11 (sd=1.56) and a placebo change score of -0.61 (sd=1.44), which represent the average across trials (weighted by number of patients)

With model B, we were now able to consider the evidence from trials only reporting information on BASDAI50 to estimate the change in BASDAI score – an example being evidence on golimumab. The class effect of anti-TNFs is evaluated to be slightly higher -1.91 (0.48) in comparison to model A5 [reporting a class effect on the change score of -1.70 (SD=0.87)], reflecting the inclusion of BASDAI50 evidence. By using the indirect evidence on BASDAI50, model B returns more precise estimates of the pooled change score than model A5 (standard error of 0.48 in B compared to 0.87 in A5). This modelling approach, despite pooling absolute change scores, can be used to evaluate BASDAI50 response for a specific baseline BASDAI score and change score in the placebo arm. We assumed a baseline BASDAI score of 6.11 (SD=1.56) and a change score for placebo of 0.61 (SD=1.44), which represent the average across trials (weighted by number of patients). According to these, the assumed probability of having a BASDAI50 response to placebo is evaluated at 0.10. Based

on the change score evaluated in the synthesis model, the probability of having a BASDAI50 response when on anti-TNFs is evaluated at 0.40 (SD= 0.08), which results in an OR for BASDAI 50 response of 5.94 (SD=4.06).

Drug specific (shrunken) estimates from model B are shown in Table 72.

Table 72: Shrunken estimates of treatment effect from model B.

Shrunken estimates of treatment effect for model B	**change in BASDAI** (mean, SD)
Adalimumab	-1.77 (0.25)
Certolizumab	-2.01 (0.37)
Etanercept	-1.88 (0.18)
Golimumab	-1.92 (0.30)
Infliximab	-2.02 (0.32)

Interpretation/discussion

The current modelling approach, by synthesising together evidence on both BASDAI outcomes, is a theoretically coherent approach to the synthesis. Moreover, it allows using the whole of the evidence on this outcome. Also, given these outcomes are to be both used is the decision model, the combined synthesis model will generate consistent estimates by considering their structural relation explicitly.

The results of modelling approach B show that using information on BASDAI50 alongside direct evidence on change scores from baseline results in slightly higher estimates of effectiveness when compared to approach A. There are two possible explanations for this. One is that higher treatment effects are observed in the trials only reporting BASDAI50 compared to the remaining studies. The few studies that only report BASDAI50 are studies 11, 12 and 13: these report ORs for BASDAI of, respectively, 5.9, 4.4 and 10.42. The second possible explanation relates to the assumptions used when defining the relation between the outcomes in the model. While we expected the model to use the BASDAI50 evidence in such a way that would exactly predict the value of change score observed in the sample, we cannot guarantee this is the case as our analysis is based on assumptions over the distribution of BASDAI scores across patients. Given we did not have access to individual patient data when developing this relationship, and thus the validity of the assumptions of analysis cannot be established. The differences observed are, however, not significant and any misspecification of the model can be thus deemed irrelevant.

6.1.5 Extending the modelling framework to synthesise change in BASFI scores (modelling approach C)

The models implemented here extend those in subsection 1.4.1 by adding the syntheses of changes in BASFI score. This is of particular relevance to the economic modelling since BASFI scores are used

together with BASDAI scores. Given we expect that, within each trial, changes to BASDAI scores to be related to changes in BASFI scores, this section will model the trial evidence to reflect this correlation. Figure 14 plots the BASDAI change scores against the BASFI change scores observed in the trials, showing support for the existence of correlation.

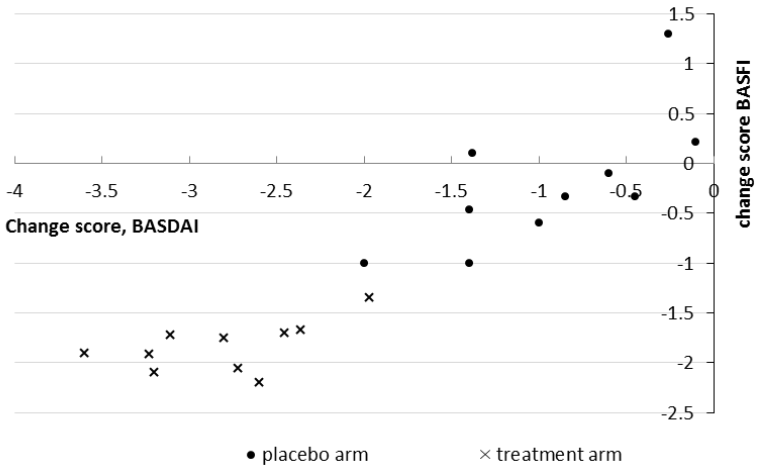


Figure 14: Scatter plot of BASDAI and BASFI change scores observed in the trials (AS).

Brief description of synthesis methods

The data on mean change in BASFI score reported in some of the studies was assumed normally distributed. The mean of this distribution was the treatment effect, defined as the sum of the change score for the placebo arm plus the difference in change score for the treatments (analogous to BASDAI). Treatment effects on BASFI were considered correlated to those on BASDAI across trials. The variation in treatment effects for both BASDAI and BASFI and the correlation parameter between these were estimated from the data. As in the previous subsection, we assumed again exchangeability across the effects of the different treatments (analogous to models '5' in modelling approach A).

Results of modelling approach C

The results on differences between treatment and placebo on change score form baseline are reported in Table 73, both for BASDAI and BASFI scores.

Table 73: Modelling approach C: results

	estimated Difference in change score from baseline (mean, SD)	**assumed* Probability of having a BASDAI50 response, placebo** (mean, SD)	**predicted Probability of having a BASDAI50 response, anti-TNF** (mean, SD)	**OR for BASDAI50 response, anti-TNF vs. placebo** (median, SD)
Effect of anti-	-1.95 (0.30)	0.10 (--)	0.41 (0.05)	6.30 (1.56)

TNFs on BASDAI Effect of anti-TNFs on BASFI	-1.40 (0.28)	--	--	--

* Based on a BASDAI baseline score of 6.11 (sd=1.56) and a placebo change score of -0.61 (sd=1.44), which represent the average across trials (weighted by number of patients)

Based on the change score evaluated in the synthesis model, the probability of having a BASDAI50 response when on anti-TNFs is evaluated at 0.41 (SD= 0.05), which returns an OR for BASDAI50 response of 6.3 (SD=1.56). Note that estimates on BASDAI treatment effects are more precise than in modelling approach B, reflecting the support to inferences from the data on BASFI – the correlation between outcomes observed in the data and allowed in the synthesis model allows inferences in BASDAI to borrow strength from those on BASFI.

Table 74: Shrunken estimates of treatment effect from model C.

Shrunken estimates of treatment effect for model C	**change in BASDAI** (mean, SD)	**change in BASFI** (mean, SD)
Adalimumab	-1.89 (0.22)	-1.34 (0.17)
Certoluzimab	-2.02 (0.28)	-1.36 (0.21)
Etanercept	-1.94 (0.18)	-1.43 (0.16)
Golimumab	-1.98 (0.25)	-1.42 (0.17)
Infliximab	-2.03 (0.27)	-1.49 (0.25)

Interpretation/discussion

We hypothesised that treatments improving AS symptoms are expected to affect both disease activity and function, and thus we expected changes to these two measures to be correlated. We have thus extended the synthesis model to consider BASFI scores. This not only allows all relevant evidence to contribute to the synthesis, but also ensures that all measures are synthesised together to reflect the expected correlations between the two outcomes.

The results obtained with this modelling approach for BASDAI outcomes are similar to those of modelling approach B, the difference being that estimates are now more precise due to the borrowing of strength between outcomes.

6.2 nr-axSpA population

This section examines the evidence on the effectiveness of anti-TNFs on the nr-axSpA population.

6.2.1 Brief description of the data

On the nr-axSpA population, 5 RCTs were considered directly relevant to the decision problem (studies 17 to 21 in Table 75). All studies reported BASDAI and BASFI outcomes and one study did not report BASDAI 50 (study 21).

Table 75: Evidence on BASDAI and BASFI related outcomes for the nr-axSpA population

	Trial name	treat	N treat	N PLA	BASDAI50	change BASDAI	change BASFI
17	Haibel 2008	ADA	22	24	x	x	x
18	ABILITY-1 (2013)	ADA	69	73	x	x	x
19	RAPID-axSpA (2014)	CER	46+51	50	x	x	x
20	Dougados 2014	ETA50	106	109	x	x	x
21	Barkham 2009	INF	20	20		x	x

6.2.2 Description of approaches to the synthesis

To synthesise these data we used the same implementation and software specifications as described in section 6.1. Analyses explored two different scenarios to consider these data:

Scenario 1. data from nr-axSpA trials were considered in isolation

Scenario 2. data from AS population were also used, no difference between the populations was assumed

All models implemented here jointly synthesise BASDAI and BASFI outcomes (our preferred modelling approach, C, see description in section 6.1.5).

6.2.3 Results of the synthesis

In what concerns scenario 1, where only data from the nr-axSpA trials has been considered, we implemented two models one assuming an equal effect across treatments and another assuming exchangeable treatment effects. Both models represented the data equally well (DIC of 87.6 vs 88.7), thus we only present results in Table 76 for the latter model (preferred model, see Section 6.1.3). Results are qualitatively similar to those in AS, but slightly lower estimates for both change scores -- BASDAI: -1.95 in AS and -1.86 in the nr-axSpA population, BASFI: -1.40 in AS and -1.30 in the nr-axSpA population. The uncertainty over these estimates is higher in the nr-axSpA population, which was expected as the number of trials (and overall number of patients in the set of trials) is substantially lower.

Table 76: nr-axSpA population: results

	estimated Difference in change score from baseline (mean, SD)	**assumed* Probability of having a BASDAI50 response, placebo** (mean, SD)	**predicted Probability of having a BASDAI50 response, anti-TNF** (mean, SD)	**OR for BASDAI50 response, anti-TNF vs. placebo** (median, SD)
Scenario 1. data from nr-axSpA trials				
Effect of anti-TNFs on BASDAI	-1.86 (0.79)	0.20 (--)	0.53 (0.13)	4.39 (6.59)
Effect of anti-TNFs on BASFI	-1.30 (0.84)	--	--	--
Scenario 2. data from AS and nr-axSpA trials, no difference between the populations				
Effect of anti-TNFs on BASDAI	-1.97 (0.32)	0.20 (--)	0.55 (0.06)	4.94 (1.48)
Effect of anti-TNFs on BASFI	-1.37 (0.3)	--	--	--

* Based on a BASDAI baseline score of [redacted] and a placebo change score of [redacted]), which represent the results seen in the certolizumab trial (RAPID-axSpA)

When the data from the nr-axSpA trials were considered together with data on AS (scenario 2), inferences were more precise. Because treatment effects in AS trials are not significantly different to those observed in the nr-axSpA population, pooled treatment effect estimates do not differ significantly from those reported in AS.

6.2.4 Interpretation/discussion

The evidence base of the effect of anti-TNFs in the nr-axSpA population consists of 5 trials that observed 4 treatments and conventional care in a total of 590 patients. The effect measures pooled across the five trials were not significantly different from the outcomes expected in the AS population. Thus, it may be reasonable to consider the evidence in nr-axSpA and AS together for inferences over treatment effects.

6.3 BASDAI and BASFI scores conditional on BASDAI response

We previously highlighted that NICE guidance determines that BASDAI50 at 12 weeks defines treatment continuation with anti-TNFs in clinical practice. Given much of the evidence on prognosis, costs and utility scores links to the absolute values of BASDAI and BASFI scores, it is important to consider absolute changes in BASDAI and BASFI separately for responders and non-responders, i.e. the conditional scores. However, the published clinical effectiveness evidence does not report the conditional scores. In this section we use the results from the extended synthesis model to evaluate the conditional scores by simulating BASDAI and BASFI scores for two equivalent cohorts of patients one treated with an anti-TNF and the other with conventional therapy.

Brief description of methods

From the inferences obtained using the synthesis model above it is possible to derive the conditional change score in responders and non-responders using simulation. Whereas the synthesis focusses on the pooling of mean estimates of change scores and proportion of responders to BASDAI50, to derive conditional mean scores there is the need to consider the distributions at the individual patient level. Hence, conditional scores could not directly be derived from the synthesis, but through a simulation procedure based on the assumptions and results of the synthesis model. The simulation procedure is described in detail in Appendix 11. Briefly, we used a simulation sample size of 10000 patients. Given results depend on the baseline distributions of BASDAI and BASFI and on the change scores from baseline for placebo, we used the averages across trials (weighted by the number of patients in each trial) in AS. Baseline BASDAI scores were thus assumed normally distributed with mean 6.11 and standard deviation of 1.56; change from baseline for placebo was simulated from a normal distribution with mean -0.61 and standard deviation of 1.44. For BASFI, the baseline was assumed to have a mean of 5.27 and a standard deviation of 1.79 and change from baseline for placebo a mean of -0.19 and a standard deviation of 0.22. The correlation between baseline BASFI and BASDAI scores was valued at [redacted]. This value was based on the sample correlation on BASDAI and BASFI at baseline from etanercept studies (the individual patient data were available in the Excel file for the etanercept submission; the Spearman correlation coefficient was [redacted] in study 314 in AS and [redacted] in study 1031 in nr-axSpA).

Results for AS

The conditional change scores derived from the synthesis model (and underlying assumptions) are reported in Table 77. While it is natural to consider that conditional change in BASDAI scores differ between respondents and non-respondents, differences in the baseline of respondents and non-respondents may be less intuitive. These are, however, natural. If we consider two patients that obtained the same change score in BASDAI from anti-TNF treatment, say -2 units, but one started with a baseline of 4 and another with a baseline of 5, the first would be considered a responder and the second would not. For this reason, respondents are expected to have a lower BASDAI than non-responders. Results of the prediction of conditional scores using the synthesis model are presented in Table 77.

Results show, as expected, that the change in BASDAI score for respondents in more negative than the mean change score (-3.86 for the 42% predicted anti-TNF responders vs. -2.63 for all anti-TNF users; in the control arm, responders were predicted to have a change score of -2.70 vs. -0.66 for all participants). Non-respondents were still expected to have a negative change score in both arms revealing some level of symptom control, but this was lower than the mean (1.73 vs. -2.63 for anti-TNF users and -0.45 vs. -0.66 in control arm). The baseline BASDAI and BASFI were predicted to be

lower for respondents than non-respondents (for example, the BASDAI baseline for responders to treatment was 4.76 in respondents when the group baseline was 6.08).

Table 77: Conditional scores predicted for the AS population using the synthesis model

	BASDAI		**BASFI**	
	control	*Treat*	*control*	*treat*
Scenario 1				
% responders to BASDAI50	0.10	0.42		
Change in score				
Responders	-2.70	-3.86	-1.41	-3.02
Non-responders	-0.45	-1.73	-0.17	-0.63
All	-0.66	-2.63	-0.29	-1.64
Baseline				
Responders	3.83	4.76	3.42	4.17
Non-responders	6.31	7.03	5.43	6.02
All	6.08	6.08	5.24	5.24

We requested the conditional data from the pivotal trials in AS from each manufacturer. These data were subsequently provided by several but not all manufacturers (AbbVie, Pfizer, and MSD). Conditional scores observed in the trials are summarised in Table 78. The results show that there are some differences between the conditional results predicted using the synthesis and the ones observed in trials. Differences are especially relevant for the conditional baseline scores – while the synthesis model predicts, for example, that treated patients that respond have a baseline BASDAI of 4.76 and those that do not respond a baseline of 7.03, the trials show much smaller differences. Despite incorporating all evidence available at the aggregate level, the predictive ability of the conditional baseline score from the synthesis could only be improved if we had access to the IPD as this methodology is strongly dependent on assumptions over the distribution of scores across patients.

Table 78: Conditional scores observed in trials in AS

	BASDAI		**BASFI**	
	control	*Treat*	*control*	*treat*
ATLAS trial (adalimumab, study=4)				
% responders to BASDAI50	0.16	0.46		
Change in score				
Conditional on response	-4.5	-4.64	-2.74	-2.92
Conditional on non-response	-0.2	-0.82	-0.17	-0.72
total	-0.90	-2.58	-0.59	-1.73
Baseline				
Conditional on response	6.31	6.14	4.50	4.53
Conditional on non-response	6.37	6.35	5.91	5.78
total	6.36	6.25	5.68	5.21
GO-RAISE (golimumab, study =12)				
	control	*Treat*	*control*	*treat*
% responders to BASDAI50	0.15	0.46		
Change in score				
Conditional on response	-4.25	-4.74	-1.80	-3.03
Conditional on non-response	-0.18	-1.22	0.38	-0.53
total	-0.81	-2.84	0.05	-1.68
Baseline				
Conditional on response	6.52	6.25	3.56	4.45
Conditional on non-response	6.63	6.69	5.39	5.48
total	6.61	6.49	5.11	5.01
314-EU (etanercept, study=11)*				
	control	*Treat*	*control*	*treat*
% responders to BASDAI50				
Change in score				
Conditional on response				
Conditional on non-response				
total				
Baseline				
Conditional on response				
Conditional on non-response				
total				

* Pooled results for etanercept arms (ETN 25 mg twice weekly and ETN 50 mg once weekly).
For adalimumab and etanercept's trials = week 12 responders, for golimumab = week 14 responders (week 12 data for week 14 responders is available but not reported in the table)

Results for nr-axSpA

The conditional results were also predicted for the nr-axSpA population using both scenarios implemented of the synthesis model.

Table 79: Conditional scores predicted for the nr-axSpA population using results and assumptions of the synthesis model

	BASDAI		BASFI	
	control	*Treat*	*control*	*treat*
Scenario 1				
% responders to BASDAI50				
Change in score				
Responders				
Non-responders				
All				
Baseline				
Responders				
Non-responders				
All				
Scenario 2				
% responders to BASDAI50				
Change in score				
Responders				
Non-responders				
All				
Baseline				
Responders				
Non-responders				
All				

* Based on a BASDAI baseline score of [redacted] a placebo change in BASDAI score of [redacted]), a BASFI baseline score of [redacted]) and a placebo change in BASFI score of [redacted]), which represent the results seen in the certolizumab trial (RAPID-axSpA) .

For this population, conditional data were provided by only two manufacturers (Pfizer, and AbbVie).

Conditional scores observed are summarised in Table 79.

Table 80: Conditional scores observed in trials in nr-axSpA

	BASDAI		BASFI	
	control	*Treat*	*control*	*treat*
ABILITY-1 trial (adalimumab, study=18)				
% responders to BASDAI50	0.14	0.40		
Change in score				
Conditional on response	-3.9	-4.79	-2.78	-2.75
Conditional on non-response	-0.69	-0.55	-0.40	-0.32
total	-1.16	-2.23	-0.75	-1.29
Baseline				
Conditional on response	5.64	6.21	4.37	3.60
Conditional on non-response	6.46	6.53	4.91	4.97
total	6.34	6.40	4.83	4.43
EU 1031(etanercept, study=20)				
	control	*Treat*	*control*	*treat*
% responders to BASDAI50				
Change in score				
Conditional on response				
Conditional on non-response				
total				
Baseline				
Conditional on response				
Conditional on non-response				
total				

Etanercept and adalimumab = week 12 responders, Pfizer only reported results for ETN 50 mg

Prediction results are consistent with those in AS, and the differences between the conditional results predicted using the synthesis and the ones observed in trials are also present in this analysis.

Interpretation/discussion

Conditional scores predicted using synthesis model C differ from those seen in the trials. Differences are probably due to distributional assumptions over the baseline and change scores. Only with access to the individual patient data such predictions could be improved. Note that the synthesis model itself does not rely as heavily on such assumptions, and thus any concerns should not be transposed to the results obtained in sections 6.1 and 6.2.

6.4 Discussion/conclusion

The analyses developed in this section focussed on extending the synthesis evidence on the short-term clinical effectiveness of anti-TNF drugs in Section 4 that considered individually multiple outcomes of interest reported in the trials, namely: the mean change in BASDAI scores at 12 weeks, the proportion of BASDAI50 responders (that is, those that had, at 12 weeks, a change in the baseline BASDAI score of 50% or more), and the mean change in BASFI scores at 12 weeks.

Initially, within such a univariate framework, we further explored assumptions over the relative effectiveness of anti-TNFs. We evaluated the possibility of the evidence suggesting treatment effects to be independent, equal or similar effects (treatment effects were assumed to come from a 'common' distribution, i.e. a 'class effect'). Independence was ruled out through statistical checks of goodness of fit - this is in line with the published evidence that, in AS, does not demonstrate one anti-TNF treatment to be significantly more effective than another. The data were as well represented by the other two models. However, unless we believe the equality assumption to hold AND the trials to be homogeneous in design and in the populations included, assuming equality in treatment effects will provide over-precise estimates. For this reason, our preferred assumption was that of similarity, however, it should be noted that this model is not explicit about the source of the differences in the effects of treatments. Whereas heterogeneity may be a plausible explanation, further research needs to examine data at the individual patient level to avoid the potential for ecological bias.

We also extended the synthesis in a way that allowed multiple outcomes to be jointly modelled. We did so by *i)* structurally relating the BASDAI based outcomes, allowing for trials reporting BASDAI50 to inform BASDAI change scores, and *ii)* by concomitantly synthesising BASFI outcomes, allowing correlation between outcomes and the borrowing of strength between results to BASDAI and BASFI. For these reasons, the synthesis model developed here more directly addresses

the decision problem. It also generates appropriate effect size estimates and their associated uncertainty to inform the main input parameters of the economic model.

In the decision model, treatment continuation is determined by response to BASDAI50 at 12 weeks. Given prognosis, costs and QALY are determined by absolute BASDAI and BASFI scores it is important to evaluate the absolute change in BASDAI and BASFI separately for responders and non-responders, i.e. the conditional scores. We used the results from the extended synthesis model to develop a simulation model that allowed prediction of the conditional scores. The results obtained differ from those seen in three pivotal trials (data provided by the manufacturers upon request), probably because of distributional assumptions over the baseline and change scores. Only with access to the individual patient data such predictions could be improved.

7 Independent economic assessment: York model

7.1 Overview

Section 5 indicates that there are significant conceptual concerns and uncertainties arising from previously published studies and the submissions made by manufacturers. For this reason, it has been necessary to develop a *de-novo* model (hereafter referred to as the 'York model'). Although it shares some of the assumptions and parameter estimates from the manufacturer models, it has a different conceptual structure and applies a more generalised framework for the synthesis of data from the double-blind periods of existing RCTs, combined with a more explicit approach to modelling the progressive nature of AS and nr-axSpA and the potential impact of the anti-TNFs.

The aim of the York model is to assess the cost-effectiveness of adalimumab, certolizumab, etanercept, golimumab, and infliximab, in accordance with their respective licences, for the treatment of AS and nr-axSpA. The model uses short-term trial data, based on the extended evidence synthesis, to model the response of patients to TNF-alpha inhibitor therapy at 12 weeks based on BASDAI 50 measured in the trials. In contrast to the models submitted by the manufacturers, the York model is based on an assumption of similar (but not identical) effects for the alternative biologics based on the results of the extended synthesis reported in Section 6.

In common with all existing cost-effectiveness studies, measures of disease activity (BASDAI) and functioning (BASFI) are used to characterise the chronic, progressive nature of AS and nr-axSpA and the effect of anti-TNFs. However, the York model uses an alternative conceptual model applied to estimate longer term BASFI scores. The effect of response to TNF-alpha therapy is modelled in terms of the short and longer term impact on BASDAI and BASFI scores.

NHS and PSS costs are based on the cost of the TNF-alpha therapies (acquisition, administration and monitoring) and disease costs linked to BASFI scores. HRQoL, in terms of utility, is based on both BASDAI and BASFI scores. Health effects are subsequently expressed in terms of QALYs. Both costs and QALYs are discounted at 3.5% per annum. Costs are presented based on current prices.

The model is developed in accordance with the NICE reference case. The model has a lifetime horizon (60 years) and considers costs from the perspective of the National Health Services and Personal Social Services.

7.2 Contribution of the York model

Although the York model shares some of the assumptions and parameters from existing studies and manufacturer submissions, it also provides a number of significant developments to existing cost-effectiveness analyses. Firstly, the short-term clinical effectiveness inputs are based on an evidence synthesis approach which is based on all available trial data for each biological therapy and which jointly synthesises 'related' parameters ensuring uncertainty is more appropriately characterised. Secondly, the evidence synthesis approach is more explicitly linked to the decision problem and the requirements of the economic model. That is, the model requires estimates of response and the impact on BASDAI/BASFI conditional upon this. Since the conditional response scores are not conventionally reported in existing publications, existing models have largely been based on selective approaches (i.e. using conditional scores from single studies or assumptions) or appear to have ignored the conditional scores entirely and instead utilise estimates from longer term follow-up and/or open-label sources (i.e. implicitly assuming that patients who continue to participate in longer-term follow up and open label sources are more likely to be responders than patients who do not). Neither approach appears satisfactory in terms of meeting the requirements of the economic model and ensuring that all relevant evidence is considered. The evidence synthesis approach which underpins the York model is based on a joint synthesis of related parameters which makes fuller use of existing evidence and which can more appropriately estimate the input parameters which are required to populate existing models and better characterise the uncertainty surrounding these.

Another important development of the York model is the approach to modelling longer term BASFI changes over time to characterise the progressive nature of AS and nr-axSpA. In previous sections we highlighted our concerns over how this has been previously modelled and the implicit assumptions underlying the effect of anti-TNFs (i.e. potential disease modification properties resulting in halting further 'progression', or reducing the rate of progression, while patients respond and continue to receive anti-TNFs). Within the York model, we attempt to model the impact of different processes on BASFI over time, relating the changes more explicitly to the existing clinical effectiveness data for anti-TNFs on these different processes. Specifically we consider the independent effects on BASFI

due to disease activity (BASDAI) and the extent and progression of radiographic disease (as measured by the Modified Stoke Ankylosing Spondylitis Spinal Score [mSASSS]) for AS. For the nr-axSpA population, we assume a similar underlying clinical process relating to BASFI.

This approach confers several advantages over current approaches by linking changes in BASFI to a more explicit clinical/biological process and facilitating a more formal consideration of the potential impact of anti-TNFs on BASFI, via the specific effects these drugs have on the different processes which independently relate to this parameter. This approach allows consideration of the impact on BASFI that might be achieved via symptomatic improvements (i.e. in terms of reductions in disease activity) and those which might be conferred by disease modification properties (i.e. the effect on the likelihood and/or rate of further radiographic progression). The latter aspect is particularly important given the increasing amount of published evidence reported on the potential impact of anti-TNFs on radiographic progression which has not been formally considered or incorporated within existing cost-effectiveness studies.

7.3 Comparators

Table 81 summarises the comparators included in each of the populations, in line with the relevant existing (or likely to be granted by the time of the NICE appraisal) marketing authorisations for each manufacturer.

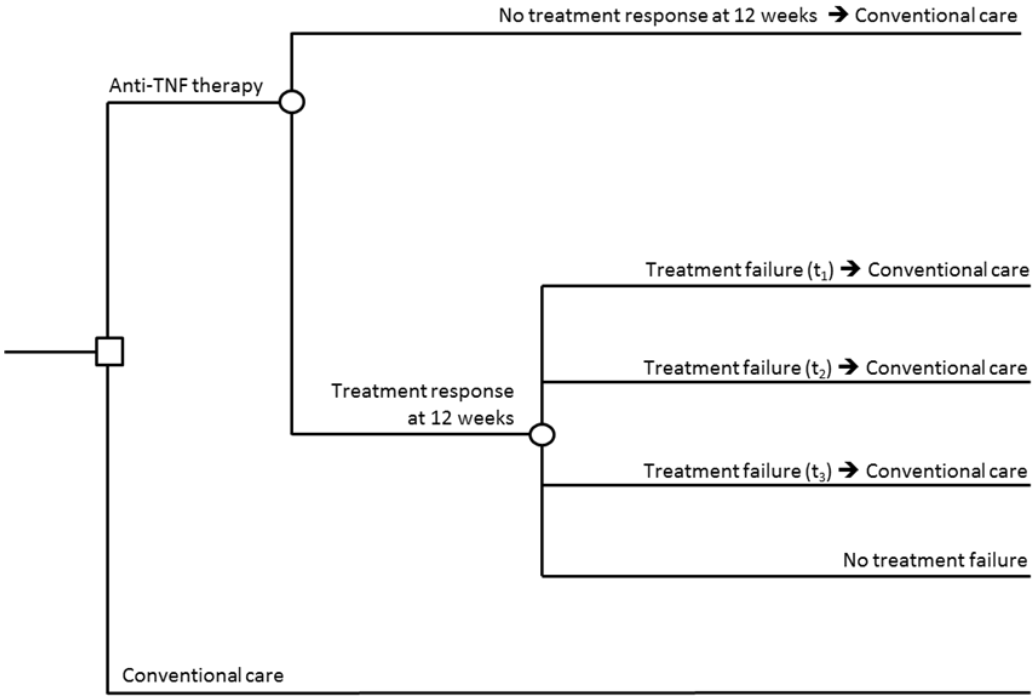
Table 81 - Comparators evaluated in the different indications

Comparator	Manufacturer	AS	nr-axSpA
Conventional Care	-	Yes	Yes
Adalimumab	AbbVie	**Yes**	**Yes**
Certolizumab	UCB	**Yes**	**Yes**
Etanercept	Pfizer	**Yes**	**Yes**
Golimumab	MSD	**Yes**	No
Infliximab	MSD	**Yes**	No

7.4 Model Structure

The York model is a cohort model and takes the form of a modified decision tree for AS and nr-axSpA. A simplified version of the structure is shown in Figure 15. A similar structure has been previously been used to evaluate the cost-effectiveness of anti-TNFs in psoriatic arthritis.[165]

Figure 15- A simplified schematic of the York model structure



For the alternative TNF-alpha inihibitors, initial response is determined on the basis of a short-term BASDAI 50 response (12 weeks). For those who respond, there is then an on-going risk of withdrawal of treatment at any time point in the model. Initial or later treatment failures are assumed to move on to conventional care. The use of BASDAI 50 is consistent with existing BSR guidelines and previous NICE appraisals for AS.[1, 2, 159] Ensuring consistency in the response measure between the various appraisals provides a more comparable basis for exploring any subsequent differences in results. In addition, using BASDAI 50 as a response measure for the economic model maximises the evidence base used to inform the various clinical effectiveness parameters required and, as outlined in Section 6, utilises the same clinical constructs to inform response and subsequent BASDAI changes.

Those patients who receive anti-TNFs will experience an initial improvement which is based on results of the evidence synthesis (average of mean change in BASDAI and BASFI estimated for responders and non-responders). From week 12, patients who continue to receive anti-TNFs are assigned the conditional mean change in BASDAI and BASFI estimated from the evidence synthesis which is assumed to remain constant for the treatment duration period. In addition to this initial improvement in BASDAI and BASFI, patients continuing on anti-TNFs treatment are also assumed to experience a slower progression rate in BASFI as long as they are responding (see section 7.5.3).

Patients who fail on TNF-alpha inhibitor therapy after the initial (12-week) period will experience some form of rebound in terms of BASDAI/BASFI, but trial data are too short-term to be able to characterise this accurately. The model, therefore, considers two rebound scenarios:

1. *Rebound equal to gain (BASDAI and BASFI).* When patients fail therapy (after initially responding), their BASDAI and BASFI deteriorates by the same amount by which it improves when they responded to therapy.
2. *Rebund back to natural history/conventional care (BASFI only).* When patients fail therapy (after initially responding), their BASFI deteriorates to the level and subsequent trajectory it would have been had they not initially responded to therapy. Since BASDAI is not assumed to progress over time on conventional care, the same assumptions are applied to BASDAI in both scenarios.

Given the absence of evidence on rebound, both scenarios (rebound equal to gain and rebound back to natural history) are presented as the 'best-case' and 'worst-case' scenarios possible. In other words, the reality regarding rebound is likely to be somewhere between these two scenarios which should, therefore, be seen as the limits.

Importantly, the York model explores the impact of assuming different baseline BASDAI and BASFI scores for responders and non-responders. Hence, in contrast to existing models, the York model assumes that response is unlikely to be independent of baseline patient characteristics and hence the baseline characteristics of responders/non-responders to anti-TNFs may be systematically different from each other. Importantly, the results from the extended synthesis model estimated higher baseline BASDAI and BASFI scores for non-responders vis-à-vis responders and a similar relationship was also reported by those manufacturers who provided conditional response data requested by the Assessment Group. Consequently, assuming that non-responders revert back to the 'average' of the baseline BASDAI/BASFI scores of all patients randomised to receive TNF-alpha inhibitor treatment, or the 'average' of patients receiving conventional care is likely to be overly optimistic towards the subsequent cost-effectiveness of anti-TNFs. The model thus employs different baselines for responders and non-responders (at 12 weeks) and at the point of discontinutation patients are assumed to revert to their respective baseline BASDAI and BASFI scores (i.e. at 12-weeks, non-responders revert back to the non-responder baseline and after 12-weeks patients who subsequently discontinue from their TNF-alpha therapy revert back to their responder baseline). The impact of using these data is explored as part of the sensitivity analysis.

Patients are at risk of all-cause mortality at every time point in the model, but no differential mortality risk between the therapies being evaluated. Aside from the cost of the TNF-alpha therapies themselves (i.e. acquisition, administration, monitoring and AEs), all other costs of AS and nr-axSpA

are assumed to vary according to BASFI score. Costs are presented based on current prices. HRQoL (in terms of utility) is implemented as a function of BASDAI and BASFI scores.

7.5 Model input parameters

The parameter estimates used in the York model, together with their sources, are detailed in Tables 82 and 83.

Table 82 - List of parameter estimates used in the York model – AS population

Parameter	Mean value	Standard error	Distribution	Source
Annual discount rate costs / QALYs	3.5%	-	Fixed	
Time horizon (years)	60	-	Fixed	
Cycle length (years)	0.25	-	Fixed	
Baseline patient characteristics				
Average age	40	-	Fixed	Assumption
Proportion male %	0.7	-	Fixed	Assumption
Average Weight (kg)	73	-	Fixed	Assumption
Average Baseline BASDAI	6.12	N/A	Derived from responder & non-responder baseline	Evidence synthesis (Section 6)
Average Baseline BASFI	5.28	N/A		
Baseline BASDAI CC Responders	4.01	N/A	From evidence synthesis	Evidence synthesis (Section 6)
Baseline BASDAI CC Non-responders	6.33	N/A	From evidence synthesis	
Baseline BASFI CC Responders	3.52	N/A	From evidence synthesis	
Baseline BASFI CC Non-responders	5.46	N/A	From evidence synthesis	
Baseline BASDAI anti-TNF Responders	4.80	N/A	From evidence synthesis	
Baseline BASDAI anti-TNF Non-responders	7.08	N/A	From evidence synthesis	
Baseline BASFI anti-TNF Responders	4.20	N/A	From evidence synthesis	
Baseline BASFI anti-TNF Non-responders	6.07	N/A	From evidence synthesis	
Response (12 week BASDAI 50)				
anti-TNF	42.0%	N/A	From evidence synthesis	Evidence synthesis (Section 6)
Conventional therapy	9.1%	N/A	From evidence synthesis	
Treatment Effect				
Initial BASDAI Change| Tx response - anti-TNF	-3.86	N/A	From evidence synthesis	Evidence synthesis (Section 6)
Initial BASDAI Change| Tx response - CC	-2.89	N/A	From evidence synthesis	
Initial BASDAI Change| Tx no response - anti-TNF	-1.64	N/A	From evidence synthesis	
Initial BASDAI Change| Tx no response - CC	-0.36	N/A	From evidence synthesis	
Initial BASFI Change| Tx response - anti-TNF	-3.08	N/A	From evidence synthesis	
Initial BASFI Change| Tx response - CC	-1.72	N/A	From evidence synthesis	
Initial BASFI Change| Tx no response - anti-TNF	-0.44	N/A	From evidence synthesis	
Initial BASFI Change| Tx no response - CC	-0.04	N/A	From evidence synthesis	
Long-term annual BASFI Progression				
BASFI annual progression anti-TNF	0.034	-	Derived from probabilistic inputs below.	
BASFI annual progression CC	0.082	-		
Annual rate of MSASSS change for MSASSS≥10	1.44	0.133	Normal	Ramiro et al (2013) [140]
BASFI change with 1 unit change in MSASSS	0.057	0.0049	Normal	Landewe et al (2009) [12]
Treatment effect on progression (RR)	0.42	0.122	Normal	Haroon et al (2013) [113]
Time to treatment effect (years)	4	-		Haroon et al (2013) [113], Baraliakos et al

Parameter	Mean value	Standard error	Distribution	Source
				(2014) [114]
Long-term annual BASDAI Progression				
BASDAI annual progression anti-TNF	0	N/A		
BASDAI annual progression CC	0	N/A		
Annual withdrawal probability				
Constant rate of annual withdrawal	0.11	[redacted]	Lognormal; from exponential model (coefficient: [redacted], SE: [redacted])	Pfizer submission
Mortality				
SMR Women	1.38	0.163	Normal	Bakland (2011)
SMR Men	1.63	0.163	Normal	Bakland (2011)
Quality of life				
Intercept	[redacted]	Uncertainty from reported variance-covariance matrix	Multivariate normal	Pfizer submission
BASDAI coefficient	[redacted]		Multivariate normal	
BASFI coefficient	[redacted]		Multivariate normal	
BASDAI^2 coefficient	[redacted]		Multivariate normal	
BASFI^2 coefficient	[redacted]		Multivariate normal	
Initial 12-week Period Costs [Drug + Initiation + Administration]				
Adalimumab	2422	-	Fixed	As discussed in section 7.5.6
Certolizumab Pegol	3884	-	Fixed	
Etanercept	2454	-	Fixed	
Golimumab	2415	-	Fixed	
Infliximab	6878	-	Fixed	
Certolizumab Pegol PAS	309	-	Fixed	
Subsequent 12 week Costs [Drug + Monitoring + Administration]				
Adalimumab	2171	-	Fixed	As discussed in section 7.5.6
Certolizumab Pegol	2203	-	Fixed	
Etanercept	2203	-	Fixed	
Golimumab	2164	-	Fixed	
Infliximab	3435	-	Fixed	
Certolizumab Pegol PAS	2203	-	Fixed	
Disease related costs – annual				
Intercept	1284	0.165	Lognormal	OASIS data, AbbVie submission
BASFI coefficient	0.213	0.038	Normal	
Adverse event costs (£ per patient)				
Year 1	18.2	-	Fixed	Excess rates for anti-TNFs from Cochrane review[127], Costs from NHS Reference costs[166]
Subsequent years	0	-	Fixed	

Abbreviations: CC: Conventional Care; Tx: treatment

Table 83: List of parameter estimates used in the York model – nr-axSpA population

Parameter	Mean value	Standard error	Distribution	Source
Annual discount rate costs / QALYs	3.5%	-	Fixed	
Time horizon (years)	60	-	Fixed	
Cycle length (years)	0.25	-	Fixed	
Baseline patient characteristics				
Average age	40	-	Fixed	Assumption
Proportion male %	0.5	-	Fixed	Assumption
Average Weight (kg)	73	-	Fixed	Assumption
Average Baseline BASDAI	6.42	N/A	Derived from responder & non-responder baseline	Evidence synthesis (Section 6)
Average Baseline BASFI	4.92	N/A		
Baseline BASDAI CC Responders	4.54	N/A	From evidence synthesis	Evidence synthesis (Section 6)
Baseline BASDAI CC Non-responders	6.86	N/A	From evidence synthesis	
Baseline BASFI CC Responders	2.95	N/A	From evidence synthesis	
Baseline BASFI CC Non-responders	5.38	N/A	From evidence synthesis	
Baseline BASDAI anti-TNF Responders	5.45	N/A	From evidence synthesis	
Baseline BASDAI anti-TNF Non-responders	7.51	N/A	From evidence synthesis	
Baseline BASFI anti-TNF Responders	3.92	N/A	From evidence synthesis	
Baseline BASFI anti-TNF Non-responders	6.04	N/A	From evidence synthesis	
Response (12 week BASDAI 50)				
anti-TNF	52.9%	N/A	From evidence synthesis	Evidence synthesis (Section 6)
Conventional therapy	18.9%	N/A	From evidence synthesis	
Treatment Effect				
Initial BASDAI Change| Tx response - anti-TNF	-4.31	N/A	From evidence synthesis	Evidence synthesis (Section 6)
Initial BASDAI Change| Tx response - CC	-3.34	N/A	From evidence synthesis	
Initial BASDAI Change| Tx no response - anti-TNF	-2.28	N/A	From evidence synthesis	
Initial BASDAI Change| Tx no response - CC	-1.06	N/A	From evidence synthesis	
Initial BASFI Change| Tx response - anti-TNF	-3.24	N/A	From evidence synthesis	
Initial BASFI Change| Tx response - CC	-1.88	N/A	From evidence synthesis	
Initial BASFI Change| Tx no response - anti-TNF	0.08	N/A	From evidence synthesis	
Initial BASFI Change| Tx no response - CC	-0.05	N/A	From evidence synthesis	
Long-term annual BASFI Progression				

Parameter	Mean value	Standard error	Distribution	Source
BASFI annual progression anti-TNF	0.017		Derived from probabilistic inputs below.	
BASFI annual progression CC	0.039			
Annual rate of MSASSS change for MSASSS<10	0.69	0.031	Normal	Ramiro et al (2013) [140]
BASFI change with 1 unit change in MSASSS	0.057	0.0049	Normal	Landewe et al (2009) [12]
Treatment effect on progression (RR)	0.42	0.122	Normal	Haroon et al (2013) [113]
Time to treatment effect (years)	4	-		Haroon et al (2013) [113], Baraliakos et al (2014) [114]
Long-term annual BASDAI Progression				
BASDAI annual progression anti-TNF	0	N/A		
BASDAI annual progression CC	0	N/A		
Annual withdrawal probability				
Constant rate of annual withdrawal	0.06	[redacted]	Lognormal; from exponential model (coefficient: [redacted], SE: [redacted])	Pfizer submission
Mortality				
SMR Women	1.38	0.163	Normal	Bakland (2011)
SMR Men	1.63	0.163	Normal	Bakland (2011)
Quality of life				
Intercept	[redacted]	Uncertainty from reported variance-covariance matrix	Multivariate normal	Pfizer submission
BASDAI coefficient	[redacted]		Multivariate normal	
BASFI coefficient	[redacted]		Multivariate normal	
Male coefficient	[redacted]		Multivariate normal	
Age coefficient	[redacted]		Multivariate normal	
BASDAI^2 coefficient	[redacted]		Multivariate normal	
BASFI^2 coefficient	[redacted]		Multivariate normal	
BASFI * BASDAI coefficient	[redacted]		Multivariate normal	
Initial 12-week Period Costs [Drug + Initiation + Administration]				
Adalimumab	2573	-	Fixed	As discussed in section 7.5.6
Certolizumab Pegol	4035	-	Fixed	
Etanercept	2606	-	Fixed	
Golimumab	2566	-	Fixed	
Infliximab	7213	-	Fixed	
Certolizumab Pegol PAS	460	-	Fixed	
Subsequent 12 week Costs [Drug + Monitoring + Administration]				
Adalimumab	2177	-	Fixed	As discussed in section 7.5.6
Certolizumab Pegol	2210	-	Fixed	
Etanercept	2210	-	Fixed	
Golimumab	2170	-	Fixed	
Infliximab	3441	-	Fixed	
Certolizumab Pegol PAS	2210	-	Fixed	
Disease related costs – annual				
Intercept	1284	0.165	Lognormal	OASIS data, AbbVie submission
BASFI coefficient	0.213	0.038	Normal	

Parameter	Mean value	Standard error	Distribution	Source
Adverse event costs (£ per patient)				
Year 1	18.2	-	Fixed	Excess rates for anti-TNFs from Cochrane review [127], Costs from NHS Reference costs
Subsequent years	0	-	Fixed	

Abbreviations: CC: Conventional Care; Tx: treatment

7.5.1 Baseline patient characteristics

Baseline characteristics applied to the AS and nr-axSpA populations are summarised in Tables 82 and 83, respectively.

7.5.2 Response, change in BASDAI/BASFI and conditional baselines

BASDAI50 response, conditional change scores for BASDAI and BASFI at 12 weeks and the separate conditional baselines estimated for BASDAI and BASFI (responders vs. non-responders) were derived directly from the results of the extended synthesis model reported in Section 6. In the base-case, it was assumed that the percentage of BASDAI50 responders, change in BASDAI/BASFI and conditional baselines were the same for all anti-TNFs. The outputs (CODA) from the simulations were incorporated directly into the model to maintain correlation and to avoid any additional distributional assumptions.

7.5.3 Longer term BASFI progression

As previously highlighted in the overview section, the York model attempts to address some of the conceptual concerns outlined in Section 5 surrounding the assumptions applied within existing models in relation to modelling BASFI progression over time. Specifically we assume that BASFI is a function of separate processes which are independently related to disease severity/activity (BASDAI) and to the extent and subsequent progression of radiographic disease (mSASSS). The rationale for this is that the association between BASDAI and BASFI is already accounted for in the separate mean change scores applied to both BASDAI and BASFI for responders vs. non-responders/conventional care patients. Differences in BASDAI are assumed to remain constant over the longer-term horizon (an assumption which is common across all models). Hence, any additional changes which might affect BASFI need to be more explicitly related to a separate clinical process (or processes). Based on the studies included in the reviews reported in Section 4 for natural history (Section 4.2.6) and the effect on anti-TNFs on radiographic progression (Section 4.2.4.1), we modelled longer term changes in BASFI (for conventional care and anti-TNFs) as a function of mSASSS scores.

The approach applied in the AS population is based on the following studies and assumptions:

1. The multivariate relationship reported in Landewe et al (2009)[12], based on longitudinal assessments of BASFI, BASDAI and mSASSS, was used to estimate the independent effect of a 1 unit change in mSASSS on BASFI scores (mean= 0.057, SE = 0.0049).
2. Data from a 12-year prospective follow-up of the OASIS study was used to estimate the annual rate of change in mSASSS. Although at the individual level, progression of mSASSS is highly variable, the study by Ramiro et al (2013) demonstrated that at a group level (i.e. akin to the cohort approach applied in the York model) changes in mSASSS were stable, progressing at an annual rate of 0.98 mSASSS units per year.[140] Combining the estimates reported across the studies implies a change in BASFI of 0.056 units per annum (0-10 scale). However, since the population included in the study by Ramiro et al (2013) included patients who would not be eligible to receive anti-TNFs, we used data in the subgroup of patients with baseline mSASSS>=10. The annual rate of mSASSS progression in this subgroup was 1.44 (95% CI 1.18-1.70) units per year with an implied annual BASFI change of 0.082 units per year. This compares with an annual change of BASFI of between 0.056 to 0.07 assumed across the manufacturer submissions. The specific subgroup (mSASSS>=10) was chosen to reflect that AS patients eligible to receive anti-TNFs are likely to be more similar to this subgroup than the entire cohort reported by Ramiro et al (2013). This also provided a basis for differentiating between the AS and nr-axSpA populations which is discussed in the following section.
3. Given the uncertainties noted in Section 4.2.4.1 surrounding the effect of anti-TNFs on radiographic progression, we explored alternative scenarios in the decision-model. In the base-case we assumed that the effect was related to the duration of therapy which has been reported in recent studies by Haroon et al (2013)[113] and Baraliakos et al (2014)[114]. Both studies consistently reported evidence that the difference in mSASSS between patients who received anti-TNFs and historical controls only became different in patients who had received treatment for approximately 4-years or more. In the absence of any relative effect measure reported by Baraliakos et al (20014), we used results reported by Haroon et al (2013) applying a zero-inflated binomial model with a relative rate of mSASSS change of 0.42 (95% CI 0.18-0.98). Hence, in the model, no effect on mSASSS was assumed until year 4 of the model and then only applied to patients who continued to receive therapy beyond this period.
4. Given the inherent uncertainties regarding the effect of anti-TNFs on radiographic progression we explored alternative scenarios based on: (i) an assumption of no impact on radiographic progression and; (ii) an immediate effect – applying the estimate of 0.42 from the outset.

For the nr-axSpA population, we assume a similar underlying clinical process relating to BASFI but model separate BASFI processes for patients depending upon the probability of developing

radiographic disease over time and thereafter modelling the extent and progression of radiographic disease via mSASSS changes. Hence, our intention in the nr-axSpA model was to employ a constant BASFI score (on and off-treatment) until a patient develops radiographic progression. At the time point of 'progression' an increasing BASFI would be assumed using a similar approach applied to the AS population. However, programming the additional transition to allow separate BASFI progression estimates based on the time of progression (and time since progression for patients who had previously progressed) proved more complex than anticipated. Consequently, a more simplified assumption was made such that all patients were assumed to incur progression in BASFI albeit at a lower rate relative to the AS population.

The approach we intended to apply in the nr-axSpA population was based on the following studies and assumptions:

1. Poddubnyy et al (2012) is used to estimate the probability of nr-axSpA patients progressing to radiographic disease based on the outcome '% progressed by >=2 mSASSS over 2 years' (7.4%) reported.[146] These estimates are converted into a rate to estimate the cycle specific probability.
2. Following progression, the mSASSS scores of patients are subsequently assumed to increase at a rate of 0.69 (95% CI 0.63 to 0.75) units per year, based on the subgroup of patients with baseline mSASSS<10 reported by Ramiro et al (2013).[140] BASFI is assumed to remain constant for patients who do not progress in each cycle of the model.
3. The same results reported by Haroon et al (2013)[113], applying a zero-inflated binomial model with a relative rate of mSASSS change of 0.42 (95% CI 0.18-0.98), were applied to the mSASSS scores for patients who progressed to estimate the treatment effect of anti-TNFs. Hence, in common with the AS model, no effect on mSASSS was assumed until year 4 and then only applied to patients who continued to receive therapy beyond this period.
4. Given the inherent uncertainties regarding the effect of anti-TNFs on radiographic progression we explored alternative scenarios based on: (i) an assumption of no impact on radiographic progression and; (ii) an immediate effect – applying the estimate of 0.42 from the outset. We also considered an exploratory scenario where we assumed no radiographic progression for nr-axSpA for patients receiving anti-TNFs, to investigate the untested hypothesis that early intervention in patients, prior to established radiographic disease, might halt subsequent progression.

Given the additional programming challenges that could not be overcome within the remaining time and funding constraints, the mSASSS scores of all nr-axSpA patients were assumed to increase at the rate of 0.69 units per year. Hence, the subsequent results reported for the nr-axSpA population are potentially optimistic since not all patients will develop radiographic progression. However, the use of

mSASSS in this context inevitably represents an uncertain proxy process for BASFI changes. Further, it should also be noted that the BASFI trajectory of nr-axSpA patients has been reported in publications to be similar to early AS patients.[167] Consequently, applying the change in mSASSS reported in the subgroup of patients with baseline mSASSS<10 reported by Ramiro et al (2013) may not be an unreasonable proxy for the purposes of predicting future changes in BASFI over longer periods.[140]

7.5.4 Longer term discontinuation

Patients who achieve a response at 12-weeks are subsequently assumed to remain on that treatment until the treatment is discontinued (i.e. due to loss of efficacy or adverse events). Hence, the evidence required to inform the decision model is the post-12 week withdrawal data for responders. The rationales for this are: (i) that discontinuation for lack of efficacy is higher during the first 3 months, and this has already been accounted for in the model using the probability of no BASDAI 50 response during the initial treatment period; and (ii) discontinuation rates in responders may differ from withdrawal rates in studies which potentially include both responders and non-responders. Although Section 4.2.4.2 identified 12 studies reporting on longer-term drug survival from registries, none of these appear to directly inform the model requirements (i.e. either including the initial 3-month period and/or not being specific to responders).

The most relevant estimates appeared to be those presented in previous and current submissions by the manufacturers. Three alternative approaches and sources were identified which appeared to meet the requirements of the economic model. These included:

1) A constant annual probability of 15% applied in the study by Kobelt et al (2007)[151] based on data from infliximab responders (BASDAI 50) reported as part of the 2nd-year of the open-label extension period of the Braun trial (n=18).
2) Separate time-dependent estimates of the probability for AS and nr-axSpA reported in the AbbVie submission. These estimates were based on a parametric function (log-normal distribution) estimated from responders (ASAS20 for AS and ASAS40 for nr-axSpA at week 12) from the open-label extensions of ATLAS (up to 260 weeks; n= not stated)) and ABILITY-1 (up to 156 weeks; n=28).
3) A constant annual estimate (approximately 5% for nr-axSpA and 11% for AS) reported in the Pfizer submission. These estimates were based on a parametric function (exponential distribution) estimated from responders (BASDAI 50 at week 12) from the open-label extensions of studies 311-EU, 312-EU and 907-EU (up to approx. 250 weeks for 311-EU; n= not stated) for the AS population and study 1031 (up to approximately 110 weeks; n=46) for the nr-axSpA population.

Figure 16 provides a comparison of the different estimates in terms of the subsequent drug survival over a longer-time horizon for AS.

Figure 16- Comparison of withdrawal rates – AS population

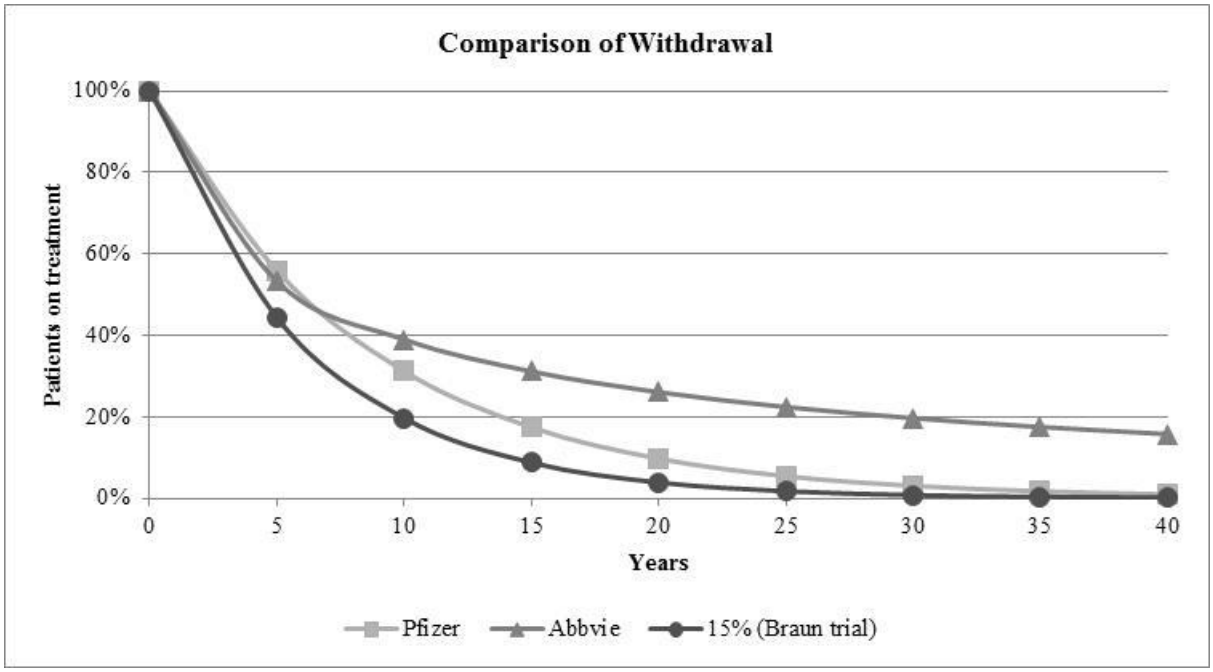
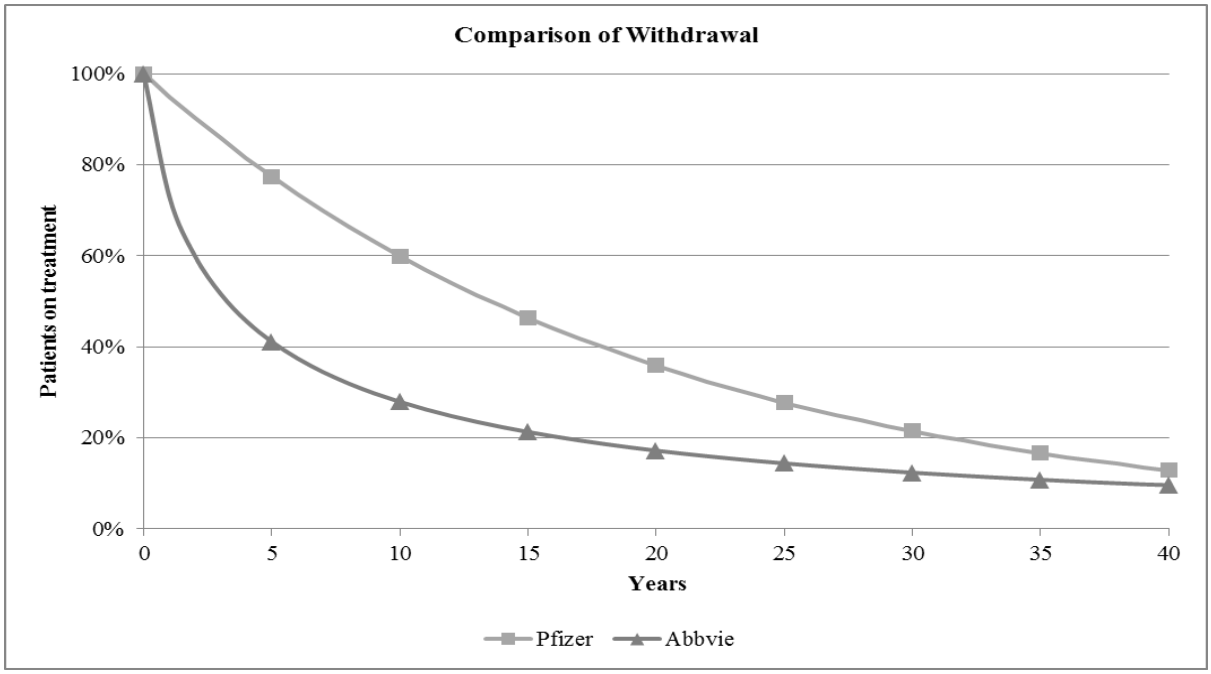


Figure 17 provides a comparison of the different estimates in terms of the subsequent drug survival over a longer-time horizon for nr-axSpA.

Figure 17 - Comparison of withdrawal rates – nr-axSpA population



The base-case of the York model is based on the estimates reported in the submission by Pfizer for both populations. The justification for this is that: (i) the estimates relate to the response endpoint used in the York model (BASDAI 50); (ii) full details were reported by Pfizer concerning the alternative parametric models and associated goodness of fit statistics and the exponential model appeared the most appropriate function; (iii) the continued use of a time-dependent function with long-tails such as the lognormal distribution results in a significant proportion of patients who would still be assumed to be on TNF-alpha therapy even after 40 years. Although it is not possible to completely rule out this possibility, the approach by Pfizer was deemed to be a more appropriate basis for informing the York model based on a series of considerations.

7.5.5 Health-related quality of life

The current manufacturer submissions are based on alternative mapping algorithms to link BASDAI and BASFI scores to a generic utility measure. The approach used by AbbVie in their base-case was based on separate mapping algorithms for the AS and nr-axSpA populations using data from the ATLAS and ABILITY-1 trials, respectively. For the nr-axSpA population, BASDAI and BASFI were mapped to EQ-5D, whereas, the algorithm for the AS population mapped to HUI3; reflecting the use of different generic utility measures used in the two trials. The approach employed by Pfizer in their base-case was similarly based on separate algorithms for each population estimated using data from the 1031 study (nr-axSpA) and the 314-EU study (AS) both mapped to EQ-5D. Both regressions were based on the relationship between BASDAI, BASFI and EQ-5D. The approach employed by UCB in

their base-case was based on the same, single mapping algorithm from the RAPID-axSpa trial that included both patient populations. MSD adopted the algorithm reported in McLeod et al (2007)[34].

We undertook a separate search for other published utility algorithms and only identified the algorithm reported in Ara et al (2007)[152] which was based on the cost-effectiveness analysis submitted by Pfizer to NICE for TA143. Full details of the search and associated review of utility studies are reported in Appendices 1 and 13, respectively. A summary of the alternative algorithms based on EQ-5D is provided in Tables 84 and 85.

Table 84 - Comparison of alternative EQ-5D utility regression models (AS)

	Ara 2007	MSD	UCB	Pfizer
BASDAI/BASFI scale	**0-10**	**0-10**	**0-10**	**0-100**
Regression model	**Linear**	**Linear**	**Logistic**	**Non-linear**
Intercept	0.92300000	0.877213	[redacted]	[redacted]
BASFI	-0.04318800	-0.032252	[redacted]	[redacted]
BASDAI	-0.04019000	-0.038409	[redacted]	[redacted]
Male	0.00000000	-0.027891	[redacted]	[redacted]
Age	0.00000000	0.001681	[redacted]	[redacted]
BASFI^2	0.00000000	0.000000	[redacted]	[redacted]
BASDAI^2	0.00000000	0.000000	[redacted]	[redacted]
BASFI * BASDAI	0.00000000	0.000000	[redacted]	[redacted]

Table 85- Comparison of alternative EQ-5D utility regression models (nr-axSpA)

nr-axSpA	UCB	AbbVie	Pfizer
BASDAI/BASFI scale	**0-10**	**0-10**	**0-100**
Regression model	**Logistic**	**Linear**	**Non-linear**
Intercept	[redacted]	0.9220000	[redacted]
BASFI	[redacted]	-0.0411700	[redacted]
BASDAI	[redacted]	-0.0392400	[redacted]
Male	[redacted]	0.0000000	[redacted]
Age	[redacted]	0.0000000	[redacted]
BASFI^2	[redacted]	0.0000000	[redacted]
BASDAI^2	[redacted]	0.0000000	[redacted]
BASFI * BASDAI	[redacted]	0.0000000	[redacted]

Figures 18 to 21 provide a comparison of the utility predictions for each algorithm in each population. For each population, 2 separate figures are presented. Each figure is based on the impact of holding either BASDAI or BASFI constant (at the mean value) and allowing the other measure to vary across the entire range. The baseline characteristics (BASDAI, BASFI and age) were derived from a weighted average of the baseline characteristics of the clinical trials for the AS population used in the manufacturer's economic models. For nr-axSpA, baseline characteristics (BASDAI, BASFI and age) of the nr-axSpA sub-population from the RAPID-axSpa study were used. Gender was assumed to be 65% male in AS and 35% male in nr-axSpA.

Figure 18 - Illustration of predicted EQ-5D values using different mapping algorithms - constant BASDAI and varying BASFI (AS)

Figure 19 - Illustration of predicted EQ-5D values using different mapping algorithms - constant BASFI and varying BASDAI (AS)

Figure 20 - Illustration of predicted EQ-5D values using different mapping algorithms - constant BASDAI and varying BASFI (nr-axSpA)

Figure 21 - Illustration of predicted EQ-5D values using different mapping algorithms - constant BASFI and varying BASDAI (nr-axSpA)

It is evident that there is significant variation in the utility predictions arising from each separate algorithm. In particular, the non-linear function estimated by Pfizer results in important differences

across several of the figures at the extremes of the BASDAI/BASFI ranges. However, limited details were provided in relation to goodness of fit and/or predictive performance for the majority of algorithms. Hence, a formal assessment of the validity of the different approaches is problematic. Only the submission by Pfizer reported additional detail on these aspects and hence was subsequently used in the York model base-case (separate algorithms for the different populations). The non-linear function for utilities was also considered to be more consistent with the non-linear approach applied to costs.

A potential limitation of all the manufacturer analyses is that their algorithms are based on trial data. These data may represent a more limited range of BASDAI and BASFI values and hence there maybe issues associated with their subsequent predictive performance in the context of the longer-term economic model. Although, from the data reported by Pfizer at least, it appeared as if the full range of BASDAI and BASFI scores were represented in the sample used. However, a separate sensitivity analysis was also undertaken based on the algorithm used by MSD. This algorithm is based on a re-analysis of the Kobelt et al (2004)[143] data from patients (n=1,144) who had BASDAI and BASFI scores across the whole 0-10 scale and was previously used by Mcleod et al (2007)[34] for the previous MTA. Hence, this scenario also provides a more consistent basis for comparing the results from our new analysis.

7.5.6 Resource use and costs

7.5.6.1 Drug acquisition costs

The unit costs of anti-TNFs were sourced from the British National Formulary. Doses were calculated in accordance with their respective licences. Tables 86 and 87 summarise the drug acquisition costs and the licensed dosage for AS and nr-axSpA patients

PAS details

Certolizumab PAS: UCB will make Cimzia available free of charge to all NHS patients for the first three months of therapy, at which point clinical response should be clear. Only after this three month stage will the NHS be charged for continuing to use this therapy. However, it should be noted that the proposed PAS is not yet formally agreed with the Department of Health and NICE.

Golimumab PAS: the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme.

Table 86 - Drug acquisition costs

Drug	Dose	Cost (£)	Source
Infliximab (Remicade)	IV infusion - 100 mg vial	419.62	BNF[168] – Nov 2014

Golimumab (Simponi)	Injection - 50-mg prefilled pen or prefilled syringe	762.97	BNF – Nov 2014
	100-mg prefilled pen	1525.94	
Adalimumab (Humira)	Injection - 40-mg prefilled pen/prefilled syringe or 40 mg/0.8-mL vial	352.14	BNF – Nov 2014
Certolizumab (Cimzia)	Injection - 200-mg prefilled syringe	357.5	BNF – Nov 2014
Etanercept (Enbrel)	Injection - powder for reconstitution, 25-mg vial or 25-mg prefilled syringe	89.38	BNF – Nov 2014
	Injection - 50-mg prefilled pen or prefilled syringe	178.75	BNF – Nov 2014

Table 87 Anti-TNFs licensed dosage in AS and nr-axSpA

Drug	Licensed dosage in AS and nr-axSpA
Infliximab (Remicade)	- 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks. - If a patient does not respond by 6 weeks (i.e. after 2 doses), no additional treatment with infliximab should be given.
Golimumab (Simponi)	- 50 mg given once a month, on the same date each month - For patients with a body weight of more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered
Adalimumab (Humira)	-Recommended dose for patients with ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of AS is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection
Certolizumab (Cimzia)	- The recommended starting dose of Cimzia for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. - After the starting dose, the recommended maintenance dose of Cimzia for adult patients with axial spondyloarthritis is 200 mg every 2 weeks or 400 mg every 4 weeks.
Etanercept (Enbrel)	- The recommended dose is 25 mg Enbrel administered twice weekly, or 50 mg administered once weekly.

7.5.6.2 Drug administration costs

Administration costs for intravenous therapies were based on a regular chemotherapy cost (HRG code SB15Z, Deliver subsequent elements of a chemotherapy cycle), similarly to NICE TA143.[1] Therapies administered subcutaneously were assumed to be self-administered following instruction. The cost of instruction in the model was based on one hour of nurse time (PSSRU 2013).[169] Drug administration did not differ between the AS and nr-axSpA indications.

Table 88 - Drug administration costs

	Cost (£)	Source
Subcutaneous therapies	£49	Cost of nurse training for self-administration (PSSRU 2013)[169]
Intravenous therapies	£291	HRG code SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle (NHS Reference costs 2012-13)[166]

7.5.6.3 Initiation and monitoring costs

The initiation and monitoring costs for anti-TNF therapies were restricted to the additional costs incurred compared to patients receiving conventional care alone as these drugs are used in addition to current practice. The resource use assumptions for laboratory testing for anti-TNF initiation and monitoring have been sourced from the York model for psoriatic arthritis (TA199)[165] and conform to guidelines from the British Society for Rheumatology (BSR)[159] for the use of biologics.

Specifically, during the initial 12-week period AS patients on anti-TNF therapy are assumed to undertake a series of tests at treatment initiation and at week 12 when assessing treatment response (i.e. a Full Blood Count (FBC), Erythrocyte Sedimentation Rate (ESR), Liver Function Test (LFT), Urea and Electrolytes (U&E)). Additional testing is conducted once during the initial period (i.e. chest X-Ray, Tuberculosis (TB) Heaf test, antinuclear antibody (ANA) and a double-stranded DNA test). AS patients on anti-TNF therapy are also assumed to visit a specialist twice during the initial 12-week period (at treatment initiation and when assessing 12-week response) and 2 times per year thereafter for monitoring. For quarterly monitoring, AS patients are assumed to receive a series of laboratory tests once every three months (i.e. a Full Blood Count (FBC), Erythrocyte Sedimentation Rate (ESR), Liver Function Test (LFT), Urea and Electrolytes (U&E)).

Nr-axSpa patients, in addition to the initiation and monitoring resource use assumed for AS patients on anti-TNF therapy, are also assumed to get an MRI test and a CRP test at treatment initiation, as well as an X-ray once per year after the initial period for monitoring, in order to assess radiographic progression.

Cost estimates for laboratory testing have been sourced from the York model for psoriatic arthritis (TA199) and have been inflated to 2012/13 prices, using the Hospital & Community Health Services (HCHS) Pay & Prices Index.[165, 169] The CRP test cost is derived from Henriksson 2010.[170] Specialist visits are costed at £100 (outpatient rheumatology follow-up attendance), using the NHS Reference Costs 2012-13.[166]

A summary of the initiation and monitoring resource use assumptions for anti-TNF therapies and the subsequent costs for the AS and nr-axSpA populations is reported in Tables 89 and 90.

Table 89 - Initiation and monitoring resource use and costs– AS population

	Resource use		Cost	
Item	Initiation period (12 weeks)	Quarterly Monitoring	Initiation period (12 weeks)	Quarterly Monitoring
Full blood count (FBC)	2	1	£5.97	£2.98
Erythrocyte sedimentation rate (ESR)	2	1	£5.90	£2.95
Liver function test (LFT)	2	1	£1.50	£0.75
Urea and Electrolytes (U&E)	2	1	£2.77	£1.38
Chest X-ray	1	0	£26.19	£0.00
Tuberculosis (TB) Heaf test	1	0	£8.72	£0.00
Antinuclear antibody (ANA)	1	0	£4.65	£0.00
Double-stranded (ds) DNA test	1	0	£4.65	£0.00
Specialist visit	2	0.5	£200.00	£50.00
C reactive protein (CRP) test	0	0	£0.00	£0.00
Total	-	-	£260	£58

Table 90 - Initiation and monitoring resource use and costs– nr-axSpA population

	Resource use		Cost	
Item	Initiation period (12 weeks)	Quarterly Monitoring	Initiation period (12 weeks)	Quarterly Monitoring
Full blood count (FBC)	2	1	£5.97	£2.98
Erythrocyte sedimentation rate (ESR)	2	1	£5.90	£2.95
Liver function test (LFT)	2	1	£1.50	£0.75
Urea and Electrolytes (U&E)	2	1	£2.77	£1.38
Chest X-ray	1	0.25	£26.19	£6.55
Tuberculosis (TB) Heaf test	1	0	£8.72	£0.00
Antinuclear antibody (ANA)	1	0	£4.65	£0.00
Double-stranded (ds) DNA test	1	0	£4.65	£0.00
Specialist visit	2	0.5	£200.00	£50.00
MRI cost	1	0	£144.45	£0.00
C reactive protein (CRP) test	1	0	£6.62	£0.00
Total	-	-	£411	£65

7.5.6.4 Summary of drug acquisition, administration and monitoring costs

Tables 91 and 92 summarise the drug acquisition, administration and monitoring costs applied in the economic model, for the initial 12-week period and on an annual basis thereafter.

Table 91 - Summary of drug acquisition, administration and monitoring costs used in economic model – AS population

	Initial period (3 months)			Annual cost (after initial 3 months)			Total costs	
Treatment – Dosage	Acquisition cost	Administration cost	Monitoring costs	Acquisition cost	Administration cost	Monitoring costs	Initial period (3 months)	Subsequent annual costs
Adalimumab (40 mg eow)	£2,112.8	£49.0	£260.4	£8,451.4	£0.0	£232.3	£2,422.2	£8,683.6
Certolizumab 200 mg/2wks	£3,575.0	£49.0	£260.4	£8,580.0	£0.0	£232.3	£3,884.4	£8,812.3
Certolizumab 200 mg/2wks, with PAS	£0.0	£49.0	£260.4	£8,580.0	£0.0	£232.3	£309.4	£8,812.3
Etanercept 25 mg twice/week	£2,145.1	£49.0	£260.4	£8,580.5	£0.0	£232.3	£2,454.5	£8,812.8
Etanercept 50 mg once/week	£2,145.0	£49.0	£260.4	£8,580.0	£0.0	£232.3	£2,454.4	£8,812.3
Golimumab 50mg once monthly, with PAS	£2,105.6	£49.0	£260.4	£8,422.4	£0.0	£232.3	£2,415.0	£8,654.7
Infliximab 5mg/kg every 7 weeks, 4 vials	£5,639.7	£978.8	£260.4	£11,509.6	£1,997.5	£232.3	£6,878.8	£13,739.3

Table 92 - Summary of drug acquisition, administration and monitoring costs used in economic model – nr-axSpA population

	Initial period (3 months)			Annual cost (after initial 3 months)			Total costs	
Treatment – Dosage	Acquisition drug cost	Administration cost	Monitoring costs	Acquisition drug cost	Administration cost	Monitoring costs	Initial period (3 months)	Subsequent annual costs
Adalimumab (40 mg eow)	£2,112.8	£49.0	£411.4	£8,451.4	£0.0	£258.5	£2,573.3	£8,709.8
Certolizumab 200 mg/2wks	£3,575.0	£49.0	£411.4	£8,580.0	£0.0	£258.5	£4,035.4	£8,838.5
Certolizumab 200 mg/2wks, with PAS	£0.0	£49.0	£411.4	£8,580.0	£0.0	£258.5	£460.4	£8,838.5
Etanercept 25 mg twice/week	£2,145.1	£49.0	£411.4	£8,580.5	£0.0	£258.5	£2,605.5	£8,838.9
Etanercept 50 mg once/week	£2,145.0	£49.0	£411.4	£8,580.0	£0.0	£258.5	£2,605.4	£8,838.5
Golimumab 50mg once monthly, with PAS	£2,105.6	£49.0	£411.4	£8,422.4	£0.0	£258.5	£2,566.0	£8,680.9
Infliximab 5mg/kg every 7 weeks, 4 vials	£5,796.08	£1,005.9	£411.4	£11,509.6	£1,997.5	£258.5	£7,213.4	£13,765.5

7.5.6.5 Long-term disease management costs

Patients who remain on anti-TNF treatment incur disease management costs. Previously published economic evaluations employed observational cohort studies to estimate disease management costs and modelled these according to BASDAI and/or BASFI. (for example, NICE TA143). Also, as discussed in Section 5, the majority of the manufacturer submissions within this appraisal (and the LRiG model in TA 143) have analysed healthcare resource use data from the Outcomes in Ankylosing Spondylitis International Study (OASIS)[157] to estimate disease management costs. The submission by Pfizer estimated disease-related costs using data from Rafia et al (2012)[158] arguing that it is a more recent study and provides a UK specific cost estimate. However, the comparative analysis of the different long-term cost models in Appendix 14 showed that the Rafia model provided considerably lower cost estimates; the reasons for this discrepancy are not clear.

In NICE TA143 the committee judged that the OASIS data were the most reliable source, being a two-year prospective study of 208 AS patients from four centres in France, Belgium and the Netherlands, and collecting clinical assessments and economic data including BASDAI and BASFI every 2 or 6 months. The NICE committee also decided that only BASFI should be employed as the major predictor of costs as it reflects long-term disease progression, whilst BASDAI appears to fluctuate but not increase over time.

The base case of the York model uses the exponential BASFI regression model from the AbbVie submission, which is a re-analysis of the OASIS resource utilisation data using up-to-date published tariffs (NHS Reference costs 2012-13[166], PSSRU 2013[169]).

Table 93 - Disease-related costs

	Cost (£)	Source
Base-case	£1284.186 * EXP(0.213 × BASFI)	AbbVie submission; re-analysis of OASIS[157] data

7.5.7 Adverse events

Only serious infections and TB reactivation were included in the economic model. Anti-TNF excess rates versus conventional care for serious infections and TB reactivation for were sourced from the Cochrane review of adverse events[127] which has been discussed in Section 4.2.5. The cost of a serious infection was sourced from the Pfizer submission and was assumed to be £1,457 based on a weighted average of relevant HRG costs from NHS Reference costs 2012-2013[166] (Table 94). The cost of tuberculosis was estimated to be £3,204.5 per episode and was based on a weighted average of the relevant HRG codes with different levels of severity (codes DZ14C, DZ14D, DZ14E) from NHS Reference costs 2012-2013.

Table 94 - Costs of serious infection (from Pfizer submission)

Currency Code	Currency Description	Activity	National Average Unit Cost
WA03C	Septicaemia, with CC Score 0-1	44956	£1,792
DZ23G	Bronchopneumonia with CC Score 0-4	5231	£1,252
LA04M	Kidney or Urinary Tract Infections, with Interventions, with CC Score 0-2	2587	£2,289
PA16B	Major Infections with CC Score 0	7859	£1,573
DZ22J	Unspecified Acute Lower Respiratory Infection with CC Score 0-1	21109	£657
DZ21U	Chronic Obstructive Pulmonary Disease or Bronchitis, without NIV, without Intubation, with CC Score 0-3	52421	£1,453
Weighted average cost			£1,457

Abbreviations: CC, complications; NIV, Non-invasive ventilation.
Source: NHS reference costs schedule 2012-13[166]

7.5.8 Mortality

Gender-specific SMRs are applied to the mortality rates from the general population to calculate separate adjusted mortality rates for AS and nr-axSpA populations in the model (Bakland [2011])[18].

7.6 Analytic methods

The expected costs and QALYs of the alternative anti-TNFs are estimated and cost-effectiveness assessed based on the incremental cost per additional QALY gained. Since an assumption is made concerning the similarity in terms of clinical effect between the alternative anti-TNFs, the differences between each of the treatments are driven entirely by their respective acquisition, administration and monitoring costs. Under this assumption, inevitably the lowest cost TNF-alpha inhibitor would clearly dominate (i.e. lower cost and equal effect) in a fully incremental comparison of cost-effectiveness. Consequently, each TNF-alpha inhibitor is compared separately versus conventional care alone. This provides a more consistent basis for assessing the impact that the different drug costs have across each separate scenario.

Probabilistic sensitivity analysis (PSA) is used to assess the implications of parameter uncertainty (the imprecision with which input parameters are estimated). The mean costs and QALY reported in the tables are derived from the PSA analysis and the probabilities that each TNF-alpha inhibitor is more cost-effective than conventional care alone are reported at thresholds of £20,000 and £30,000 per QALY.

7.6.1 Sensitivity analyses

A number of separate scenarios are presented to assess the implications of key parameter assumptions and sources of structural uncertainty in the model. These include:

Scenario 1: No response to conventional care assumed at 12 weeks.

The base-case model incorporates the probability of response to conventional care at 12 weeks and assigns separate baselines to responders and non-responders. Although the changes in BASDAI/BASFI estimated at 12-weeks for conventional care are assumed to disappear in the following 12-week cycle, the separate baselines estimated for responders and non-responders are retained for the remainder of the model horizon. Given uncertainties surrounding the nature of the 'placebo' response assumed to apply to conventional care and whether this would be evident in actual clinical practice, a separate scenario was modelled which assumed that no patients receiving conventional care would achieve a BASDAI50 response. This scenario was based on a separate simulation using the extended synthesis model where the magnitude of 'placebo' effect was assumed to be 0. Hence, employing this scenario, the impact of the 'placebo' effect is effectively netted out of the model for both conventional care and the anti-TNFs. Hence, while the difference in response rates and BASDAI/BASFI scores for responders to anti-TNFs remains similar to the base-case model, the absolute response rate for anti-TNFs and the absolute BASDAI/BASFI scores are lower when the adjustment is applied. Also, since no response is assumed for conventional care, a single baseline BASDAI and BASFI score is applied to conventional care patients.

Scenario 2: Different baselines assumed for responders and non-responders.

In the base-case analysis, the extended synthesis model is used to estimate both changes in BASDAI and BASFI conditional upon BASDAI50 response as well as different baseline BASDAI/BASFI scores for responder and non-responders. It was noted in Section 6 that there appeared a disparity in the magnitude of the difference in the conditional baseline scores estimated from the extended synthesis model compared to the differences reported by those manufacturers who provided additional data on request. Specifically, the difference between responders and non-responders appeared higher in our extended synthesis compared to the direct data reported by manufacturers. To explore the potential impact of this difference on the cost-effectiveness results, a separate scenario was undertaken wherein the difference in the conditional baselines was based on a pooled estimate of the differences across the trials provided by manufacturers rather than those estimated by the extended synthesis model.

In addition to exploring the impact of assuming different baselines, this scenario also included a pooled estimate of the change in BASDAI/BASFI scores for responders and non-responders reported by manufacturers. Hence, in this scenario, the extended synthesis model is only used to predict the response to BASDAI50; the differences in the conditional baselines and change scores being derived from pooled estimates from the data reported by manufacturers.

Scenario 3: No effect of anti-TNFs on BASFI progression.

In the base-case model, a treatment effect is applied from year 4 of the model on the rate of further BASFI progression for patients who continue to receive TNF-alpha inhibitors beyond this time point. Given the uncertainty reported in Section 4 surrounding existing evidence for anti-TNFs in relation to disease modification, a separate scenario was explored which assumed that the rate of BASFI progression would be the same for patients receiving anti-TNFs and conventional care alone.

Scenario 4: Treatment effect of anti-TNFs applied from start of model (BASFI progression).
A separate scenario was also undertaken assuming that the treatment effect on further BASFI progression would be incurred from the start of the model, as opposed to year 4. This scenario assumes that any disease modification would be achieved immediately compared to the delayed effect assumed in the base-case.

Scenario 5: Utilities – linear BASDAI/BASFI model.
The base-case analysis in both the AS and nr-axSpA populations are based on the non-linear mapping algorithms reported in the submission by Pfizer. A separate scenario was run in both populations using an alternative linear model which has been applied in previous NICE appraisals (referred to as the 'MSD' algorithm in Section 7.5.5). This scenario was incorporated to explore the impact of using a linear model and to provide results which are more consistent with the utility approach applied in previous NICE appraisals (TA143, 233).

Scenario 6 (nr-axSpA only): Trials in nr-axSpA and AS populations combined.
The base-case analysis for the nr-axSpA population is based on the extended synthesis model using only the trials reporting in this population. A separate scenario was undertaken based on the results from the extended synthesis model which combined the AS and nr-axSpA trials.

7.6.2 Model validation

The conceptualisation of the model and related structural assumptions were informed by the review of existing models and discussions with two clinical advisors. The face validity of the model structure, data sources and key assumptions was addressed using inputs based on systematic reviews, targeted searching and clinical input. Verification of the model and the associated inputs was undertaken using a staged process. One researcher developed the initial model structure and the preliminary coding. This was then checked and extended for the final model by a second researcher. Both researchers were subsequently involved in the subsequent quality assurance process entailing detailed cross-checks of input data against their respective sources and undertook extensive logical checks and scenarios to assess the performance of the model. Two other researchers were involved in further checks of key aspects including the integration of the results from the extended synthesis within the Excel model. A 5th researcher was involved in all stages with preparing and checking parameter

inputs for the model. Cross-validation was assessed by comparing the results with existing models and identifying differences and their causes.

7.7 Results of the independent economic assessment

7.7.1 Base case results – AS population

The base-case results for the AS population, for the alternative rebound assumptions, are reported in Tables 95 and 96.

Table 95 - Base-case cost-effectiveness results - AS (rebound equal to gain)

Strategy	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	7.245	-	110,821	-	-	-	-
Certolizumab PAS	8.163	0.918	128,485	17,665	19,240	0.550	0.895
Golimumab	8.163	0.918	130,173	19,352	21,079	0.427	0.841
Adalimumab	8.163	0.918	130,257	19,436	21,170	0.423	0.839
Etanercept	8.163	0.918	130,630	19,810	21,577	0.402	0.826
Certolizumab	8.163	0.918	132,059	21,238	23,133	0.299	0.761
Infliximab	8.163	0.918	148,073	37,252	40,576	0.001	0.089

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

In the rebound equal to gain scenario, the ICER of the alternative anti-TNFs varied between £19,240 (certolizumab with the proposed PAS) to £40,576 per additional QALY (infliximab). Infliximab had the highest ICER (£40,576 per QALY) and the lowest probability of being cost-effective at a £20,000 and £30,000 per QALY threshold (0.001 and 0.089, respectively). Excluding infliximab, the ICERs of the other anti-TNFs were similar, ranging from £19,240 (certolizumab with the proposed PAS) to £23,133 (certolizumab without the proposed PAS).

As previously highlighted, the difference in the ICERs between the individual anti-TNFs is driven entirely by the different acquisition and administration costs associated with each. Excluding infliximab, the probability that each TNF-alpha inhibitor was more cost-effective than conventional care alone ranged between 0.299 and 0.550 at a £20,000 per QALY threshold and 0.761 to 0.895 at a £30,000 threshold. There was less variation in these probabilities when the proposed PAS for certolizumab was included, ranging from 0.402 to 0.550 at a £20,000 per QALY threshold and from 0.826 to 0.895 at a £30,000 threshold.

Table 96 - Base-case cost-effectiveness results (rebound to conventional care)

Strategy	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	7.265	-	109,933	-	-	-	-
Certolizumab PAS	7.867	0.603	130,277	20,344	33,762	0.035	0.399
Golimumab	7.867	0.603	131,960	22,027	36,554	0.019	0.299
Adalimumab	7.867	0.603	132,045	22,111	36,695	0.017	0.293
Etanercept	7.867	0.603	132,423	22,489	37,322	0.017	0.275
Certolizumab	7.867	0.603	133,851	23,918	39,693	0.011	0.203
Infliximab	7.867	0.603	150,022	40,088	66,529	0.000	0.001

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

In the rebound to conventional care scenario, the ICER of the alternative anti-TNFs varied between £33,762 (certolizumab with the proposed PAS) to £66,529 per additional QALY (infliximab). Infliximab had the highest ICER (£66,529 per QALY) and the lowest probability of being cost-effective at a £20,000 and £30,000 per QALY threshold (0.000 and 0.001, respectively). Excluding infliximab, the ICERs of the other anti-TNFs varied between £33,762 (certolizumab with the proposed PAS) to £39,693 (certolizumab without the proposed PAS) and the probability that each TNF-alpha inhibitor was more cost-effective than conventional care alone ranged between 0.011 and 0.035at a £20,000 per QALY threshold and 0.203 to 0.399 at a £30,000 threshold. There was less variation in these probabilities when the proposed PAS for certolizumab was included, ranging from 0.017 to 0.035 at a £20,000 per QALY threshold and from 0.275 to 0.399 at a £30,000 threshold.

7.7.2 Base case results – nr-axSpA population

The base-case results for the nr-axSpA population, for the alternative rebound assumptions, are reported in Tables 97 and 98.

Table 97 - Base-case cost-effectiveness results – nr-axSpA (rebound equal to gain)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	9.956	-	89,493	-	-	-	-
Certolizumab PAS	11.351	1.395	128,911	39,418	28,247	0.139	0.591
Adalimumab	11.351	1.395	130,316	40,823	29,253	0.106	0.545
Etanercept	11.351	1.395	131,057	41,563	29,784	0.093	0.529
Certolizumab	11.351	1.395	132,484	42,991	30,807	0.066	0.482

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

In the rebound equal to gain scenario, the ICER of the alternative anti-TNFs varied between £28,247 (certolizumab with the proposed PAS) to £30,807 per additional QALY (certolizumab without the

proposed PAS). The probability that each TNF-alpha inhibitor was more cost-effective than conventional care alone ranged between 0.066 and 0.139 at a £20,000 per QALY threshold and 0.482 to 0.591 at a £30,000 threshold. Again, there was less variation in these probabilities when only the proposed PAS for certolizumab was considered, ranging from 0.093 to 0.139 at a £20,000 per QALY threshold and from 0.529 to 0.591 at a £30,000 threshold.

Table 98 - Base-case cost-effectiveness results – nr-axSpA (rebound to conventional care)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	9.880	-	89,395	-	-	-	-
Certolizumab PAS	11.139	1.259	130,341	40,946	32,528	0.062	0.429
Adalimumab	11.139	1.259	131,740	42,346	33,639	0.045	0.387
Etanercept	11.139	1.259	132,486	43,091	34,232	0.039	0.369
Certolizumab	11.139	1.259	133,913	44,518	35,365	0.030	0.312

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

In the rebound to conventional care scenario, the ICER of the alternative anti-TNFs varied between £32,528 (certolizumab with the proposed PAS) to £35,365 per additional QALY (certolizumab without the proposed PAS). The probability that each TNF-alpha inhibitor was more cost-effective than conventional care alone varied between 0.030 and 0.062 at a £20,000 per QALY threshold and 0.312 to 0.429 at a £30,000 threshold. Again, there was less variation in these probabilities when only the proposed PAS for certolizumab was included, ranging from 0.039 to 0.062 at a £20,000 per QALY threshold and from 0.369 to 0.429 at a £30,000 threshold.

7.7.3 Sensitivity analyses results – AS population

Table 99 summarises the scenarios undertaken for the AS population.

Table 99 - Summary of cost-effectiveness scenarios – AS population

No.	Parameter/structural	Approach in scenario	Approach in base-case
1	Conventional care ('placebo') response	No response to conventional care assumed at 12 weeks	Response to conventional care included at 12 weeks
2.	Different baselines assumed for responders and non-responders and change in BASDAI/BASFI scores	Separate baselines based on pooled estimates provided by manufacturers. Changes in BASDAI/BASFI conditioned on response also based on pooled estimates provided by manufacturers	Separate baselines and changes in BASDAI/BASFI conditioned on responses estimated via extended synthesis model
3.	BASFI Progression	No effect of anti-TNFs on BASFI progression	Treatment effect applied from year 4 onwards
4.	BASFI progression	Treatment effect of anti-TNFs	Treatment effect applied from

		applied from start of model	year 4 onwards
5.	Utilities	Linear BASDAI/BASFI model (based on Kobelt)	Non-linear BASDAI/BASFI model (Pfizer submission)

Each of these scenarios was undertaken for the two alternative rebound assumptions. Tables 100 and 101 summarise the ICER estimates for each scenario. Full ICER tables for each scenario are reported in Appendix 15.

Table 100 - Summary of ICERs across scenarios (rebound equal to gain) – AS population

		Scenario				
Strategy	**Base-case**	**1**	**2**	**3**	**4**	**5**
Conventional Therapy	-	-		-	-	
Certolizumab (PAS)	19,240	20,319	11,527	20,655	18,466	23,290
Golimumab	21,079	22,920	12,785	22,581	20,213	25,469
Adalimumab	21,170	23,013	12,851	22,677	20,301	25,579
Etanercept	21,577	23,425	13,143	23,106	20,695	26,073
Certolizumab	23,133	25,495	14,220	24,739	22,180	27,926
Infliximab	40,576	43,510	26,699	43,125	39,037	49,021

Table 101 - Summary of ICERs across scenarios (rebound to conventional care) – AS population

		Scenario				
Strategy	**Base-case**	**1**	**2**	**3**	**4**	**5**
Conventional Therapy	-	-		-	-	-
Certolizumab (PAS)	33,762	34,229	25,530	36,518	32,222	29,414
Golimumab	36,554	38,068	27,986	39,483	34,910	31,827
Adalimumab	36,695	38,207	28,107	39,634	35,045	31,950
Etanercept	37,322	38,824	28,652	40,306	35,647	32,499
Certolizumab	39,693	41,885	30,731	42,828	37,928	34,554
Infliximab	66,529	68,815	54,045	71,565	63,684	58,022

The ICER estimates appeared to remain relatively stable across the majority of scenarios compared to the base-case ICER estimates. The exception to this appeared to be Scenario 2 which utilised data submitted on request by several manufacturers which was used to inform the differences in the conditional baselines and the change scores assumed for responders vs. non-responders. In summary, when the manufacturer's data were used the ICER estimates became more favourable towards the anti-TNFs. The more favourable results are driven by smaller differences between responders and

non-responders in terms of their conditional baselines and marginally higher differences in the conditional change scores. Both differences result in improvements in the ICER estimates compared to the base-case results derived from the extended synthesis model.

7.7.4 Sensitivity analyses results – nr-axSpA population

Table 102 summarises the scenarios undertaken for the nr-axSpA population.

Table 102 - Summary of cost-effectiveness scenarios – nr-axSpA population

No.	Parameter/structural	Approach in scenario	Approach in base-case
1	Conventional care ('placebo') response	No response to conventional care assumed at 12 weeks	Response to conventional care included at 12 weeks
2	Different baselines assumed for responders and non-responders and change in BASDAI/BASFI scores	Separate baselines based on pooled estimates provided by manufacturers. Changes in BASDAI/BASFI conditioned on response also based on pooled estimates provided by manufacturers	Separate baselines and changes in BASDAI/BASFI conditioned on responses estimated via extended synthesis model
3.	BASFI Progression	No effect of anti-TNFs on BASFI progression	Treatment effect applied from year 4 onwards
4.	BASFI progression	Treatment effect of anti-TNFs applied from start of model	Treatment effect applied from year 4 onwards
5.	Utilities	Linear BASDAI/BASFI model (based on Kobelt)	Non-linear BASDAI/BASFI model (Pfizer submission)
6.	Treatment effect of anti-TNFs	Trials in nr-axSpA and AS populations combined	Only trials in nr-axSpA included

Each of these scenarios was undertaken for the two alternative rebound assumptions. Tables 103 and 104 summarise the ICER estimates for each scenario. Full ICER tables for each scenario are reported in Appendix 15.

Table 103 - Summary of ICERs across scenarios (rebound equal to gain) – nr-axSpA population

		Scenario					
Strategy	**Base-case**	**1**	**2**	**3**	**4**	**5**	**6**
Conventional Therapy	-	-	-	-	-	-	-
Certolizumab (PAS)	28,247	34,841	25,482	28,643	27,471	25,324	28,282
Adalimumab	29,988	37,884	27,302	29,670	28,466	29,228	29,512
Etanercept	29,253	38,507	27,821	30,208	28,988	29,753	30,041
Certolizumab	30,807	40,949	29,378	31,250	29,996	30,732	31,034

Table 104 - Summary of ICERs across scenarios (rebound to conventional care) – nr-axSpA population

		Scenario					
Strategy	**Base-case**	**1**	**2**	**3**	**4**	**5**	**6**
Conventional Therapy	-	-	-	-	-	-	-
Certolizumab (PAS)	32,528	40,928	29,884	34,416	31,841	26,900	33,184
Adalimumab	33,639	44,365	31,942	35,615	32,940	27,850	34,270
Etanercept	34,232	45,078	32,528	36,241	33,523	28,343	34,866
Certolizumab	35,365	47,842	34,288	37,456	34,642	29,303	35,985

In common with the AS scenarios, the ICER estimates appeared to remain relatively stable across the majority of scenarios compared to the base-case ICER estimates. However, the impact of applying adjustments to the conditional baseline estimates and BASDAI/BASFI scores provided by the manufacturers (Scenario 2) had less of an impact in the nr-axSpA population. The scenario which showed the largest variation compared to the base-case analysis was Scenario 1. This scenario was based on results from the extended synthesis which excluded any placebo effect and resulted in a single baseline applied to all conventional care patients. The differences in the ICERs appear largely as a result of the impact of ignoring the non-linear relationship between baseline BASDAI/BASFI scores due to variation in the baseline of responders vs. non-responders in Scenario 1. Interestingly, the impact of this approach appears more marked in the nr-axSpA population, compared to the AS population, which is likely to be driven by several inter-related factors including the magnitude of difference assumed between the conditional baseline scores and the absolute BASDAI and BASFI scores which differ across the populations.

7.8 Discussion and comparison with manufacturer models

Based on an underlying assumption of similarity in the clinical effectiveness of each of the anti-TNFs, the York model demonstrates that the cost-effectiveness results are dependent on several factors, including: (i) the different acquisition and administration costs; (ii) the rebound assumption applied to patients who discontinue therapy; (iii) the magnitude of the change in BASDAI/BASFI scores assumed for responders vs. non-responders; (iv) the different baseline BASDAI/BASFI scores assumed for responders vs non-responders and (v) the impact of anti-TNFs on the rate of longer term BASFI progression.

Interestingly, the importance of specific factors also appears to vary across the separate indications. For example, the impact of the alternative rebound assumptions appears more marked in the AS population compared to the nr-axSpA population. This appears largely driven the smaller rate of BASFI progression applied in the York model to the nr-axSpA population, such that the impact of

alternative assumptions regarding possible rebound effects has a less significant impact within this population. This difference also has an important bearing on the subsequent interpretation of the base-case ICERs estimated by the York model in the separate populations. Our findings suggest that the ICER estimates for anti-TNFs appear more favourable for the AS population, relative to those estimated for the nr-axSpA population, based on the rebound equal to gain scenario. The more favourable results in the AS population based on the rebound equal to gain scenario appears to be driven by 2 main factors: (i) the smaller conditional change in BASDAI/BASFI scores estimated for the nr-axSpA population and (ii) the lower rate of BASFI progression assumed for the nr-axSpA population. However, this finding appears reversed in the rebound to conventional care scenario. Interestingly, within this scenario, the lower conditional change in BASDAI/BASFI scores appears offset by the less significant influence of BASFI progression in the nr-axSpA model. That is, the impact on the ICERs of the 2 rebound assumptions is closely related to the underlying rate of BASFI progression assumed and the contribution that this makes to the respective ICER estimates under the separate scenarios. However, it should also be noted that, although the ICERs for the nr-axSpA population appear more favourable in this scenario compared to those estimated for the AS population, all of the ICER estimates exceeded £30,000 per QALY in the York base-case across both populations.

Tables 105 and 106 compare the results of the York model with the base-case results reported by each manufacturer for the alternative populations. In contrast to the manufacturer models which reported a single base-case based on an assumption of either rebound equal to gain (AbbVie, Pfizer, MSD) or rebound to conventional care (UCB), the York model presents both rebound scenarios in order to represent the potential limits to the ICER; recognising that the reality lies somewhere between these scenarios.

Table 105 - Comparison of cost-effectiveness results from York model vs manufacturers (AS population)

	AbbVie	UCB	Pfizer	MSD	York (Rebound equal to gain)	York (Rebound to conventional care)
	ICER (£)	ICER (£)	ICER (£)	ICER (£)	ICER (£)	ICER (£)
Conventional care	-	-	-	-	-	-
Adalimumab	16,391	19,932	20,909	19,275	21,170	36,695
Certolizumab	17,067	16,647*	19,586*	19,401*	19,240*	33,762*
Etanercept	16,897	19,272	20,938	21,972	21,577	37,322
Golimumab	16,535	19,049	21,288	19,070	21,079	36,554
Infliximab	44,448	42,671	37,741	42,532	40,576	66,529

*PAS costs assumed for certolizumab

Table 106 - Comparison of cost-effectiveness results from York model vs manufacturers (nr-axSpA population)

	AbbVie (Adalimumab)	UCB (Certolizumab)	Pfizer (Etanercept)	York (Rebound equal to gain)	York (Rebound to conventional care)
	ICER (£)	ICER (£)	ICER (£)	ICER (£)	ICER (£)
Conventional care	-	-	-	-	-
Adalimumab	13,228	30,370	23,242	29,988	33,639
Certolizumab	12,866	15,615*	23,575*	28,247*	32,528*
Etanercept	Not Assessed	50,692	23,195	29,253	34,232

*PAS costs assumed for certolizumab

Although there are a number of important differences in approaches both amongst the different manufacturer models and compared to the York model, the comparison of ICERs based on the York rebound equal to gain scenario appear broadly consistent in the AS population. This might appear surprising given that the York model is based on 2 key assumptions that appear less favourable than those used by manufacturers, specifically: (i) incorporating separate baseline BASDAI/BASFI scores for responders and non-responders which assume that responders are likely to be less severe in terms of their baseline BASDAI and BASFI scores than non-responders and (ii) only incorporating an effect of anti-TNFs on disease progression for patients remaining on therapy for at least 4-years. However, these appear counterbalanced by the higher rate of BASFI progression applied to AS patients (0.082 [0-10 scale] units per annum compared to estimates between 0.056 and 0.07 assumed by the manufacturers). As we highlighted at the start of this section, it is our view that the York model has a more coherent basis for modelling longer term BASFI progression.

Another important counterbalancing effect is the use of the conditional scores for responders and non-responders obtained via the extended synthesis within the York model. This contrasts with the

selective approaches (i.e. using conditional scores from single studies or assumptions) or use of longer term follow-up and/or open-label sources (i.e. implicitly assuming that patients who continue to participate in longer-term follow up and open label sources are more likely to be responders than patients who do not). Consequently, the change scores assumed in the York model for BASDAI50 responders appear higher than those assumed by several of the manufacturers. The approach applied within the York model is based on a more generalised framework for synthesis and hence utilises more evidence than considered by the manufacturers. This approach directly informs the conditional change scores which are fundamental to an appropriate assessment of the cost-effectiveness when a response-based assessment is incorporated to determine eligibility for continued treatment.

In Section 5 it was noted that there appeared more variation in the ICER estimates reported across the manufacturer submissions in the nr-axSpA population compared to those reported in the AS population. Again, the ICER estimates reported by the York model in the nr-axSpA population do not appear inconsistent with the range of ICERs reported across the separate manufacturers. However, any attempt to formally cross-validate the results from the York model with those reported by the manufacturers is difficult given the contrasting approaches and assumptions employed. Since the York model utilises several of the key parameter inputs reported in the submission by Pfizer, a comparison may be more usefully made by comparing the results between the York model and those reported by Pfizer. In general the ICER estimates appear less favourable in the York model compared to those reported by Pfizer. One possible explanation for these differences is that the York model employs a lower rate of BASFI progression and only assumes that anti-TNFs affect this rate after at least 4-years of treatment. However, our results have also shown that the impact of progression appears less of a driver of cost-effectiveness in the nr-axSpA model. Another possible explanation is the use of different baselines assumed for responders and non-responders assumed in the York model. That is, the York model assumes that responders and typically less severe in terms of baseline BASDAI/BASFI scores compared to non-responders. Consequently, an additional scenario was undertaken using the York model to further assist in cross-validation. For this scenario, an assumption was made that the responders and non-responders did not differ in terms of baseline BASDAI/BASFI scores.

The results of the additional validation scenario are reported in Table 107. The ICERs in this scenario appeared closer to those reported by Pfizer. Hence, this additional validation scenario is important in helping to identify potential drivers of difference between the results of the York model and those reported by the manufacturers. The scenario also demonstrates that the assumption made concerning potential differences (and the magnitude of any difference) between the baseline BASDAI/BASFI scores of responders and non-responders has an important impact on the cost-effectiveness results. Hence, studies which are based on similar baselines are likely to be potentially overly optimistic in the

subsequent ICER estimates reported for anti-TNFs. Equally, it might be argued that the results from the York base-case model maybe conservative towards the anti-TNFs, since the magnitude of differences in the baseline scores estimated from the extended synthesis model appeared higher than those obtained on request from manufacturers (although the direction of the difference was consistent). Hence, in a similar manner to which the different rebound assumptions represent the potential limits on the ICER given uncertainties surrounding rebound, the differences in the ICERs based on assuming no difference in baselines and the magnitude of differences employed in the York base-case may also represent the limits of the ICER based on uncertainty surrounding the magnitude of this difference. Given the potential importance of this assumption, Appendix 15 reports the full ICER results for each population (and under each rebound assumption) assuming identical baselines for responders and non-responders.

Table 107 - Nr-axSpA – Additional validation scenario (rebound equal to gain and responders/non-responders do not differ in terms of baseline BASDAI/BASFI scores)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	9.977	-	88,692	-	-	-	-
Certolizumab (PAS)	11.551	1.574	125,205	36,513	23,199	0.390	0.759
Adalimumab	11.551	1.574	126,606	37,914	24,089	0.341	0.733
Etanercept	11.551	1.574	127,350	38,658	24,562	0.319	0.720
Certolizumab	11.551	1.574	128,777	40,085	25,469	0.272	0.702

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Although the York model provides a number of significant developments to existing cost-effectiveness analyses, there are still several potential limitations. Firstly, in common with all existing models, subsequent linkages to costs and QALYs are related to BASDAI and BASFI, largely due to the existence of data. Secondly, the cost-effectiveness estimates are based on uncertain projections of BASDAI and BASFI over a longer time-horizon in order to generate more appropriate lifetime estimates of costs and QALYs required for cost-effectiveness assessments. Although extensive efforts have been made to identify a more appropriate basis for informing these longer term estimates (particularly for BASFI), inevitably, significant uncertainty remains. Thirdly, it should be noted that there are potential benefits which have not been formally captured and quantified within the current model. Specifically any potential impact on productivity costs and any additional benefits that anti-TNFs may confer for other co-morbidities (e.g. IBD, psoriasis etc). A final limitation is that it was not possible to include the generic version of infliximab (Inflectra) within the analysis since a formal list price was not available at the time of the assessment.

In addition, the York model has not specifically addressed important clinical questions concerning the issue of intermittent and sequential use of anti-TNFs. However, in the absence of robust clinical evidence from RCTs, existing evidence is clearly subject to potential confounding. Consequently, existing attempts to model sequential therapy within the current manufacturer submissions (Pfizer only) are largely based on applying simple adjustments to 1st line efficacy but which are unlikely to provide a robust basis for informing these decisions. Clearly, until such time that more robust data are available, a rough rule of thumb could similarly be applied to the results presented from the York model, such that the ICERs of a 2nd line TNF-alpha inhibitor in a patient who had previously responded but subsequently lost response, might be in the order of one-third higher than the results presented here.

Finally, it is important to appreciate that the assessments of cost-effectiveness reported in the York model are based on a normative approach. That is, they are based on the assumption that 12-week continuation rules (and ongoing monitoring of response) would be fully adhered to in clinical practice. Hence, they do not necessarily reflect the cost-effectiveness of how anti-TNFs are currently used in the management of AS within the NHS or how they might be used, in the event of positive guidance from the NICE in nr-axSpA. The findings of West Midland Rheumatology Audit from 2010 give some grounds for potential concern.[171] This regional audit was undertaken to assess compliance with the NICE guidelines (TA143) in 17 rheumatology centres across the East and West Midlands. The findings from this audit revealed that: (i) the proportion of patients being assessed at 12 weeks after treatment initiation was sub-optimal; (ii) less than 20% of patients with an inadequate response at 12 weeks had their treatment discontinued and (iii) less than half of the patients received regular 12 weekly assessments. During the course of our assessment we contacted the BSRBR Ankylosing Spondylitis Register to assess the feasibility of obtaining access to data which has been collected since the register was set up in 2012. Although our request was positively received, it was clear during ongoing discussions that the data and analyses requested could not be undertaken within the timeframe of our assessment.

8 Assessment of factors relevant to the NHS and other parties

The results of this technology assessment have some implications for clinical practice. Existing NICE guidance recommends adalimumab, certolizumab, etanercept, and golimumab for the treatment of AS and therefore their use is already widespread in the NHS. However, in the light of the additional evidence presented here the use of these agents in AS may increase further.

Furthermore the available clinical evidence indicates that adalimumab, certolizumab and etanercept and are effective in patients with nr-axSpA, although there is some uncertainty regarding the definition of the nr-axSpA patient population who would benefit most from these anti-TNFs. The

effectiveness demonstrated in the nr-axSpA population suggests that early treatment of AS/nr-axSpA patients is warranted. A key study on flares in AS suggested that the 12 week period required to confirm sustained active spinal disease in AS patients commencing an anti-TNF may be too long. The findings suggest that shorter time-periods might therefore be considered in future guidance, which would minimise the delay in starting treatment and the discomfort experienced by patients.

The potential extra cost to the NHS of providing anti-TNFs for patients with nr-axSpA in addition to AS patients is unclear since the prevalence of nr-axSpA in the UK is somewhat uncertain. The potentially large volume of new patients to be assessed for eligibility for anti-TNF treatment could add a large burden to existing services. NICE guidance recommending the use of adalimumab, certolizumab and etanercept in nr-axSpA would further increase the impact of these agents on the NHS budget.

9 Discussion

Statement of principal findings

The systematic review of clinical efficacy identified a substantial, and generally high quality evidence-base on the efficacy and safety of anti-TNFs in patients with AS, either as individual treatments or as a common class; there was limited evidence to suggest meaningful differences between the therapies in terms of efficacy, other than infliximab providing more rapid improvements during the first few months of treatment. The results of our meta-analyses demonstrated that anti-TNFs (when compared with placebo) produce statistically significant and clinically important benefits in patients with AS in terms of improving function and reducing disease activity over a three to six month period (none of the trials maintained randomised treatment allocations across groups beyond six months). Of the limited number of trials which reported quality of life outcomes, significant improvements were found following anti-TNF therapy, but very little data were available on efficacy relating to any peripheral symptoms (other than enthesitis) or other possible symptoms such as uveitis, inflammatory bowel disease, and psoriasis.

Although far fewer trials have been performed in the nr-axSpA population, similar, though slightly smaller, benefits were achieved. The smaller benefit was most noticeable for the function (BASFI) and disease activity (BASDAI 50) outcomes. However, in the nr-axSpA trials, both clinical and statistical heterogeneity were evident, bringing into question both the reliability of the nr-axSpA meta-analysis results and their true relevance to patients seen in clinical practice. This heterogeneity may have been compounded by the inclusion criteria applied in previous nr-axSpA trials. For example, ABILITY-1 recruited patients who fulfilled the ASAS classification criteria and relied on the expertise of the local clinicians and/or radiologists to read SIJ radiographs and MRI scans, as

happens in real clinical practice. RAPID-axSpA selected its population carefully by requiring objective evidence of disease activity at study entry either by a positive MRI showing signs of SIJ inflammation according to the ASAS/OMERACT definition, or an elevated than normal CRP. The difficulty of identifying which nr-axSpA patients should receive anti-TNFs remains.

Results from open-label trial extension studies suggested that across all the anti-TNFs around half of patients still achieve a good level of response after around two years of treatment. The data also suggest that at five years around 60% of golimumab patients, 50% of etanercept patients and 30% of adalimumab patients still achieve a good treatment response. However, these longer-term studies were not as well-reported as the RCTs, and their results were derived from less reliable data; it is therefore unknown if these are true treatment differences, or whether they are due to differences in follow-up protocols (e.g. stopping rules) and/or methods used to impute missing data.

Evidence for an effect of anti-TNFs on radiographic disease progression was limited: the relatively short-term follow-up available to date and the insensitivity of x-rays as an imaging tool precluded the drawing of firm conclusions regarding the role of anti-TNFs in preventing or delaying the progression of AS; there is some data to suggest an identifiable benefit from around four years, but results from ongoing long-term studies should help to clarify this issue.

The results from studies based on registry data demonstrated that sequential treatment with anti-TNFs can be worthwhile in patients with AS. However, the drug survival, response rates, and benefits were reduced with second and third anti-TNFs, with the proportion of BASDAI 50 responders falling approximately 10% with each subsequent anti-TNF and the median BASDAIs and BASFIs achieved increasing (worsening).

Data from large systematic reviews, which included patients with a wide range of diseases, suggest that, in the short-term, anti-TNFs as a group are associated with significantly higher rates of serious infections, TB reactivation, non-melanoma skin cancer, total adverse events, and withdrawals due to adverse events, when compared with control treatments. Specifically, infliximab is associated with significantly higher rates of total adverse events and withdrawals due to adverse events, and certolizumab pegol is associated with significantly higher rates of serious infections and serious adverse events. Evaluations of longer-term data are more scarce, and are limited by small sample sizes and uncontrolled designs. They suggest similar safety profiles across anti-TNFs, other than a higher incidence of injection site reactions following treatment with etanercept.

The systematic review of cost-effectiveness studies revealed significant conceptual issues and uncertainties arising from previously published studies and the submissions made by manufacturers. For this reason, a *de-novo* model (‘York model’) was developed. Although it shared some of the

assumptions and parameter estimates from the manufacturer models, it was based on a different conceptual structure and applies a more generalised framework for the synthesis of data from the double-blind periods of existing RCTs, combined with a more explicit approach to modelling the progressive nature of AS and nr-axSpA and the potential impact of the TNF-alpha inhibitors.

Based on an underlying assumption of similarity in the clinical effectiveness of each of the TNF-α inhibitors, the York model demonstrates that the cost-effectiveness results are dependent on several factors, including: (i) the different acquisition and administration costs; (ii) the rebound assumption applied to patients who discontinue therapy; (iii) the magnitude of the change in BASDAI/BASFI scores assumed for responders vs. non-responders; (iv) the different baseline BASDAI/BASFI scores assumed for responders vs non-responders and (v) the impact of TNF-α inhibitors on the rate of longer term BASFI progression.

Although there are a number of important differences in approaches both amongst the different manufacturer models and compared to the York model, the comparison of ICERs based on the York rebound equal to gain scenario appear broadly consistent with those reported by the manufacturers in both populations.

9.2 Strengths and limitations of the assessment

Strengths

Through our comprehensive searches we sought to identify all relevant published and unpublished trials, which minimised the possibility of publication or language biases affecting the review results. A full evaluation of the risk of bias in each RCT was performed, which incorporated an additional assessment of key baseline characteristics to allow firmer judgements to be made on the risk of selection bias. The use of multiple-treatment meta-analyses allowed for greater precision in random effect models, and the calculation of relative risks was based on the population risk across all the trials. A key further strength of our review lies in the extensive breadth of other types of study we included, such as: non-randomised trial extension studies; registry studies of patients taking anti-TNFs; systematic reviews and other large studies of adverse effects of anti-TNFs; and a review of the natural history of AS and nr-axSpA. Our review of adverse events incorporated a wealth of data from RCTs in patients on anti-TNFs with diseases other than AS and nr-axSpA, although the results only relate to short-term use. Our review was performed according to CRD guidance, so the potential for reviewer errors and biases was minimised. Our review was reported according to the PRISMA statement.

The York model confers several advantages over current cost-effectiveness studies by linking changes in BASFI to a more explicit clinical/biological process and facilitating a more formal consideration of the potential impact of TNF-alpha inhibitors on BASFI, via the specific effects these drugs have on

the different processes which independently relate to this parameter. This approach allows consideration of the impact on BASFI that might be achieved via symptomatic improvements (i.e. in terms of reductions in disease activity) and those which might be conferred by disease modification properties (i.e. the effect on the likelihood and/or rate of further radiographic progression). The latter aspect is particularly important given the increasing amount of published evidence reported on the potential impact of TNF-alpha inhibitors on radiographic progression which has not been formally considered or incorporated within existing cost-effectiveness studies. In addition, the evidence synthesis approach which underpins the York model is based on a joint synthesis of related parameters which makes fuller use of existing evidence and which can more appropriately estimate the input parameters and better characterise the uncertainty surrounding these.

Limitations

A key limitation of the systematic review was the variation in the reporting of outcomes across trials. ASAS 20 was the most commonly reported responder outcome, but its value in determining efficacy was somewhat limited by the relatively high rates of 'placebo' response associated with the 20% threshold. Results for 40%, 50%, and 70% improvements (i.e. ASAS 40, ASAS 50 and ASAS 70) were reported less frequently, despite the fact that trial investigators would have had the data available to do so. Many trials did not report health-related quality of life outcomes and most trials were also limited in their assessment (or reporting) of improvement in any peripheral symptoms or symptoms of extra-articular manifestations. Although largely free of important biases, most RCTs had quite short durations (generally around 3 months) and several were limited by their small sample sizes (increasing the possibility of chance results for some outcomes).

Although we sought data beyond those available from RCTs, much of the data reported in studies using other designs may have been affected by biases or confounding; furthermore, key method details (e.g. imputation methods, or anti-TNF stopping rules) were often absent from publications. Much less reliability and certainty could therefore be ascribed to the results obtained from these other studies.

The York model did not directly address important clinical questions concerning the issue of intermittent and sequential use of ant-TNFs due to the lack of robust clinical evidence from RCTs.

9.3 Uncertainties

- The magnitude of treatment effect of anti-TNFs in patients with nr-axSpA remains uncertain due to the heterogeneous nature of the trials performed to date.

- The limited design and reporting of the studies looking at the long-term use of anti-TNFs means there is uncertainty as to whether there are differences in efficacy between the different anti-TNFs in the long-term.

- The evidence on the long-term risk of adverse events is uncertain due to small study sample sizes, and the study designs used.

- The long-term impact of anti-TNFs on other important outcomes in AS and nr-axSpA remain uncertain, such as AS-related causes of death (cardiac valvular disease, amyloidosis and fractures), and extra-articular symptoms such as uveitis, inflammatory bowel disease, and psoriasis. Studies based on ongoing anti-TNF registries (e.g. BSRBR, which record such data) should inform this.

- With the patents of some anti-TNFs studied in this assessment due to expire shortly, biosimilars are likely to become available in the next few years (Inflectra will become available early in 2015). As they are difficult to produce, the number of biosimilars which become available, and their price, is uncertain.

10 Conclusions

Meta-analysis results derived from a substantial, and generally high quality evidence-base on the efficacy of anti-TNFs in patients with AS (considered either as individual treatments or as a common class) show statistically significant and clinically important benefits in terms of improved function and reduced disease activity. Smaller benefits were seen across outcomes in patients with nr-axSpA, being most noticeably smaller for the function and disease activity outcomes. Data from (less robust) observational studies suggest that good levels of treatment response are maintain in around 50% of patients after around two years of treatment. Evidence for an effect of anti-TNFs on radiographic disease progression is limited, although results from ongoing studies should clarify whether or not progression rates are reduced in the longer-term. The results from studies based on registry data demonstrated that sequential treatment with anti-TNFs can be worthwhile in patients with AS, although the drug survival, response rates, and benefits were reduced with second and third anti-TNFs. Data from large systematic reviews, which included patients with a wide range of diseases, suggested that, in the short-term, anti-TNFs as a group were associated with significantly higher rates of serious infections, TB reactivation, non-melanoma skin cancer, total adverse events, and withdrawals due to adverse events, when compared with control treatments. Longer-term data on adverse effects were limited.

10.1 Implications for service provision

- From our review of natural history a key study on flares suggested that the 12 week period required to confirm sustained active spinal disease in AS patients commencing an anti-TNF may be too long. The findings suggest that shorter time-periods might therefore be considered in future guidance, which would minimise the delay in starting treatment and the discomfort experienced by patients.

10.2 Suggested research priorities

- Randomised trials are needed to identifying the nr-axSpA population who will benefit the most from TNF-inhibitors: trials using stratified randomisation and pre-planned analyses by stratified group should inform this issue. Groups could be stratified according to their imaging status (i.e. MRI positive or not) and their CRP level; both the cut-offs to be used for CRP elevation, and the eligibility criteria used for CRP elevation, should be given careful consideration, given the variation evident in previous trials. These studies should help to inform clearer guidance as to what ASAS and the anti-TNF licenses mean when referring to 'elevated CRP' in patients with nr-axSpA. In the previous nr-axSpA trials the placebo-controlled phases typically lasted around 3 months; a placebo-controlled follow up period of at least 6 months in future trials would therefore be useful for studying persistence of response.
- Long-term longitudinal studies are needed on the natural history of nr-axSpA to help clarify the characteristics of patients who do (or do not) eventually develop AS. Similar to the RCT recommendations, these studies should include analyses stratified by how patients were diagnosed: a comparison of patients with imaging (MRI) evidence of nr-axSpA versus patients who are diagnosed with only clinical criteria evidence, would be particularly useful, albeit difficult to perform.
- Large, long-term longitudinal, cohort studies are needed to clarify the effect of anti-TNFs on the progression of structural damage in AS. In the absence of a gold standard imaging tool across the spectrum from nr-axSpA to AS, sequential MRI and x-ray assessment should be used at pre-defined endpoints to ascertain the true sensitivity and specificity of these tools in the diagnosis and assessment of neo-formation and ankyloses characteristic of structural progression in the spine and sacroiliac joints of these patients.
- Studies are also needed to better inform the efficacy estimates relating to sequential use of anti-TNFs. An ongoing study is looking at comparing the effect of intermittent versus standard use of anti-TNFs in patients with stable (low active) disease.[172]

11 Appendices

11.1 Appendix 1 Search strategies for clinical and economic reviews

MEDLINE & MEDLINE In-Process

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Searched 05/06/14 via OVID interface

Strategy;

1 spondylarthritis/ or spondylitis, ankylosing/ (12386)

2 ((ankyl$ or axial) adj2 spondyl$).ti,ab. (10322)

3 (ankyl$ adj2 (spine$ or spinal or vertebra$)).ti,ab. (402)

4 ((Bechtere$ or Bekhtere$ or "Marie Strumpell$" or "Marie Struempell$") adj2 (disease or syndrome)).ti,ab. (451)

5 1 or 2 or 3 or 4 (14886)

6 (adalimumab or humira or 331731-18-1).af. (3751)

7 (certolizumab or CDP870 or cimzia or 428863-50-7).af. (497)

8 (etanercept or enbrel or altebrel or 185243-69-0).af. (5540)

9 (golimumab or CNTO 148 or simponi or 476181-74-5).af. (328)

10 (infliximab or remicade or 170277-31-3 or inflectra or remsima or CT-P13).af. (9166)

11 6 or 7 or 8 or 9 or 10 (13950)

12 randomized controlled trial.pt. (375396)

13 controlled clinical trial.pt. (88473)

14 randomized.ab. (295232)

15 placebo.ab. (154473)

16 drug therapy.fs. (1704080)

17 randomly.ab. (213686)

18 trial.ab. (306623)

19 groups.ab. (1359351)

20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (3348700)

21 animals/ not (animals/ and humans/) (3855883)

22 20 not 21 (2872482)

23 5 and 11 and 22 (1008)

EMBASE

Database: Embase 1974 to 2014 Week 22

Searched 05/06/14 via OVID interface

Strategy;

1 exp spondylarthritis/ or exp ankylosing spondylitis/ (20531)

2 ((ankyl$ or axial) adj2 spondyl$).ti,ab. (14760)

3 (ankyl$ adj2 (spine$ or spinal or vertebra$)).ti,ab. (542)

4 ((Bechtere$ or Bekhtere$ or "Marie Strumpell$" or "Marie Struempell$") adj2 (disease or syndrome)).ti,ab. (551)

5 1 or 2 or 3 or 4 (22426)

6 (adalimumab or humira or 331731-18-1).af. (15439)

7 (certolizumab or CDP870 or cimzia or 428863-50-7).af. (3097)

8 (etanercept or enbrel or altebrel or 185243-69-0).af. (19368)

9 (golimumab or CNTO 148 or simponi or 476181-74-5).af. (2124)

10 (infliximab or remicade or 170277-31-3 or inflectra or remsima or CT-P13).af. (29667)

11 6 or 7 or 8 or 9 or 10 (41065)

12 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).ti,ab,kw. (1351644)

13 crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/ (390984)

14 12 or 13 (1428385)

15 5 and 11 and 14 (603)

16 limit 15 to embase (581)

17 animals/ not (animals/ and humans/) (1188711)

18 16 not 17 (581)

CINAHL Plus

Database: CINAHL Plus

Searched 05/06/14 via EBSCO interface

Strategy;

S19 S6 AND S12 AND S18 (87)

S18 S13 OR S14 OR S15 OR s16 OR S17 (148,267)

S17 singl* N blind* or doubl* N blind* or singl* N mask* or doubl* N mask (285)

S16 (ZT "randomized controlled trial") (38,240)

S15 (allocate* or assign* or divid*) N5 (condition* or experiment* or treatment* or control* or group*) (26,737)

S14 crossover or "cross over" or "latin square" or placebo* (41,898)

S13 randomi* or random N allocate* or random N assign* or random N divid* or random N trial* or random N study or random N studies (108,710)

S12 S7 OR S8 OR S9 OR S10 OR S11 (3,091)

S11 TX (infliximab or remicade or 170277-31-3 or inflectra or remsima or CT-P13) (1,792)

S10 TX (golimumab or CNTO 148 or simponi or 476181-74-5) (119)

S9 TX (etanercept or enbrel or altebrel or 185243-69-0) (1,298)

S8 TX (certolizumab or CDP870 or cimzia or 428863-50-7 (91)

S7 TX (adalimumab or humira or 331731-18-1) (647)

S6 S1 OR S2 OR S3 OR S4 OR S5 (2,566)

S5 TX ((Bechtere* or Bekhtere* or "Marie Strumpell*" or "Marie Struempell*") N2 (disease or syndrome)) (3)

S4 TX (ankyl* N2 (spine* or spinal or vertebra*)) (91)

S3 TX ((ankyl* or axial) N2 spondyl*) (2,277)

S2 MH spondylitis, ankylosing (1,803)

S1 MH spondylarthritis (500)

Science Citation Index

Searched 16/06/14 via Web of Science

Indexes=SCI-EXPANDED Timespan=1900-2014

Strategy;

13 1,001 #12 AND #11 AND #5

12 2,435,907 TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*)

11 20,446 #10 OR #9 OR #8 OR #7 OR #6

10 13,285 TOPIC: ((infliximab or remicade or 170277-31-3 or inflectra or remsima or CT-P13))

9 494 TOPIC: ((golimumab or CNTO 148 or simponi or 476181-74-5))

8 7,138 TOPIC: ((etanercept or enbrel or altebrel or 185243-69-0))

7 916 TOPIC: ((certolizumab or CDP870 or cimzia or 428863-50-7))

6 4,754 TOPIC: ((adalimumab or humira or 331731-18-1))

5 14,918 #4 OR #3 OR #2 OR #1

4 191 TOPIC: (((Bechtere* or Bekhtere* or "Marie Strumpell*" or "Marie Struempell*") NEAR/2 (disease or syndrome)))

3 644 TOPIC: ((ankyl* NEAR/2 (spine* or spinal or vertebra*)))

2 13,854 TOPIC: (((ankyl* or axial) NEAR/2 spondyl*))

1 2,394 TOPIC: (spondylarthritis OR spondyloarthritis)

NIH ClinicalTrials.gov Register

Searched 23/07/14 online at http://clinicaltrials.gov/ct2/search

Strategy;

((spondylarthritis OR spondyloarthritis OR spondylitis) AND (infliximab OR remicade OR inflectra OR remsima OR golimumab OR simponi OR etanercept OR enbrel OR altebrel OR certolizumab OR cimzia OR adalimumab OR humira))

160 results

Cochrane Library (includes Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), Cochrane Central Register of Controlled Trials (CENTRAL) and NHS Economic Evaluation Database (NHSEED)

Searched 05/06/14 online at http://onlinelibrary.wiley.com/o/cochrane/cochrane_search_fs.html

Strategy;

#1 MeSH descriptor: [Spondylitis, Ankylosing] explode all trees

#2 MeSH descriptor: [Spondylarthritis] explode all trees

#3 ((ankyl* or axial) near/2 spondyl*):ti,ab,kw (Word variations have been searched)

#4 (ankyl* near/2 (spine* or spinal or vertebra*)):ti,ab,kw (Word variations have been searched)

#5 ((Bechtere* or Bekhtere* or "Marie Strumpell*" or "Marie Struempell*") near/2 (disease or syndrome)):ti,ab,kw

#6 #1 or #2 or #3 or #4 or #5

#7 (adalimumab or humira or 331731-18-1):ti,ab,kw

#8 (certolizumab or CDP870 or cimzia or 428863-50-7):ti,ab,kw

#9 (etanercept or enbrel or altebrel or 185243-69-0):ti,ab,kw

#10 (golimumab or CNTO 148 or simponi or 476181-74-5):ti,ab,kw

#11 (infliximab or remicade or 170277-31-3 or inflectra or remsima or CT-P13):ti,ab,kw

#12 #7 or #8 or #9 or #10 or #11

#13 #6 and #12

284 total results comprised of 2 CDSR, 5 DARE, 21 HTA, 233 CENTRAL and 14 NHSEED.

Conference Proceedings Citation Index - Science

Searched 02/09/14 via Wiley Web of Science interface

Indexes=CPCI-S Timespan=1900-2014

Strategy;

12 341 #11 AND #5

11 4,745 #10 OR #9 OR #8 OR #7 OR #6

10 2,537 TOPIC: ((infliximab or remicade or 170277-31-3 or inflectra or remsima or CT-P13))

9 141 TOPIC: ((golimumab or CNTO 148 or simponi or 476181-74-5))

8 1,221 TOPIC: ((etanercept or enbrel or altebrel or 185243-69-0))

7 291 TOPIC: ((certolizumab or CDP870 or cimzia or 428863-50-7))

6 1,140 TOPIC: ((adalimumab or humira or 331731-18-1))

5 2,117 #4 OR #3 OR #2 OR #1

4 4 TOPIC: (((Bechtere* or Bekhtere* or "Marie Strumpell*" or "Marie Struempell*") NEAR/2 (disease or syndrome)))

3 55 TOPIC: ((ankyl* NEAR/2 (spine* or spinal or vertebra*)))

2 1,906 TOPIC: (((ankyl* or axial) NEAR/2 spondyl*))

1 393 TS=(spondylarthritis OR spondyloarthritis)

International Prospective Register of Systematic Reviews (PROSPERO)

Searched 07/10/14 online at http://www.crd.york.ac.uk/prospero/search.asp

Strategy;

spondylitis [In All Fields]

OR

spondylarthritis [In All Fields]

OR

spondyloarthritis [In All Fields]

6 results.

National Guideline Clearinghouse

Searched 07/10/14 online at http://www.guideline.gov/

Strategy;

spondylitis OR spondylarthritis OR spondyloarthritis

15 results

NHS Evidence

Searched 27/10/14 online at https://www.evidence.nhs.uk/

Strategy;

((((ankyl* or axial) near/2 spondyl*) OR (ankyl* near/2 (spine* or spinal or vertebra*)) AND (adalimumab or humira or certolizumab or CDP870 or cimzia or etanercept or enbrel or altebrel or golimumab or CNTO 148 or simponi or infliximab or remicade or inflectra or remsima or CT-P13))

350 results

NHS Clinical Knowledge Summaries

Searched 27/10/14 online at http://cks.nice.org.uk/#?char=A

1 result for ankylosing spondylitis.

Searches for economic review

NHS Economic Evaluation Database (NHSEED)

Searched 05/06/14 online at http://onlinelibrary.wiley.com/o/cochrane/cochrane_search_fs.html

Strategy;

#1 MeSH descriptor: [Spondylitis, Ankylosing] explode all trees

#2 MeSH descriptor: [Spondylarthritis] explode all trees

#3 ((ankyl* or axial) near/2 spondyl*):ti,ab,kw (Word variations have been searched)

#4 (ankyl* near/2 (spine* or spinal or vertebra*)):ti,ab,kw (Word variations have been searched)

#5 ((Bechtere* or Bekhtere* or "Marie Strumpell*" or "Marie Struempell*") near/2 (disease or syndrome)):ti,ab,kw

#6 #1 or #2 or #3 or #4 or #5

#7 (adalimumab or humira or 331731-18-1):ti,ab,kw

#8 (certolizumab or CDP870 or cimzia or 428863-50-7):ti,ab,kw

#9 (etanercept or enbrel or altebrel or 185243-69-0):ti,ab,kw

#10 (golimumab or CNTO 148 or simponi or 476181-74-5):ti,ab,kw

#11 (infliximab or remicade or 170277-31-3 or inflectra or remsima or CT-P13):ti,ab,kw

#12 #7 or #8 or #9 or #10 or #11

#13 #6 and #12

14 results

Searches for EQ5D;

MEDLINE

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Searched 16/06/14 via OVID interface

Strategy;

1 spondylarthritis/ or spondylitis, ankylosing/ (12394)

2 ((ankyl$ or axial) adj2 spondyl$).ti,ab. (10334)

3 (ankyl$ adj2 (spine$ or spinal or vertebra$)).ti,ab. (402)

4 ((Bechtere$ or Bekhtere$ or "Marie Strumpell$" or "Marie Struempell$") adj2 (disease or syndrome)).ti,ab. (451)

5 1 or 2 or 3 or 4 (14899)

6 (5d or 5-d or 5 dimension or eq-5d or eq5d or eq 5d).ti,ab. (13976)

7 5 and 6 (27)

EMBASE

Database: Embase <1974 to 2014 June 13>

Searched 16/06/14 via OVID interface

Strategy;

1 exp spondylarthritis/ or exp ankylosing spondylitis/ (20653)

2 ((ankyl$ or axial) adj2 spondyl$).ti,ab. (14855)

3 (ankyl$ adj2 (spine$ or spinal or vertebra$)).ti,ab. (545)

4 ((Bechtere$ or Bekhtere$ or "Marie Strumpell$" or "Marie Struempell$") adj2 (disease or syndrome)).ti,ab. (552)

5 1 or 2 or 3 or 4 (22550)

6 (5d or 5-d or 5 dimension or eq-5d or eq5d or eq 5d).ti,ab. (17019)

7 5 and 6 (60)

8 limit 7 to embase (55)

Searches for economic models;

MEDLINE

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Searched 25/07/14 via OVID interface

Strategy;

1 spondylarthritis/ or spondylitis, ankylosing/ (12505)

2 ((ankyl$ or axial) adj2 spondyl$).ti,ab. (10436)

3 (ankyl$ adj2 (spine$ or spinal or vertebra$)).ti,ab. (407)

4 ((Bechtere$ or Bekhtere$ or "Marie Strumpell$" or "Marie Struempell$") adj2 (disease or syndrome)).ti,ab. (455)

5 1 or 2 or 3 or 4 (15038)

6 exp models, economic/ (10268)

7 ((economic$ or cost$ or pric$ or value or statistic$) and model$).ti,ab. (245686)

8 6 or 7 (250668)

9 5 and 8 (107)

EMBASE

Database: Embase <1974 to 2014 July 24>

Searched 25/07/14 via OVID interface

Strategy;

1 exp spondylarthritis/ or exp ankylosing spondylitis/ (20858)

2 ((ankyl$ or axial) adj2 spondyl$).ti,ab. (14996)

3 (ankyl$ adj2 (spine$ or spinal or vertebra$)).ti,ab. (553)

4 ((Bechtere$ or Bekhtere$ or "Marie Strumpell$" or "Marie Struempell$") adj2 (disease or syndrome)).ti,ab. (553)

5 1 or 2 or 3 or 4 (22760)

6 statistical model/ (102203)

7 ((economic$ or cost$ or pric$ or value or statistic$) adj2 model$).ti,ab. (24642)

8 6 or 7 (119366)

9 5 and 8 (63)

10 limit 9 to embase (55)

11.2 Appendix 2 Synthesis methods for clinical efficacy network meta-analyses

Estimating standard deviations from inter-quartile ranges

Where Q_1 is the lower quartile, Q_3 is the upper quartile, and σ is the standard deviation then the standard deviation was estimated as

$$\sigma = \frac{(Q_3 + Q_1)}{2 \times 0.67}$$

Calculating change from baseline outcomes and standard deviations

Given baseline and final values and their standard deviations, the change from baseline values and standard deviations can be calculated if the within-study correlation between baseline and final values is known. Similarly, the final values can be computed.

The within-study correlation ρ between baseline and final values can be calculated as follows as stated in the Cochrane Handbook, where

$$\rho = \frac{SD_{baseline}^2 + SD_{final}^2 - SD_{change}^2}{2 \times SD_{final} \times SD_{baseline}}$$

The standard deviation of the change from baseline can be found by rearranging the above equation. The standard deviation of the final value can be found by rearranging the above equation which produces a quadratic. As a range of correlation estimates were obtained from the studies available, we tested 0.3 and 0.7 correlation estimates in our analyses. In calculating the standard deviation of final values, this sometimes resulted in complex roots. In these cases, the lowest correlation estimate that allowed a real root was used in the calculation.

Prior distribution for the between-study standard deviation for the placebo absolute risk

In running fixed effect and random effect models to estimate the placebo absolute risk, the random effect models had better fit. For ASAS 70 response, there were insufficient trials to run a random effects model, so a prior distribution for the between-study standard deviation was specified. This was derived from the between-study standard deviation from the ASAS40 analysis. The prior distribution was specified as a log-normal distribution and the log-normal distribution parameters μ and σ^2 were derived from the following equations.

$$Mean = e^{\mu + {\sigma^2}/{2}}$$

$$Median = e^{\mu}$$

I-squared

As noted in Higgins et al.[173], the I-squared I^2 was calculated as

$$I^2 = \frac{\tau^2}{\tau^2 + s^2}$$

where τ^2 is the between-study variance estimated in the multiple-treatment meta-analysis,

$$s^2 = \frac{\sum w_i(k-1)}{(\sum w_i)^2 - \sum w_i^2}$$

which was calculated in Excel, and w_i is the precision of study *i*.

Correlation

Table 108 presents the results for BASDAI change from baseline assuming a class effect and independent treatment effects, and assuming 0.3 and 0.7 within-study correlation. It is clear that the different correlation assumptions make no difference in this case. This is perhaps because the studies affected by the correlation assumption were small studies.

Table 108: The class and independent BASDAI change from baseline of the anti-TNFs vs placebo assuming 0.3 and 0.7 within-study correlation

	0.3 correlation		0.7 correlation	
	Mean	95% CrI	Mean	95% CrI
Class	-1.66	(-1.89 to -1.43)	-1.66	(-1.88 to -1.43)
ADA	-1.55	(-1.88 to -1.23)	-1.56	(-1.88 to -1.24)
CER	-1.46	(-2.16 to -0.74)	-1.46	(-2.16 to -0.74)
ETA	-1.76	(-2.15 to -1.37)	-1.76	(-2.15 to -1.37)
INF	-2.28	(-3.18 to -1.38)	-2.28	(-3.18 to -1.38)

11.3 Appendix 3 Risk of bias data

Table 109 Full risk of bias results

Trial	Sequence generation	Allocation concealment	Important baseline imbalance	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Exclude in sensitivity analysis?
Haibel 2008[55]	Unclear	Unclear	Unclear	Low	Low	Low	Low	N
			imbalance for HLA-B27+ and MRI+			No of withdrawals and Dropouts: 0 Imputation used for continuous outcomes: NA	All main relevant outcomes reported	
Hu 2012[59]	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear	Y

	There is no description of the randomisation procedure and no explanation for the imbalance in number of patients in treatment arms 26 vs 20	No details reported	Main prognostic indicators similar across trial arms at baseline	No details reported		No of withdrawals and Dropouts: Not reported Imputation used for continuous outcomes: NR	No reporting of adverse effects	
Huang 2014[60]	Low	Low	Low	Low	Low	Low	Low	N
	centralised computer based system	centralised computer based system	Groups comparable for all important factors	Matching placebo and all study personnel and patients stated to be blinded		No of withdrawals and Dropouts: 12 Imputation used for continuous outcomes: LOCF	All main outcomes reported	
Lambert 2007[61]	Unclear	Unclear	Low	unclear	Low	Low	low	N
			No imbalances in possible prognostic	Stated to be double blind		No of withdrawals and Dropouts:) 0 at week 12; 2 from	BASDAI not reported at	

			factors			placebo arm at week 52 Imputation used for continuous outcomes: No imputation for missing SPARCC score	follow-up	
ABILITY-1 2013[52]	Low	Low	Low	Low	Low	Low	Low	N
	Centralised randomisation with interactive voice response system			Matching placebo		No of withdrawals and Dropouts: 6 Imputation used for continuous outcomes: LOCF imputed values		
ATLAS 2006[63]	Unclear	Unclear	Low	Low	Low	Low	Low	N

			balanced across treatment arms	Matching placebo		No of withdrawals and Dropouts: 4 from placebo, 4 from active by week 12, 6 from placebo and 13 from active by week 24 (NB wk 24 still RCT though none rsponders permitted early escape after week 12) Imputation used for continuous outcomes: LOCF	Primary and all main outcomes reported	N
RAPID-axSpA (Landewe 2014)[46]	Low	Low	Low	Unclear	Low	Low	Low	N

	Central randomisation	Central randomisation	Small difference in baseline CRP and HLA-B27 positive, making placebo group slightly increased risk (but unclear possible impact)	Administration of treatment was by unblinded trained personnel. Their role in assessment is unclear and so the impact of their unblinded status is unclear		No of withdrawals and Dropouts: Unclear at 12 weeks, but at 24 weeks: PLA 10, 200mg 6, 400 mg 9. Imputation used for continuous outcomes: LOCF	Hierarchical analysis plan adhered to.	
Barkham 2010[72]	Unclear	Unclear	Unclear	Low	Low	Unclear	Low	Y
						No of withdrawals and dropouts: Unclear, although it appears to be 9 for etanercept and 8 for placebo (the number for which ASAS40 data were available).		

						Imputation used for continuous outcomes: ITT LOCF		
Davis 2003[47]	Unclear	Unclear	Low	Low	Low	Low	Low	N
						No of withdrawals and Dropouts: 12 weeks: ETA 6 pts, PLA 5 pts. 24 wks: ETA 12 pts, PLA 19 pts Imputation used for continuous outcomes: LOCF using ETA n=138, PLA n=139		
Dougados 2011[74]	Unclear	Unclear	Low	Low	Low	Low	Low	N

						No of withdrawals and Dropouts: ETA 1, PLA 4 Imputation used for continuous outcomes: mITT (at least one dose) with LOCF		
Dougados 2014[54]	Low	Low	Low	Low	Low	Low	Low	N
						No of withdrawals and Dropouts: 6 ETA, 3 PLA. In addition to this, 5 patients in each group were excluded from analyses due to misdiagnosis Imputation used for		

						continuous outcomes: LOCF in mITT population: 106 ETA, 109 PLA		
Gorman 2002[49]	Low	Low	High (chance imbalance)	Low	Low	Low	Low	Y
			BASFI			No of withdrawals and Dropouts:3 Imputation used for continuous outcomes: Not totally clear, but appears to be proper ITT with LOCF		
Calin 2004[48]	Unclear	Unclear	High	Low	Low	Low	Low	Y
			Important difference in CRP,			No of withdrawals and Dropouts: 2		

			borderline important difference in age			etanercept pts Imputation used for continuous outcomes: LOCF for mITT population (placebo n=39, ETA n=45)		
Van der Heijde 2006[51]	Unclear	Unclear	Unclear	Low	Low	Low	Low	N
			No data for HLA-B27			No of withdrawals and Dropouts: 14 in 50mg group, 14 in 25mg group, 7 in placebo group. In addition to this, 5 patients did not receive one dose of treatment (no further details). Imputation used for continuous outcomes: mITT		

						population analysed (had at least one dose) using the 155,150,51 group sizes and LOCF was used to impute missing data		
Giardina 2010[84]	High	High	Low	High	High	Low	Low	Y
						No of withdrawals and Dropouts:0 Imputation used for continuous outcomes: None needed		
GO-RAISE 2008[86]	Low	Low	Low	Low	Low	Low	Low	N

	Random assignment using voice response system	Random assignment using voice response system	No important imbalance in key prognostic variables	Matching placebo used		No of withdrawals and Dropouts:17 to week 24 (2 PLA, 9 50mg, 6 100mg). Not clear how many at week 14 (primary time point) Imputation used for continuous outcomes: LOCF (ITT population)	Primary endpoint and all other main outcomes(BAS DAI, BASFI, BASMI, SF-36) reported	
Bao 2012[91]	Unclear	Unclear	Unclear	Low	Low	Unclear	Low	N
			No HLA-B27 data			No of withdrawals and Dropouts: not reported for wk 14 Imputation used for continuous outcomes: Not reported	Primary outcome and other main outcomes reported.	

Tam 2013[107]	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	N
	Abstract only. Very small study (Chinese)	Abstract only. Very small study (Chinese)	Abstract only. Very small study (Chinese)	Abstract only. Very small study (Chinese)		No of withdrawals and Dropouts: not reported Imputation used for continuous outcomes: not reported	Abstract only. Very small study (Chinese)	
Barkham 2009[56]	Unclear	Unclear	High	Low	Low	Low	Low	Y
			median CRP 11.5 vs 5. Likely due to chance as higher CRP in placebo group (and higher CRP associated with better responses)			No of withdrawals and Dropouts: 1 in the placebo group (at 12 weeks) Imputation used for continuous outcomes: not reported, but ITT population analysed		

Braun 2002[94]	Low	Low	Low	Low	Low	Low	Low	N
						No of withdrawals and Dropouts: 0 Imputation used for continuous outcomes: none required		
Marzo-Ortega (2005)[50]	Low	Low	Unclear	Low	Low	Unclear	Low	N
			The only issue is with age and the difference of 2 years could be due to rounding			No of withdrawals and Dropouts: 5/14 for placebo, 2/28 for Infliximab Imputation used for continuous outcomes: ITT with LOCF		

Van den Borsch (2002)[96]	Unclear	Unclear	High	Low	Low	Low	Low	Y
			BASFI>1 point			No of withdrawals and Dropouts: 0 Imputation used for continuous outcomes: NA		
ASSERT[97]	Unclear	Unclear	Low	Low	Low	Low	Low	N
						No of withdrawals and Dropouts: 8 (4 in each group) Imputation used for continuous outcomes: Not reported, but ITT population analysed. LOCF was used for		

						ASAS20.		
PLANETAS (2013)[105]	Low	Low	Unclear	Low	Low	Low	Low	N
			HLA-B27 was not reported			No of withdrawals and Dropouts:21 (12 vs 9) Imputation used for continuous outcomes: Not reported, though ITT population was analysed		

Table 110 Prognostic indicators of important baseline imbalance used in risk of bias assessment

Possible prognostic indicator	Study details			Implications for baseline imbalance across groups within a trial (and variation in efficacy across trials)
	Glintborg 2010 (DANBIO registry)[108] n=842 6 month time point Adalimumab, etanercept, infliximab	Vastesaeger 2011 (ASSERT & GO-RAISE trial data)* n=635, 3 month time point Infliximab, golimumab	Lord et al 2009 (BSRBR registry)[163] n=261, 6 month time point Adalimumab, etanercept, infliximab	
	Results of association			
HLA-B27 status	No data	moderate association	No data	HLA-B27 positive patients have a better outcome Use 20% group difference as an important imbalance?
CRP	≤14mg/l vs >14mg/l (OR 0.45, p<0.001)	≤6 mg/l vs >6 mg/l to 20 mg/l: moderate ≤6 mg/l vs >20 mg/l : moderate to strong	'Raised inflammatory markers' an important predictor, but result only available for CRP or ESR (not CRP alone)	Higher CRP levels are associated with a better outcome Use Glintborg and Vastesaeger cut-offs (providing there's at least a 2mg/l difference between groups)
Age	OR 0.98 per year, p=0.03	<40yrs vs >40yrs : weak to moderate	No significant association	Younger age associated with a better outcome Use Vastesaeger cut-off providing at least a 2 year difference between groups

BASFI score	OR 0.87 per cm increase, p=0.008	<6.5 vs > 6.5 Moderate to strong	Per unit increase OR 0.78 (95%CI 0.64 to 0.99)	Lower BASFI scores associated with a better outcome Use a 1 point difference as an indication of important imbalance? and Use <6.5 vs >6.5 providing there's at least a 0.5 point difference between groups.
BASDAI	Not analysed	No significant association	Per unit increase OR 1.30 (95%CI 1.04 to 1.62)	Higher BASDAI scores associated with a better outcome Use a 1 point difference as an indication of important imbalance?
Disease duration	No significant association	No significant association	No significant association	Do not assess
Gender	No significant association	No significant association	No significant association	Do not assess

11.4 Appendix 4 Trial results

Table 111 Continuous outcomes - final values results

Trial	Population	Treatment arm	Dose	Timepoint (weeks)	Patients	Mean final values (SD, SE or IQR)‡					
						BASDAI	BASFI	BASMI	MASES	SF36pcs	SF36mcs
Haibel 2008	nr	Adalimumab	40mg every 2 wks	12	22	3.8 (2.5)	3 (2.4)	1.3 (1.4)	2.5 (3.5)	38.8 (11.8)	44.6 (12.7)
	nr	placebo	-	12	24	5 (2.4)	4.1 (2.6)	1.7 (1.5)	2.8 (3.4)	34.9 (9.6)	43.9 (11.8)
Hu 2012	AS	Adalimumab	40mg every 2 wks	12	NR	2.3 (1.8)	1.8 (1.6)	-	-	-	-
	AS	Placebo	-	12	NR	4.2 (2.6)	2.9 (1.9)	-	-	-	-
Huang 2014	AS	Adalimumab	40mg every 2 wks	12	229	-	-	-	-	-	-
	AS	Placebo	-	12	115	-	-	-	-	-	-
Lambert 2007	AS	Adalimumab	40mg every 2 wks	12	38	-	-	-	-	-	-
	AS	Placebo	-	12	44	-	-	-	-	-	-
ABILITY-1 (2013)‖	nr	Adalimumab	40mg every 2 wks	12	69	-	-	-	-	-	-
	nr	Placebo	-	12	73	-	-	-	-	-	-
ATLAS (2006)	AS	Adalimumab	40mg every 2 wks	12	208	-	-1.414	-	-	-	-
	AS	Placebo	-	12	107	-	-	-	-	-	-
RAPID-axSpA (2014) AS	AS	Certolizumab pegol	200mg every 2 wks	12	65	-	-	-	-	-	-
	AS	Certolizumab pegol	400mg every 4 wks	12	56	-	-	-	-	-	-
	AS	Placebo	-	12	57	-	-	-	-	-	-
RAPID-axSpA (2014) NR	nr	Certolizumab pegol	200mg	12	46	-	-	-	-	-	-
	nr	Certolizumab pegol	400mg	12	51	-	-	-	-	-	-
	nr	Placebo	-	12	50	-	-	-	-	-	-
Barkham 2010	AS	Etanercept	25mg twice weekly	12	20	-	-	-	-	-	-
	AS	Placebo	-	12	20	-	-	-	-	-	-

Davis 2003	AS	Etanercept	25mg twice weekly	12	138	-	-	-	-	-	-
	AS	Placebo	-	12	139	-	-	-	-	-	-
	AS	Etanercept	25mg twice weekly	24	138	3.45 [0.21]	3.6 [0.22]	-	-	-	-
	AS	Placebo	-	24	139	5.51 [0.2]	5.47 [0.22]	-	-	-	-
Dougados 2011	AS	Etanercept	50mg weekly	12	39	3.7 (2.6)	4.1 (2.9)	5.1 (1.7)	-	-	-
	AS	Placebo	-	12	43	4.5 (1.9)	4.8 (2.1)	5.6 (1.3)	-	-	-
Dougados 2014	AS	Etanercept	50mg weekly	12	106	-	-	-	-	43.7 (8.9)	-
	AS	Placebo	-	12	109	-	-	-	-	41 (7.8)	-
	nr	Etanercept	50mg weekly	12	94	-	-	-	-	-	-
	nr	Placebo	-	12	95	-	-	-	-	-	-
Gorman 2002	AS	Etanercept	25mg twice a week	16	20	-	2.2 (2.1)	-	-	-	-
	AS	Placebo	-	16	20	-	3.1 (3)	-	-	-	-
Calin 2004	AS	Etanercept	25 mg twice weekly	12	45	3.38	3.96	-	-	-	-
	AS	Placebo	-	12	39	5.01	5.39	-	-	-	-
Van der Heijde 2006	AS	Etanercept	25mg twice weekly	12	150	-	-	-	-	-	-
	AS	Etanercept	50mg weekly	12	155	-	-	-	-	-	-
	AS	Placebo	-	12	51	-	-	-	-	-	-
Giardina 2010	AS	Etanercept	50mg weekly	12	25	-	5	-	-	-	-
	AS	Infliximab	5mg/kg at wk 0,2,6+	12	25	-	3.5	-	-	-	-
GO-RAISE 2008	AS	Golimumab	50mg(2 every 4 wks)	14	138	-	-	-	-	-	-
	AS	Golimumab	100mg(2 every 4 wks)	14	140	-	-	-	-	-	-
	AS	placebo	-	14	78	-	-	-	-	-	-
Bao 2012	AS	Golimumab	50mg Q4 weeks	14		-	-	-	-	-	-
	AS	Placebo	-	14		-	-	-	-	-	-
Tam 2014	AS	Golimumab	50mg monthly	26	NR	-	-	-	-	-	-

	AS	Placebo	-	26	NR	-	-	-	-	-	-
Barkham 2009	nr	Infliximab	5 mg/kg(0, 2, 6+ wks)	16	20	-	-	-	-	-	-
	nr	Placebo	-	16	20	-	-	-	-	-	-
Braun 2002	AS	Infliximab	5mg/kg(wks 0,2,6)	12	34	3.3	-	-	-	-	-
	AS	Placebo	-	12	35	5.7	-	-	-	-	-
Marzo-Ortega (2005)	AS	Infliximab+meth.	5mg/kg*	10	28	3.34 (2.56)	4.96	-	-	-	-
	AS	Placebo+meth.***	**	10	14	5.19 (2.52)	6.1	-	-	-	-
	AS	Infliximab+meth.	5mg/kg*	30	28	4.6 (2.85)	5.04	-	-	-	-
	AS	Placebo+meth.	**	30	14	5.74 (2.34)	5.68	-	-	-	-
Van den Bosch (2002)	AS	Infliximab	5mg/kg(wks 0,2,6)	12	9	2.66	2.74	4	-	-	-
	AS	Placebo	-	12	12	5.01	7.19	4	-	-	-
ASSERT (2005)	AS	Infliximab	5mg/kg(wks 0,2,6+)	24	201	-	-	-	-	-	-
	AS	Placebo	-	24	78	-	-	-	-	-	-
Park 2013	AS	Inflectra (CT-P13)	5mg/kg	14	125	-	-	-	-	-	-
	AS	Infliximab	5mg/kg	14	125	-	-	-	-	-	-
	AS	Inflectra (CT-P13)	5mg/kg	30	125	-	-	-	-	-	-
	AS	Infliximab	5mg/kg	30	125	-	-	-	-	-	-
	AS	Inflectra (CT-P13)	5mg/kg	54	125	-	-	-	-	-	-
	AS	Infliximab	5mg/kg	54	125	-	-	-	-	-	-

*5mg/kg (infusion at weeks 0,2,6,14,22)+methotrexate oral 7.5mg with folic acid (5mg twice a week which increased to 10mg a week)

**methotrexate oral 7.5mg with folic acid (5mg twice a week which increased to 10mg a week)

***meth.: methotrexate

‡: (#)=(sd); [#]=[se]; (#,#)=(IQR)

𝕀: licensed population

Table 112 Continuous outcomes - change from baseline results

Trial	Population	Treatment arm	Dose	Time point (weeks)	Patients	Mean change from baseline (SD, SE or IQR)‡					
						BASDAI	BASFI	BASMI	MASES	SF36pcs	SF36mcs
Haibel 2008	nr	Adalimumab	40mg every 2 wks	12	22	-	-	-	-	-	-
	nr	placebo	-	12	24	-	-	-	-	-	-
Hu 2012	AS	Adalimumab	40mg every 2 wks	12	NR	-	-	-	-	-	-
	AS	Placebo	-	12	NR	-	-	-	-	-	-
Huang 2014	AS	Adalimumab	40mg every 2 wks	12	229	-2.8 (1.9)	-1.75 (2.02)	-0.5 (0.6)	-1.2 (2.1)	6.6 (6.4)	5.1 (9.9)
	AS	Placebo	-	12	115	-1.4 (1.9)	-0.47 (1.64)	-0.2 (0.7)	-0.8 (1.7)	4 (6.3)	2.8 (9.4)
Lambert 2007	AS	Adalimumab	40mg every 2 wks	12	38	-	-	-	-	-	-
	AS	Placebo	-	12	44	-	-	-	-	-	-
ABILITY-1 (2013)Ⅱ	nr	Adalimumab	40mg every 2 wks	12	69	-2.2 (2.5)	-1.28 (2.02)	-0.2 (0.73)	-0.7 (2.78)	6.9 (9.32)	1.4 (8.63)
	nr	Placebo	-	12	73	-1.1 (1.96)	-0.63 (1.79)	-0.2 (0.64)	-1 (2.71)	2.3 (6.81)	0.7 (11.38)
ATLAS (2006)	AS	Adalimumab	40mg every 2 wks	12	208	-2.6 [0.2]	-	-0.5 [0.1]	-2.7 [0.4]	6.9 [0.6]	2.7 [0.7]
	AS	Placebo	-	12	107	-0.8 [0.2]	-	0.1 [0.1]	-1.3 [0.5]	1.6 [0.8]	2.4 [1]
RAPID-axSpA (2014) AS	AS	Certolizumab	200mg every 2 wks	12	65	-2.5 [0.3]	-1.7 [0.3]	-0.6 [0.1]	-	8.73 (7.63)	2.42 (9.08)
	AS	Certolizumab	400mg every 4 wks	12	56	-2.4 [0.3]	-1.7 [0.3]	-0.3 [0.2]	-	7.6 (7.65)	2.22 (10.44)
	AS	Placebo	-	12	57	-1 [0.3]	-0.6 [0.3]	-0.2 [0.1]	-	2.56 (5.67)	1.07 (10.92)
RAPID-axSpA (2014) NR	nr	Certolizumab	200mg	12	46	-3.3 [0.4]	-2.3 [0.4]	-0.6 [0.2]	-	9.56 (9.46)	4.59 (9.7)
	nr	Certolizumab	400mg	12	51	-3.4 [0.4]	-2.3 [0.4]	-0.5 [0.2]	-	8.72 (8.84)	6.12 (10.94)
	nr	Placebo	-	12	50	-1.5 [0.4]	-0.4 [0.4]	0 [0.1]	-	2.13 (7.47)	1.39 (10.24)
Barkham 2010	AS	Etanercept	25mg twice weekly	12	20	-1.97	-1.35	-	-	-	-
	AS	Placebo	-	12	20	-0.1	0.21	-	-	-	-
Davis	AS	Etanercept	25mg twice weekly	12	138	-2.36 [0.19]	-1.67 [0.2]	-	-	-	-

2003	AS	Placebo	-	12	139	-0.45 [0.18]	-0.33 [0.21]	-	-	-	-
	AS	Etanercept	25mg twice weekly	24	138	-	-	-	-	-	-
	AS	Placebo	-	24	139	-	-	-	-	-	-
Dougados 2011	AS	Etanercept	50mg weekly	12	39	-2.6 (2)	-2.2 (1.8)	-0.57 (0.65)	-	-	-
	AS	Placebo	-	12	43	-1.4 (2)	-1 (1.8)	-0.2 (0.65)	-	-	-
Dougados 2014	AS	Etanercept	50mg weekly	12	106	-2 [0.3]	-1.4 [0.2]	-0.3 [0.2]	-	-	-
	AS	Placebo	-	12	109	-1.3 [0.3]	-0.8 [0.2]	-0.3 [0.1]	-	-	-
	nr	Etanercept	50mg weekly	12	94	-	-	-	-	-	-
	nr	Placebo	-	12	95	-	-	-	-	-	-
Gorman 2002	AS	Etanercept	25mg twice a week	16	20	-	-	-	-	-	-
	AS	Placebo	-	16	20	-	-	-	-	-	-
Calin 2004	AS	Etanercept	25 mg twice weekly	12	45	-2.72 [0.34]	-2.06 [0.33]	-	-	-	-
	AS	Placebo	-	12	39	-0.85 [0.35]	-0.33 [0.31]	-	-	-	-
Van der Heijde 2006	AS	Etanercept	25mg twice weekly	12	150	-	-	-	-	-	-
	AS	Etanercept	50mg weekly	12	155	-	-	-	-	-	-
	AS	Placebo	-	12	51	-	-	-	-	-	-
Giardina 2010	AS	Etanercept	50mg weekly	12	25	-	-	-	-	-	-
	AS	Infliximab	5mg/kg at wk 0,2,6+	12	25	-	-	-	-	-	-
GO-RAISE 2008	AS	Golimumab	50mg(2 every 4 wks)	14	138	-	-1.4 (-3.1,-0.1)	0 (-1,0)	-0.5 (2.6)	7.3 (1.5,15.3)	1.5 (-2.2,7.8)
	AS	Golimumab	100mg(2 every 4 wks)	14	140	-	-1.5 (-3.0,-0.1)	0 (-1,0)	-1.3 (3.11)	8.4 (2.3,14.1)	3.7 (-3.2,12.1)
	AS	placebo	-	14	78	-	0.1 (-1.1,1.1)	0 (-1,0)	-0.2 (2.99)	2.4 (-1.4,7.8)	0.1 (-4.3,5.3)
Bao 2012	AS	Golimumab	50mg Q4 weeks	14		-	-1.26 (2.57)	-0.42 (0.91)	-	6.25 (7.95)	3.86 (8.92)
	AS	Placebo	-	14		-	0.11 (2.1)	-0.19 (0.72)	-	1.59 (6.12)	0.82 (9.44)
Tam 2014	AS	Golimumab	50mg monthly	26	NR	-1.82 (1.64)	-0.13 (0.25)†	-1 (-2,0)	-	-	-
	AS	Placebo	-	26	NR	-0.66 (1.24)	0.17 (0.72)†	0 (-1,0)	-	-	-

Barkham 2009	nr	Infliximab	5 mg/kg(0, 2, 6+ wks)	16	20	-3.41 (2.53)	-2.7 (2.36)	-	-	-	-
	nr	Placebo	-	16	20	-0.75 (2.42)	-0.47 (2.25)	-	-	-	-
Braun 2002	AS	Infliximab	5mg/kg(wks 0,2,6)	12	34	-3.2	-2.1	-	-	-	-
	AS	Placebo	-	12	35	-0.6	-0.1	-	-	-	-
Marzo-Ortega (2005)	AS	Inflix+meth.	5mg/kg*	10	28	-3.11 (2.23)	-	-	-	-	-
	AS	Pla+meth.***	**	10	14	-1.38 (2.11)	-	-	-	-	-
	AS	Inflix+meth.	5mg/kg*	30	28	-1.85 (2.84)	-	-	-	-	-
	AS	Pla+meth.	**	30	14	-0.84 (1.8)	-	-	-	-	-
Van den Bosch (2002)	AS	Infliximab	5mg/kg(wks 0,2,6)	12	9	-	-	-	-	-	-
	AS	Placebo	-	12	12	-	-	-	-	-	-
ASSERT (2005)	AS	Infliximab	5mg/kg(wks 0,2,6+)	24	201	-2.9 (-4.9,-0.9)	-1.7 (-3.6,-0.6)	-1 (-1,0)	-	10.2 (3.9,17.1)	2.7 (-2.9,8.8)
	AS	Placebo	-	24	78	-0.4 (-1.4,0.7)	0 (-1,1)	0 (-1,0)	-	0.8 (-1.9,6)	2 (-2.6,7.5)
Park 2013	AS	Inflectra	5mg/kg	14	125	-2.91 (2.17)	-2.51 (2.14)	-0.7 (1.2)	-	-	-
	AS	Infliximab	5mg/kg	14	125	-2.77 (2.08)	-2.47 (2.18)	-0.7 (1.4)	-	-	-
	AS	Inflectra	5mg/kg	30	125	-3.04 (2.23)	-2.6 (2.19)	-1 (1.4)	-	7.6	6.5
	AS	Infliximab	5mg/kg	30	125	-2.71 (2.24)	-2.54 (2.17)	-0.9 (1.4)	-	8.5	5.2
	AS	Inflectra	5mg/kg	54	125	-	-	-	-	-	-
	AS	Infliximab	5mg/kg	54	125	-	-	-	-	-	-

*5mg/kg (infusion at weeks 0,2,6,14,22)+methotrexate oral 7.5mg with folic acid (5mg twice a week which increased to 10mg a week)

**methotrexate oral 7.5mg with folic acid (5mg twice a week which increased to 10mg a week)

***Pla+meth.: placebo and methotrexate

†: these values are uncertain due to poor reporting

‡: (#)=(sd); [#]=[se]; (#,#)=(IQR)

𝕀: licensed population

Binary response outcomes results

Trial	Population	Treatment arm	Dose	Time point (weeks)	Patients	Number (%) of responders				
						ASAS 20	ASAS 40	ASAS 50	ASAS 70	BASDAI 50
Haibel 2008	nr	Adalimumab	40mg every 2 wks	12	22	15 (68)	12 (55)	-	-	11 (50)
	nr	placebo	-	12	24	6 (25)	3 (13)	-	-	5 (21)
Hu 2012	AS	Adalimumab	40mg every 2 wks	12	26	-	-	-	-	-
	AS	Placebo	-	12	20	-	-	-	-	-
Huang 2014	AS	Adalimumab	40mg every 2 wks	12	229	154 (67)	102 (45)	-	-	114 (50)
	AS	Placebo	-	12	115	35 (30)	11 (10)	-	-	19 (17)
Lambert 2007	AS	Adalimumab	40mg every 2 wks	12	38	18 (47)	-	12 (32)	-	-
	AS	Placebo	-	12	44	12 (27)	-	5 (11)	-	-
ABILITY-1 (2013)[1]	nr	Adalimumab	40mg every 2 wks	12	69	41 (59)	28 (41)	24 (35)	13 (19)	27 (39)
	nr	Placebo	-	12	73	23 (32)	10 (14)	6 (8)	3 (4)	10 (14)
ATLAS (2006)	AS	Adalimumab	40mg every 2 wks	12	208	121 (58)	83 (40)	-	-	94 (45)
	AS	Placebo	-	12	107	22 (21)	14 (13)	-	-	17 (16)
RAPID-axSpA (2014) AS	AS	Certolizumab pegol	200mg every 2 wks	12	65	37 (57)	26 (40)	-	-	27 (42)
	AS	Certolizumab pegol	400mg every 4 wks	12	56	36 (64)	28 (50)	-	-	23 (41)
	AS	Placebo	-	12	57	21 (37)	11 (19)	-	-	6 (11)
RAPID-axSpA (2014) NR	nr	Certolizumab pegol	200mg	12	46	27 (59)	22 (48)	-	-	23 (50)
	nr	Certolizumab pegol	400mg	12	51	32 (63)	24 (47)	-	-	24 (47)
	nr	Placebo	-	12	50	20 (40)	8 (16)	-	-	8 (16)
Barkham 2010	AS	Etanercept	25mg twice weekly	12	20	-	4 (20)	-	-	7 (35)

	AS	Placebo	-	12	20	-	0 (0)	-	-	1 (5)
Davis 2003	AS	Etanercept	25mg twice weekly	12	138	82 (59)	-	62 (45)	40 (29)	-
	AS	Placebo	-	12	139	39 (28)	-	18 (13)	10 (7)	-
	AS	Etanercept	25mg twice weekly	24	138	78 (57)	-	58 (42)	-	-
	AS	Placebo	-	24	139	31 (22)	-	14 (10)	-	-
Dougados 2011	AS	Etanercept	50mg weekly	12	39	25 (64)	17 (44)	15 (38)	10 (26)	18 (46)
	AS	Placebo	-	12	43	14 (33)	10 (23)	6 (14)	4 (9)	10 (23)
Dougados 2014	AS	Etanercept	50mg weekly	12	106	55 (52)	34 (32)	-	-	46 (43)
	AS	Placebo	-	12	109	39 (36)	17 (16)	-	-	26 (24)
	nr	Etanercept	50mg weekly	12	94	-	33 (35)	-	-	-
	nr	Placebo	-	12	95	-	16 (17)	-	-	-
Gorman 2002	AS	Etanercept	25mg twice a week	16	20	16 (80)	-	-	-	-
	AS	Placebo	-	16	20	6 (30)	-	-	-	-
Calin 2004	AS	Etanercept	25 mg twice weekly	12	45	26 (58)	-	-	-	-
	AS	Placebo	-	12	39	9 (23)	-	-	-	-
Van der Heijde 2006	AS	Etanercept	25mg twice weekly	12	150	107 (71)	80 (53)	-	-	87 (58)
	AS	Etanercept	50mg weekly	12	155	115 (74)	90 (58)	-	-	93 (60)
	AS	Placebo	-	12	51	19 (37)	11 (22)	-	-	10 (20)
Giardina 2010	AS	Etanercept	50mg weekly	12	25	15 (60)	11 (44)	-	-	-
	AS	Infliximab	5mg/kg at wk 0,2,6+	12	25	19 (76)	14 (56)	-	-	-
GO-RAISE 2008	AS	Golimumab	50mg(2 every 4 wks)	14	138	82 (59)	62 (45)	-	-	61 (44)
	AS	Golimumab	100mg(2 every 4 wks)	14	140	84 (60)	69 (49)	-	-	56 (40)
	AS	placebo	-	14	78	17 (22)	12 (15)	-	-	12 (15)
Bao 2012	AS	Golimumab	50mg Q4 weeks	14	108	53 (49)	38 (35)	-	-	37 (34)
	AS	Placebo	-	14	105	26 (25)	10 (10)	-	-	5 (5)

Tam 2014	AS	Golimumab	50mg monthly	26	20	11 (55)	-	-	-	-
	AS	Placebo	-	26	21	3 (14)	-	-	-	-
Barkham 2009	nr	Infliximab	5 mg/kg(0, 2, 6+ wks)	16	20	-	11 (55)	-	-	-
	nr	Placebo	-	16	20	-	3 (15)	-	-	-
Braun 2002	AS	Infliximab	5mg/kg(wks 0,2,6)	12	34	23 (68)	-	16 (47)	-	18 (53)
	AS	Placebo	-	12	35	10 (29)	-	2 (6)	-	3 (9)
Marzo-Ortega (2005)	AS	Infliximab+meth.	5mg/kg*	10	28	20 (71)	-	-	-	-
	AS	Placebo+meth.***	**	10	14	4 (29)	-	-	-	-
	AS	Infliximab+meth.	5mg/kg*	30	28	14 (50)	-	-	-	-
	AS	Placebo+meth.	**	30	14	3 (21)	-	-	-	-
Van den Bosch (2002)	AS	Infliximab	5mg/kg(wks 0,2,6)	12	9	-	-	-	-	-
	AS	Placebo	-	12	12	-	-	-	-	-
ASSERT (2005)	AS	Infliximab	5mg/kg(wks 0,2,6+)	24	201	123 (61)	93 (46)	-	-	-
	AS	Placebo	-	24	78	15 (19)	9 (12)	-	-	-
Park 2013	AS	Inflectra (CT-P13)	5mg/kg	14	125	72 (58)	48 (38)	-	-	-
	AS	Infliximab	5mg/kg	14	125	79 (63)	56 (45)	-	-	-
	AS	Inflectra (CT-P13)	5mg/kg	30	125	79 (63)	58 (46)	-	-	-
	AS	Infliximab	5mg/kg	30	125	84 (67)	55 (44)	-	-	-
	AS	Inflectra (CT-P13)	5mg/kg	54	125	71 (57)	51 (41)	-	-	-
	AS	Infliximab	5mg/kg	54	125	75 (60)	46 (37)	-	-	-

*5mg/kg (infusion at weeks 0,2,6,14,22)+methotrexate oral 7.5mg with folic acid (5mg twice a week which increased to 10mg a week)

**methotrexate oral 7.5mg with folic acid (5mg twice a week which increased to 10mg a week)

***meth.: methotrexate

Ⅱ: licensed population

11.5 Appendix 5 Relative effects of anti-TNFs

AS population

In the following tables, the intervention is stated in the top row and the comparator is in the left-hand column, which is reverse to normal.

Table 113: Relative effects **RR BASDAI50 AS**

	ADA		CER		ETA		GOL		INF	
	Md	95% CrI	Md	95% CrI	Md	95% CrI	Md	95% CrI	Md	95% CrI
ADA	-	-	1.15	(0.61 to 1.86)	1.01	(0.65 to 1.50)	1.13	(0.75 to 1.66)	1.55	(0.74 to 2.50)
CER	0.87	(0.54 to 1.63)	-	-	0.88	(0.50 to 1.70)	0.99	(0.58 to 1.89)	1.34	(0.61 to 2.74)
ETA	0.99	(0.67 to 1.53)	1.14	(0.59 to 1.98)	-	-	1.12	(0.71 to 1.78)	1.53	(0.72 to 2.66)
GOL	0.88	(0.60 to 1.33)	1.01	(0.53 to 1.74)	0.89	(0.56 to 1.40)	-	-	1.37	(0.65 to 2.30)
INF	0.65	(0.40 to 1.35)	0.74	(0.37 to 1.65)	0.65	(0.38 to 1.38)	0.73	(0.43 to 1.54)	-	-

Table 114: Relative effects **OR BASDAI50 AS**

	ADA		CER		ETA		GOL		INF	
	Md	95% CrI	Md	95% CrI	Md	95% CrI	Md	95% CrI	Md	95% CrI
ADA	-	-	1.28	(0.47 to 3.48)	1.01	(0.51 to 2.02)	1.25	(0.62 to 2.48)	2.58	(0.62 to 10.60)
CER	0.78	(0.29 to 2.14)	-	-	0.79	(0.27 to 2.32)	0.98	(0.33 to 2.89)	2.02	(0.39 to 10.33)
ETA	0.99	(0.50 to 1.97)	1.26	(0.43 to 3.71)	-	-	1.23	(0.56 to 2.73)	2.55	(0.58 to 11.01)
GOL	0.80	(0.40 to 1.61)	1.02	(0.35 to 3.03)	0.81	(0.37 to 1.80)	-	-	2.06	(0.47 to 8.91)
INF	0.39	(0.09 to 1.62)	0.50	(0.10 to 2.56)	0.39	(0.09 to 1.72)	0.49	(0.11 to 2.12)	-	-

Table 115: Relative effects **RR ASAS20 AS**

	ADA		CER		ETA		GOL		INF	
	Md	95% CrI	Md	95% CrI	Md	95% CrI	Md	95% CrI	Md	95% CrI
ADA	-	-	0.79	(0.53 to 1.07)	0.98	(0.82 to 1.17)	0.94	(0.75 to 1.15)	1.07	(0.75 to 1.38)
CER	1.27	(0.93 to 1.88)	-	-	1.24	(0.91 to 1.83)	1.19	(0.85 to 1.77)	1.35	(0.88 to 2.09)
ETA	1.03	(0.86 to 1.22)	0.81	(0.55 to 1.10)	-	-	0.96	(0.76 to 1.18)	1.10	(0.77 to 1.41)
GOL	1.07	(0.87 to 1.34)	0.84	(0.56 to 1.18)	1.04	(0.85 to 1.31)	-	-	1.14	(0.79 to 1.53)
INF	0.93	(0.73 to 1.34)	0.74	(0.48 to 1.14)	0.91	(0.71 to 1.31)	0.87	(0.66 to 1.27)	-	-

Table 116: Relative effects **OR ASAS20 AS**

	ADA		CER		ETA		GOL		INF	
	Md	95% CrI	Md	95% CrI	Md	95% CrI	Md	95% CrI	Md	95% CrI
ADA	-	-	0.57	(0.28 to 1.20)	0.94	(0.58 to 1.50)	0.85	(0.49 to 1.46)	1.23	(0.50 to 3.01)
CER	1.74	(0.84 to 3.57)	-	-	1.62	(0.78 to 3.35)	1.47	(0.67 to 3.16)	2.13	(0.74 to 6.13)
ETA	1.07	(0.67 to 1.71)	0.62	(0.30 to 1.28)	-	-	0.90	(0.52 to 1.55)	1.31	(0.54 to 3.20)
GOL	1.18	(0.69 to 2.05)	0.68	(0.32 to 1.49)	1.11	(0.65 to 1.91)	-	-	1.46	(0.57 to 3.70)
INF	0.82	(0.33 to 1.99)	0.47	(0.16 to 1.36)	0.76	(0.31 to 1.86)	0.69	(0.27 to 1.75)	-	-

Table 117: Relative effects **RR ASAS40 AS**

	ADA		CER		ETA		GOL	
	Md	95% CrI	Md	95% CrI	Md	95% CrI	Md	95% CrI
ADA	-	-	0.74	(0.41 to 1.22)	0.80	(0.51 to 1.20)	0.91	(0.61 to 1.32)
CER	1.35	(0.82 to 2.45)	-	-	1.09	(0.61 to 2.04)	1.23	(0.72 to 2.26)

ETA	1.24	(0.83 to 1.95)	0.92	(0.49 to 1.63)	-	-	1.13	(0.72 to 1.81)
GOL	1.10	(0.76 to 1.64)	0.81	(0.44 to 1.38)	0.88	(0.55 to 1.38)	-	-

Table 118: Relative effects **OR ASAS40 AS**

	ADA		CER		ETA		GOL	
	Md	95% CrI	Md	95% CrI	Md	95% CrI	Md	95% CrI
ADA	-	-	0.59	(0.25 to 1.45)	0.68	(0.33 to 1.40)	0.84	(0.42 to 1.67)
CER	1.68	(0.69 to 4.04)	-	-	1.14	(0.45 to 2.90)	1.42	(0.57 to 3.50)
ETA	1.47	(0.71 to 3.02)	0.87	(0.35 to 2.24)	-	-	1.23	(0.58 to 2.63)
GOL	1.19	(0.60 to 2.38)	0.71	(0.29 to 1.75)	0.81	(0.38 to 1.72)	-	-

Table 119: Relative effects **RR ASAS50 AS**

	ADA		ETA		INF	
	Md	95% CrI	Md	95% CrI	Md	95% CrI
ADA	-	-	1.24	(0.60 to 3.31)	2.00	(0.73 to 5.87)
ETA	0.81	(0.30 to 1.66)	-	-	1.63	(0.68 to 2.95)
INF	0.50	(0.17 to 1.36)	0.61	(0.34 to 1.46)	-	-

Table 120: Relative effects **OR ASAS50 AS**

	ADA		ETA		INF	
	Md	95% CrI	Md	95% CrI	Md	95% CrI
ADA	-	-	1.40	(0.40 to 5.05)	4.11	(0.59 to 29.29)

ETA	0.71	(0.20 to 2.49)	-	-	2.92	(0.55 to 15.51)
INF	0.24	(0.03 to 1.71)	0.34	(0.06 to 1.81)	-	-

Table 121: Relative effects **Mean difference BASDAI change from baseline AS**

	ADA		CER		ETA		INF	
	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
ADA	-	-	0.10	(-0.68 to 0.88)	-0.20	(-0.71 to 0.30)	-0.73	(-1.69 to 0.24)
CER	-0.10	(-0.88 to 0.68)	-	-	-0.30	(-1.12 to 0.52)	-0.82	(-1.98 to 0.33)
ETA	0.20	(-0.30 to 0.71)	0.30	(-0.52 to 1.12)	-	-	-0.53	(-1.50 to 0.47)
INF	0.73	(-0.24 to 1.69)	0.82	(-0.33 to 1.98)	0.53	(-0.47 to 1.50)	-	-

Table 122: Relative effects **Mean difference BASFI change from baseline AS**

	ADA		CER		ETA		GOL		INF	
	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
ADA	-	-	0.15	(-0.67 to 0.97)	-0.18	(-0.73 to 0.36)	-0.20	(-0.75 to 0.35)	-0.91	(-2.00 to 0.20)
CER	-0.15	(-0.97 to 0.67)	-	-	-0.33	(-1.16 to 0.49)	-0.35	(-1.17 to 0.47)	-1.05	(-2.31 to 0.22)
ETA	0.18	(-0.36 to 0.73)	0.33	(-0.49 to 1.16)	-	-	-0.02	(-0.57 to 0.55)	-0.72	(-1.83 to 0.39)
GOL	0.20	(-0.35 to 0.75)	0.35	(-0.47 to 1.17)	0.02	(-0.55 to 0.57)	-	-	-0.71	(-1.82 to 0.42)
INF	0.91	(-0.20 to 2.00)	1.05	(-0.22 to 2.31)	0.72	(-0.39 to 1.83)	0.71	(-0.42 to 1.82)	-	-

Table 123: Relative effects **Mean difference BASMI change from baseline AS**

	ADA	CER	ETA	GOL

	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
ADA	-	-	0.11	(-0.21 to 0.42)	0.00	(-0.32 to 0.31)	0.26	(0.06 to 0.46)
CER	-0.11	(-0.42 to 0.21)	-	-	-0.11	(-0.51 to 0.30)	0.15	(-0.17 to 0.48)
ETA	0.00	(-0.31 to 0.32)	0.11	(-0.30 to 0.51)	-	-	0.26	(-0.06 to 0.58)
GOL	-0.26	(-0.46 to -0.06)	-0.15	(-0.48 to 0.17)	-0.26	(-0.58 to 0.06)	-	-

Table 124: Relative effects **Mean difference SF-36 PCS change from baseline AS**

	ADA		CER		GOL	
	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
ADA	-	-	2.11	(-0.20 to 4.44)	1.52	(-0.24 to 3.30)
CER	-2.11	(-4.44 to 0.20)	-	-	-0.59	(-2.99 to 1.85)
GOL	-1.52	(-3.30 to 0.24)	0.59	(-1.85 to 3.00)	-	-

Table 125: Relative effects **Mean difference MASES change from baseline AS**

	GOL	
	Mean	95% CrI
ADA	-0.20	(-1.12 to 0.70)

Table 126: Relative effects **Mean difference SF-36 MCS change from baseline AS**

	ADA		CER		GOL	
	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
ADA	-	-	-0.15	(-3.83 to	1.33	(-0.97 to

				3.54)		3.63)
CER	0.15	(-3.53 to 3.83)	-	-	1.51	(-2.24 to 5.21)
GOL	-1.33	(-3.63 to 0.98)	-1.51	(-5.20 to 2.24)	-	-

Relative effects of anti-TNFs – nr-axSpA population

In the following tables, the intervention is stated in the top row and the comparator is in the left-hand column, which is reverse to normal.

Table 127: Relative effects **RR BASDAI 50 nr-axSpA**

	ADA		CER		ETA	
	Md	95% CrI	Md	95% CrI	Md	95% CrI
ADA	-	-	1.11	(0.62 to 1.96)	0.76	(0.44 to 1.30)
CER	0.90	(0.51 to 1.61)	-	-	0.69	(0.38 to 1.22)
ETA	1.31	(0.77 to 2.28)	1.46	(0.82 to 2.62)	-	-

Table 128: Relative effects **OR BASDAI50 nr-axSpA**

	ADA		CER		ETA	
	Md	95% CrI	Md	95% CrI	Md	95% CrI
ADA	-	-	1.24	(0.42 to 3.75)	0.62	(0.25 to 1.55)
CER	0.81	(0.27 to 2.40)	-	-	0.50	(0.18 to 1.40)
ETA	1.62	(0.65 to 3.99)	2.01	(0.72 to 5.68)	-	-

Table 129: Relative effects **RR ASAS 20 nr-axSpA**

	ADA		CER		ETA	
	Md	95% CrI	Md	95% CrI	Md	95% CrI
ADA	-	-	0.83	(0.54 to 1.20)	0.77	(0.52 to 1.08)
CER	1.20	(0.84 to 1.87)	-	-	0.92	(0.60 to 1.44)
ETA	1.31	(0.93 to 1.94)	1.09	(0.70 to 1.67)	-	-

Table 130: Relative effects **OR ASAS 20 nr-axSpA**

	ADA		CER		ETA	
	Md	95% CrI	Md	95% CrI	Md	95% CrI
ADA	-	-	0.62	(0.25 to 1.59)	0.52	(0.23 to 1.19)
CER	1.60	(0.63 to 3.98)	-	-	0.83	(0.34 to 2.01)
ETA	1.92	(0.84 to 4.33)	1.20	(0.50 to 2.92)	-	-

Table 131: Relative effects **RR ASAS 40 nr-axSpA**

	ADA		CER		ETA		INF	
	Md	95% CrI	Md	95% CrI	Md	95% CrI	Md	95% CrI
ADA	-	-	0.97	(0.51 to 1.78)	0.66	(0.35 to 1.21)	1.16	(0.42 to 2.29)
CER	1.04	(0.56 to 1.98)	-	-	0.68	(0.35 to 1.35)	1.20	(0.43 to 2.55)
ETA	1.51	(0.83 to 2.82)	1.46	(0.74 to 2.85)	-	-	1.74	(0.63 to 3.70)
INF	0.86	(0.44 to 2.37)	0.84	(0.39 to 2.33)	0.57	(0.27 to 1.58)	-	-

Table 132: Relative effects **OR ASAS 40 nr-axSpA**

	ADA		CER		ETA		INF	
	Md	95% CrI	Md	95% CrI	Md	95% CrI	Md	95% CrI
ADA	-	-	0.94	(0.31 to 2.90)	0.51	(0.19 to 1.35)	1.36	(0.26 to 7.22)
CER	1.07	(0.34 to 3.25)	-	-	0.54	(0.18 to 1.58)	1.45	(0.25 to 8.10)
ETA	1.98	(0.74 to 5.23)	1.86	(0.63 to 5.51)	-	-	2.68	(0.52 to 13.91)
INF	0.73	(0.14 to 3.91)	0.69	(0.12 to 3.93)	0.37	(0.07 to 1.91)	-	-

Table 133: Relative effects **Mean difference BASDAI change from baseline nr-axSpA**

	ADA		CER		ETA		INF	
	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
ADA	-	-	-0.63	(-1.77 to 0.52)	0.53	(-0.51 to 1.56)	-1.43	(-3.08 to 0.22)
CER	0.63	(-0.52 to 1.77)	-	-	1.15	(-0.12 to 2.42)	-0.81	(-2.62 to 1.00)
ETA	-0.53	(-1.56 to 0.51)	-1.15	(-2.42 to 0.12)	-	-	-1.97	(-3.70 to -0.21)
INF	1.43	(-0.21 to 3.08)	0.81	(-1.00 to 2.62)	1.97	(0.21 to 3.70)	-	-

Table 134: Relative effects **Mean difference BASFI change from baseline nr-axSpA**

	ADA		CER		ETA		INF	
	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
ADA	-	-	-1.00	(-2.10 to 0.10)	0.30	(-0.48 to 1.08)	-1.33	(-2.86 to 0.19)
CER	1.00	(-0.10 to 2.10)	-	-	1.30	(0.19 to 2.41)	-0.33	(-2.05 to 1.38)

ETA	-0.30	(-1.08 to 0.48)	-1.30	(-2.41 to -0.19)	-	-	-1.63	(-3.15 to -0.09)
INF	1.33	(-0.19 to 2.86)	0.33	(-1.38 to 2.05)	1.63	(0.09 to 3.15)	-	-

Table 135: Relative effects **Mean difference BASMI change from baseline nr-axSpA**

	ADA		CER		ETA	
	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
ADA	-	-	-0.53	(-0.93 to -0.12)	0.02	(-0.47 to 0.51)
CER	0.53	(0.12 to 0.93)	-	-	0.55	(-0.02 to 1.10)
INF	-0.02	(-0.51 to 0.47)	-0.55	(-1.10 to 0.02)	-	-

Table 136: Relative effects **Mean difference SF-36 PCS change from baseline nr-axSpA**

	ADA		CER		ETA	
	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
ADA	-	-	2	(-1.53 to 5.57)	-2.88	(-6.11 to 0.31)
CER	-2.00	(-5.57 to 1.53)	-	-	-4.88	(-8.52 to -1.29)
INF	2.88	(-0.31 to 6.11)	4.88	(1.29 to 8.52)	-	-

Table 137: Relative effects **Mean difference SF-36MCS change from baseline nr-axSpA**

	ADA		CER	
	Mean	95% CrI	Mean	95% CrI
ADA	-	-	2.87	(-1.78 to 7.49)
CER	-2.87	(-7.49 to 1.78)	-	-

11.6 Appendix 6 BASDAI and BASFI conditional on response data

Table 138 Baseline BASDAI according to conditional on response at week 12 (or nearest time point)

Anti-TNF Population (trial)	Resp criterion	Treatment	Response	n	Mean	SD
Adalimumab AS (ATLAS)	ASAS20	ADA 40mg	Non-responder	83	6.23	1.929
			Responder	121	6.27	1.542
		Placebo	Non-responder	82	6.29	1.712
			Responder	22	6.64	1.468
	ASAS40	ADA 40mg	Non-responder	119	6.21	1.802
			Responder	85	6.32	1.568
		Placebo	Non-responder	89	6.37	1.714
			Responder	15	6.34	1.362
	BASDAI50	ADA 40mg	Non-responder	119	6.21	1.802
			Responder	85	6.32	1.568
		Placebo	Non-responder	89	6.37	1.714
			Responder	15	6.34	1.362
Golimumab AS(GO_RAISE)	ASAS20	GOL 50mg	Non-responder	56	6.51	1.687
			Responder	82	6.49	1.494
		Placebo	Non-responder	61	6.65	1.622
			Responder	17	6.46	1.120
	ASAS40	GOL 50mg	Non-responder	76	6.54	1.680
			Responder	62	6.45	1.433
		Placebo	Non-responder	66	6.65	1.579
			Responder	12	6.41	1.194
	BASDAI50	GOL 50mg	Non-responder	72	6.69	1.523
			Responder	61	6.25	1.638
		Placebo	Non-responder	66	6.63	1.581
			Responder	12	6.51	1.194
Etanercept AS (EU-314)	ASAS20	ETN 25mg twice weekly	Non-responder	43	[redacted]	[redacted]
			Responder	107	[redacted]	[redacted]
		ETN 50mg once weekly	Non-responder	40	[redacted]	[redacted]
			Responder	115	[redacted]	[redacted]
		Placebo	Non-responder	32	[redacted]	[redacted]
			Responder	19	[redacted]	[redacted]
	ASAS40	ETN 25mg twice weekly	Non-responder	70	[redacted]	[redacted]
			Responder	80	[redacted]	[redacted]
		ETN 50mg once weekly	Non-responder	65	[redacted]	[redacted]
			Responder	90	[redacted]	[redacted]
		Placebo	Non-responder	40	[redacted]	[redacted]
			Responder	11	[redacted]	[redacted]
	BASDAI50	ETN 25mg twice weekly	Non-responder	63	[redacted]	[redacted]

			Responder	87	[redacted]	[redacted]
		ETN 50mg once weekly	Non-responder	62	[redacted]	[redacted]
			Responder	93	[redacted]	[redacted]
		Placebo	Non-responder	41	[redacted]	[redacted]
			Responder	10	[redacted]	[redacted]
Adalimumab M10-791 (nr-axSpA sub-population with a positive MRI and/or elevated CRP)	ASAS20	ADA 40mg	Non-responder	27	6.31	1.66
			Responder	41	6.46	1.49
		Placebo	Non-responder	46	6.49	1.37
			Responder	23	6.05	1.77
	ASAS40	ADA 40mg	Non-responder	40	6.60	1.63
			Responder	28	6.13	1.41
		Placebo	Non-responder	59	6.41	1.55
			Responder	10	5.93	1.27
	BASDAI 50	ADA 40mg	Non-responder	41	6.53	1.69
			Responder	27	6.21	1.31
		Placebo	Non-responder	59	6.46	1.52
			Responder	10	5.64	1.34
Etanercept (1031 nr-axSpA))	ASAS20	ETN 50mg	Non-responder	[redacted]	[redacted]	[redacted]
			Responder	[redacted]	[redacted]	[redacted]
		Placebo	Non-responder	[redacted]	[redacted]	[redacted]
			Responder	[redacted]	[redacted]	[redacted]
	ASAS40	ETN 50mg	Non-responder	[redacted]	[redacted]	[redacted]
			Responder	[redacted]	[redacted]	[redacted]
		Placebo	Non-responder	[redacted]	[redacted]	[redacted]
			Responder	[redacted]	[redacted]	[redacted]
	BASDAI50	ETN 50mg	Non-responder	[redacted]	[redacted]	[redacted]
			Responder	[redacted]	[redacted]	[redacted]
		Placebo	Non-responder	[redacted]	[redacted]	[redacted]
			Responder	[redacted]	[redacted]	[redacted]

Table 139 Baseline BASFI according to conditional on response at week 12 (or nearest time point)

Anti-TNF (trial)	Resp criterion	Treatment	Response	n	Mean	SD
Adalimumab AS (ATLAS)	ASAS20	ADA 40mg	Non-responder	83	53.03	23.881
			Responder	121	51.38	20.843
		Placebo	Non-responder	82	57.96	23.089
			Responder	22	52.27	16.661
	ASAS40	ADA 40mg	Non-responder	119	53.05	22.864
			Responder	85	50.65	21.005
		Placebo	Non-responder	89	57.05	22.954
			Responder	15	54.98	14.996
	BASDAI50	ADA 40mg	Non-responder	110	57.79	21.015

			Responder	94	45.34	21.514
		Placebo	Non-responder	87	59.06	21.989
			Responder	17	44.98	17.979
Golimumab AS(GO_RAISE)	ASAS20	GOL 50mg	Non-responder	56	5.35	2.530
			Responder	82	4.76	2.249
		Placebo	Non-responder	59	5.38	2.260
			Responder	17	4.13	1.985
	ASAS40	GOL 50mg	Non-responder	76	5.33	2.488
			Responder	62	4.60	2.184
		Placebo	Non-responder	64	5.33	2.247
			Responder	12	3.88	1.932
	BASDAI50	GOL 50mg	Non-responder	72	5.48	2.412
			Responder	61	4.45	2.288
		Placebo	Non-responder	64	5.39	2.179
			Responder	12	3.56	2.070
Etanercept AS (EU-314)	ASAS20	ETN 25mg twice weekly	Non-responder	43	[redacted]	[redacted]
			Responder	107	[redacted]	[redacted]
		ETN 50mg once weekly	Non-responder	40	[redacted]	[redacted]
			Responder	115	[redacted]	[redacted]
		Placebo	Non-responder	32	[redacted]	[redacted]
			Responder	19	[redacted]	[redacted]
	ASAS40	ETN 25mg twice weekly	Non-responder	70	[redacted]	[redacted]
			Responder	80	[redacted]	[redacted]
		ETN 50mg once weekly	Non-responder	65	[redacted]	[redacted]
			Responder	90	[redacted]	[redacted]
		Placebo	Non-responder	40	[redacted]	[redacted]
			Responder	11	[redacted]	[redacted]
	BASDAI50	ETN 25mg twice weekly	Non-responder	63	[redacted]	[redacted]
			Responder	87	[redacted]	[redacted]
		ETN 50mg once weekly	Non-responder	62	[redacted]	[redacted]
			Responder	93	[redacted]	[redacted]
		Placebo	Non-responder	41	[redacted]	[redacted]
			Responder	10	[redacted]	[redacted]
Adalimumab nr-axSpA M10-791 (sub-population with a positive MRI and/or elevated CRP)	ASAS20	ADA 40mg	Non-responder	27	45.17	22.07
			Responder	40	43.05	19.31
		Placebo	Non-responder	47	48.07	22.99
			Responder	23	47.91	23.75
	ASAS40	ADA 40mg	Non-responder	40	47.61	22.60
			Responder	27	39.09	15.41
		Placebo	Non-responder	60	48.26	23.46
			Responder	10	46.54	21.67

	BASDAI 50	ADA 40mg	Non-responder	40	49.71	20.05
			Responder	27	35.97	18.12
		Placebo	Non-responder	59	49.06	23.25
			Responder	10	43.66	23.07
Etanercept (1031 nr-axSpA))	ASAS20	ETN 50mg	Non-responder	[redacted]	[redacted]	[redacted]
			Responder	[redacted]	[redacted]	[redacted]
		Placebo	Non-responder	[redacted]	[redacted]	[redacted]
			Responder	[redacted]	[redacted]	[redacted]
	ASAS40	ETN 50mg	Non-responder	[redacted]	[redacted]	[redacted]
			Responder	[redacted]	[redacted]	[redacted]
		Placebo	Non-responder	[redacted]	[redacted]	[redacted]
			Responder	[redacted]	[redacted]	[redacted]
	BASDAI50	ETN 50mg	Non-responder	[redacted]	[redacted]	[redacted]
			Responder	[redacted]	[redacted]	[redacted]
		Placebo	Non-responder	[redacted]	[redacted]	[redacted]
			Responder	[redacted]	[redacted]	[redacted]

Summary

The mean baseline BASDAI and BASFI are presented by treatment response at week 12 (or 14 for golimumab) for 3 of the five anti-TNFs. This reveals that in patients with AS and patients with nr-axSpA, on average baseline BASDAI does not differ greatly between responders and non-responders either to placebo or to active anti-TNF therapy. In patients with AS or nr-axSpA from the trials of adalimumab (ATLAS and **M10-791**) and golimumab (GO-RAISE) on average baseline BASFI was higher in non-responders compared with responders. However, this was not seen in the etanercept trials.

11.7 Appendix 7 Long-term efficacy data

Table 140 data from open label extensions of included RCTs

						Results			
Study characteristics						No (%) of responders			Other outcomes
Trial cohort and references of open-label studies	Population	Treatment & dose	Time point	No of patients	Imputation methods & withdrawal criteria	ASAS 20	ASAS 40	BASDAI 50	Other results ASAS 50, ASAS 70, BASDAI, BASFI, BASMI, mSASSS, MASES, SF-36 MCS, SF-36 PCS, EQ-5D
Haibel 2008[55, 57, 58, 174-177]	nr-axSpA with inflammation	Adalimumab 40mg every other week. Non-responders at the end of the double-blind trial (week 12) and after open-label therapy for at least 12 weeks were eligible for dose escalation to 40 mg/week.	52 weeks	46	ITT Patients who withdrew from the study were counted as non-responders for categorical data. LOCF was used for continuous variables.		23/46 (50%)	24/46 (52%)	BASDAI change from baseline: 2.8 (95% CI 2.1, 3.6) BASFI change from baseline: 2 (95% CI 1.4, 2.6) BASMI change from baseline: -0.4 (95% CI -0.7 to -0.04) EQ5D change from baseline: 0.22 (95 % CI 0.13, 0.31) SF-36 MCS change from baseline: 4.9 (95% CI 1.6, 8.1) SF-36 PCS change from baseline: 10.3 (95% CI 6.9, 13.8) ASQoL change from baseline: 5.3 (95% CI 3.8, 6.7) MASES change from baseline: 0.9 (95% CI -0.02 to 1.9) 26 patients with MRIs at baseline and 52 weeks showed no change in sclerosis or in erosions
ABILITY-1 2013[52, 178-183]	nr-axSpA with inflammation	Adalimumab PLA/AD	52 weeks	61					SF-36 PCS change from baseline: 10.0 (SD 9.91)
		Adalimumab AD/AD	52 weeks	55					SF-36 PCS change from baseline: 11.0 (SD 9.93)
		Adalimumab 40mg every other week	68 weeks	111 (Pts MRI+ or CRP+)	Observed (n=142 at week 12)		77/111(69%)	74/111(67%)	
		Adalimumab 40mg every other week	104 weeks	102					
		Adalimumab 40mg every other week	156 weeks	97 (Pts MRI+ or CRP+)	Observed (n=142 at week 12)	83/97 (86%)	67/97 (69%)	70/97(72%)	ASAS 50 responders: 58 ASAS 70 responders: 47

						Results			
Study characteristics						No (%) of responders			Other outcomes
Trial cohort and references of open-label studies	Population	Treatment & dose	Time point	No of patients	Imputation methods & withdrawal criteria	ASAS 20	ASAS 40	BASDAI 50	Other results ASAS 50, ASAS 70, BASDAI, BASFI, BASMI, mSASSS, MASES, SF-36 MCS, SF-36 PCS, EQ-5D
ATLAS 2006[63, 130, 131, 184-190]	Ankylosing spondylitis	Adalimumab 40 mg every other week	52 weeks	311 had at least one dose	Observed	193/ 276 (70%)	138/ 276 (50%)	167/ 276 (61%)	BASDAI change from baseline: -3.5 (SD 2.55) n=274 BASFI change from baseline: -2.6 (SD 2.04) n=274 BASMI final value: 3.2 (SD 2.2) n=273 SF-36 MCS change from baseline: 5.6 (SD 10.35) n=265 SF-36 PCS change from baseline: 10.19 (SD 9.5) n=265 ASQoL change from baseline: -4.8 (SD 4.41) n=274 MASES final value: 2.4 (SD 4.6) n=279
		Adalimumab 40 mg every other week	76 weeks		Observed				BASDAI change from baseline: -3.8 (SD 2.33) n=270 BASFI change from baseline: -2.8 (SD 2.1) n=270 SF-36 MCS change from baseline: 5.1 (SD 11.06) n=263 SF-36 PCS change from baseline: 10.8 (SD 9.88) n=263 ASQoL change from baseline: -5 (SD 4.32) n=270
		Adalimumab 40 mg every other week	104 weeks	173	Observed	135/ 173 (78%)	109/ 173 (63%)	122/ 173 (71%)	BASDAI change from baseline: -3.9 (SD 2.44) n=262 BASFI change from baseline: -2.9 (SD 2.14) n=261 BASMI final value: 3.1 (SD 2.2) n=173 SF-36 MCS change from baseline: 5.7 (SD 10.96) n=255 SF-36 PCS change from baseline: 11 (SD 9.88) n=255 ASQoL change from baseline: -5.4 (SD 4.28) n=263 MASES change from baseline: 2.2 (SD 4.4) n=217
		Adalimumab 40 mg every other week	128 weeks		Observed				BASDAI change from baseline: -3.9 (SD 2.39) n=242 BASFI change from baseline: -2.9 (SD 2.17) n=242 SF-36 MCS change from baseline: 4.1 (SD 10.84) n=229 SF-36 PCS change from baseline: 11.3 (SD 9.68) n=229 ASQoL change from baseline: -5.3 (SD 4.35) n=242
		Adalimumab 40 mg every other	156 weeks		Observed				BASDAI change from baseline: -3.9 (SD 3.39) n=236 BASFI change from baseline: -3 (SD 2.1) n=236

						Results			
Study characteristics						No (%) of responders			Other outcomes
Trial cohort and references of open-label studies	Population	Treatment & dose	Time point	No of patients	Imputation methods & withdrawal criteria	ASAS 20	ASAS 40	BASDAI 50	Other results ASAS 50, ASAS 70, BASDAI, BASFI, BASMI, mSASSS, MASES, SF-36 MCS, SF-36 PCS, EQ-5D
		week							BASMI final value: 3.7 (SD 1.8) n=233 SF-36 MCS change from baseline: 5.6 (SD 11.59) n=227 SF-36 PCS change from baseline: 11.6 (SD 9.65) n=227 ASQoL change from baseline: -5.4 (SD 4.36) n=236
		Adalimumab 40 mg every other week	5 years	125(pts randomised to ADA and completed 5 yrs)	Observed	111/ 125 (89%)	88/ 125 (70%)	96/ 124 (77%)	BASDAI final value: 1.8 (SD 1.9) n=124 BASFI final value: 2.1 (SD 2.1) n=125 BASMI final value: 3.7 (SD 1.8) n=124 SF-36 PCS final value: 44.4 (SD 10) n=165 ASQoL final value: 4.8 (SD 4.8) n=169
RAPID-axSpA 2014[46, 191-193]	Ankylosing spondylitis	Certolizumab pegol 200 mg every 2 weeks	48 weeks	65	NRI+LOCF	47/65 (72%)	34/65 (52%)		BASDAI final value: 3.3 BASFI final value: 3
		Certolizumab pegol 400 mg every 4 weeks	48 weeks	56		42/56 (75%)	36/56 (64%)		BASDAI final value: 3 BASFI final value: 3.2
		Certolizumab pegol - all	48 weeks	121		[redacted]	[redacted]		
		Certolizumab pegol 200mg every 2 weeks	96 weeks	65	Non-responder imputation	[redacted]			
		Certolizumab pegol 400 mg every 4 weeks	96 weeks	56	Non-responder imputation	[redacted]			
		Certolizumab pegol – all	96 weeks	121	Non-responder imputation	78/ 121 (64%)	61/ 121 (50%)		

						Results			
Study characteristics						No (%) of responders			Other outcomes
Trial cohort and references of open-label studies	Population	Treatment & dose	Time point	No of patients	Imputation methods & withdrawal criteria	ASAS 20	ASAS 40	BASDAI 50	Other results ASAS 50, ASAS 70, BASDAI, BASFI, BASMI, mSASSS, MASES, SF-36 MCS, SF-36 PCS, EQ-5D
		Certolizumab pegol - all	96 weeks	93	Observed case	78/93 (84%)	61/93 (66%)		
	nr-axSpA with inflammation	Certolizumab pegol 200 mg every 2 weeks	48 weeks	46	Non-responder imputation was used for categorical measures and LOCF for quantitative measures (48 week data)	32/46 (70%)	25/46 (54%)		BASDAI final value: 2.9 BASFI final value: 2.1
		Certolizumab pegol 400 mg every 4 weeks	48 weeks	51		35/51 (69%)	30/51 (59%)		BASDAI final value: 3.3 BASFI final value: 2.8
		Certolizumab pegol - all	48 weeks	97		[redacted]	[redacted]		
		Certolizumab pegol 200mg every 2 weeks	96 weeks	46	Non-responder imputation	[redacted]			
		Certolizumab pegol 400 mg every 4 weeks	96 weeks	51	Non-responder imputation	[redacted]			
		Certolizumab pegol - all	96 weeks	97	Non-responder imputation	59/97 (61%)	49/97 (51%)		
		Certolizumab pegol - all	96 weeks	74	Observed case	59/74 (80%)	49/74 (66%)		
Davis 2003[47, 111, 134, 135, 194, 195]	Ankylosing spondylitis	Placebo then etanercept	72 weeks	105	Observed case				BASFI final value: 32.3 (SD 2.5)
		Etanercept then etanercept	96 weeks	95	Observed case	70/95 (74%)			ASAS 70 responders: 44 BASFI final value: 25.4 (SD 2.4)
		Combined groups	96 weeks	257					mSASSS change from baseline: 0.91 (SD 2.45)

						Results			
Study characteristics						No (%) of responders			Other outcomes
Trial cohort and references of open-label studies	Population	Treatment & dose	Time point	No of patients	Imputation methods & withdrawal criteria	ASAS 20	ASAS 40	BASDAI 50	Other results ASAS 50, ASAS 70, BASDAI, BASFI, BASMI, mSASSS, MASES, SF-36 MCS, SF-36 PCS, EQ-5D
		Placebo then etanercept	168 weeks	127	LOCF	77/ 127 (61%)	64/ 127 (50%)		
		Etanercept then etanercept	192 weeks	124	LOCF	83/ 124 (67%)	61/ 124 (49%)		
Dougados 2014[54, 196]	nr-axSpA mixed	Etanercept then etanercept 50mg weekly	32 weeks	100	NRI		[redacted]		
		Placebo then etanercept 50mg weekly	32 weeks	105	NRI		[redacted]		
		Etanercept then etanercept 50mg weekly	40 weeks	100	NRI		[redacted]		
		Placebo then etanercept 50mg weekly	40 weeks	105	NRI		[redacted]		
		Etanercept plus placebo groups together 50mg weekly	48 weeks	[redacted] (189 observed)	NRI +LOCF	147	108	128	[redacted]
		Etanercept then etanercept 50mg weekly	48 weeks	100			[redacted]		
		Placebo then etanercept 50mg weekly	48 weeks	105			[redacted]		

						Results			
Study characteristics						No (%) of responders			Other outcomes
Trial cohort and references of open-label studies	Population	Treatment & dose	Time point	No of patients	Imputation methods & withdrawal criteria	ASAS 20	ASAS 40	BASDAI 50	Other results ASAS 50, ASAS 70, BASDAI, BASFI, BASMI, mSASSS, MASES, SF-36 MCS, SF-36 PCS, EQ-5D
Gorman 2002[49, 195, 197]		Etanercept then etanercept	28 weeks	19	NRI	[redacted]			[redacted]
		Placebo then etanercept	28 weeks	19	NRI	[redacted]			[redacted]
		Etanercept then etanercept	40 weeks	19	NRI	[redacted]			[redacted]
		Placebo then etanercept	40 weeks	19	NRI	[redacted]			[redacted]
Calin 2004[48, 136, 137]	Ankylosing spondylitis	Etanercept then etanercept	60 weeks	42	LOCF				BASDAI final value: 2.1 BASFI final value: 2.9 mSASSS change from baseline: 0.36 (95% CI -0.1 to 0.8) n=33
		Placebo then etanercept	60 weeks	39	LOCF				BASDAI final value: 2.7 BASFI final value: 3.4 mSASSS change from baseline: -0.15 (95% CI -0.7 to 0.4) n=34
		Combined group	108 weeks	81	LOCF	[redacted]	44/81 (54%)	[redacted]	[redacted] BASFI final value: 2.9
		Etanercept then etanercept	108 weeks	42	LOCF				BASDAI final value: 2.3 BASFI final value: 3
		Placebo then etanercept	108 weeks	39	LOCF				BASDAI final value: 2.9 BASFI final value: 3.5
		Combined group	264 weeks	59	LOCF		40/59 (68%)	39/59 (66%)	[redacted] BASDAI final value: 2.7 BASFI final value: 3.2

						Results			
Study characteristics						No (%) of responders			Other outcomes
Trial cohort and references of open-label studies	Population	Treatment & dose	Time point	No of patients	Imputation methods & withdrawal criteria	ASAS 20	ASAS 40	BASDAI 50	Other results ASAS 50, ASAS 70, BASDAI, BASFI, BASMI, mSASSS, MASES, SF-36 MCS, SF-36 PCS, EQ-5D
Bao 2012[53, 91, 198, 199]	Ankylosing spondylitis	Golimumab 50 mg	52 weeks	108	ITT	76/ 108 (70%)	53/ 108 (49%)	62/ 108 (57%)	
GO-RAISE 2008[86, 112, 132, 133, 200-212]	Ankylosing spondylitis	Golimumab placebo - 50 mg	104 weeks	78	ITT	30/78 (38%)	30/78 (38%)		BASDAI final value: median 6 (IQR 1.36 to 7.79) BASFI final value: median 4.9 (IQR 0.98 to 7.07) mSASSS change from baseline: 1.6 (SD 4.6) n=66
		Golimumab 50 mg	104 weeks	138	ITT	83/ 138 (60%)	77/ 138 (56%)		BASDAI final value: median 2.7 (IQR 0.84 to 6.08) BASFI final value: median 2.2 (IQR 0.52 to 5.80) mSASSS change from baseline: 0.9 (SD 2.7) n=111
		Golimumab 100 mg	104 weeks	140	ITT	100/ 140 (71%)	76/ 140 (54%)		BASDAI final value: median 2.7 (IQR 1.08 to 5.34) BASFI final value: median 1.8 (IQR 0.49 to 4.79) mSASSS change from baseline: 0.9 (SD 3.9) n=122
		All patients randomised (all golimumab from wk 24)	104 weeks	356	NIR +LOCF	249/356 (70%)	213/356 (60%)		
		All patients randomised (all golimumab from wk 24)	160 weeks	356	NIR +LOCF	246/356 (69%)	208/356 (58%)		
		Golimumab placebo – 50 mg	208 weeks	78					mSASSS change from baseline: 2.1 (SD 5.2) n=66
		Golimumab 50 mg	208 weeks	138					mSASSS change from baseline: 1.3 (SD 4.1) n=111
		Golimumab 100 mg	208 weeks	140					mSASSS change from baseline: 2 (SD 5.6) n=122
		All patients	256 weeks	356	NIR +LOCF	235/3	203/3	199/3	

						Results			
Study characteristics						No (%) of responders			Other outcomes
Trial cohort and references of open-label studies	Population	Treatment & dose	Time point	No of patients	Imputation methods & withdrawal criteria	ASAS 20	ASAS 40	BASDAI 50	Other results ASAS 50, ASAS 70, BASDAI, BASFI, BASMI, mSASSS, MASES, SF-36 MCS, SF-36 PCS, EQ-5D
		randomised (all golimumab from wk 24)				56 (66%)	56 (57%)	56 (58%)	
Tam 2013[107]	Ankylosing spondylitis	Golimumab 50 mg monthly	54 weeks	19	UC	18			
		Placebo/golimumab	54 weeks	17	UC	14			
		Placebo/placebo	54 weeks	3	UC	1			
Park 2013[105, 213]	Ankylosing spondylitis	Inflectra (biosimilar to infliximab) 5mg/kg	78 weeks	88	ITT	61/88 (69%)	50/88 (57%)		
		Inflectra then infliximab (switched at week 54) 5 mg/kg	78 weeks	86	ITT	64/86 (74%)	43/86 (50%)		
		Inflectra (biosimilar to infliximab) 5 mg/kg	102 weeks	88	ITT	67/88 (76%)	53/88 (60%)		
		Inflectra then infliximab (switched at week 54) 5 mg/kg	102 weeks	86	ITT	60/86 (70%)	48/86 (56%)		
Braun 2002[94, 155, 214-221]	Ankylosing spondylitis	Infliximab 5 mg/kg (infusion at weeks 0, 2, 6)	54 weeks	34	NIR for binary data A completer analysis was conducted.			47%	mSASSS reported for 2 groups: patients with worsening of BASFI >1 and those <1
		Placebo/infliximab	54 weeks	35				51%	
		Aggregate	54 weeks	69				33/69	BASDAI final value: 2.5 (SD 1.7) n=52

						Results			
Study characteristics						No (%) of responders			Other outcomes
Trial cohort and references of open-label studies	Population	Treatment & dose	Time point	No of patients	Imputation methods & withdrawal criteria	ASAS 20	ASAS 40	BASDAI 50	Other results ASAS 50, ASAS 70, BASDAI, BASFI, BASMI, mSASSS, MASES, SF-36 MCS, SF-36 PCS, EQ-5D
								(48%)	BASFI final value: 3.0 (SD 2.2) n=52 BASMI final value: 2.4 (SD 2.0) n=52 SF-36 MCS final value: 50.9 (SD 8.9) n=52 SF-36 PCS final value: 40.6 (SD 10.6) n=52 BASDAI final value: 2.4 (SD 1.6) n=46 BASFI final value: 3.1 (SD 2.2) n=46 BASMI final value: 2.4 (SD 1.9) n=46 SF-36 MCS final value: 51.5 (SD 8.6) n=46 SF-36 PCS final value: 40.2 (SD 10.8) n=46
		Aggregate	102 weeks	69	NRI for binary data. A completer analysis was conducted			30/69 (43%)	BASDAI final value: 2.6 (SD 2) n=52 BASFI final value: 3.0 (SD 2.2) n=52 BASMI final value: 2.7 (SD 2.1) n=52 SF-36 MCS final value: 50.2 (SD 9.5) n=52 SF-36 PCS final value: 40.9 (SD 11.1) n=52 BASDAI final value: 2.6 (SD 2) n=46 BASFI final value: 3.1 (SD 2.3) n=46 BASMI final value: 2.7 (SD 2.1) n=46 SF-36 MCS final value: 51.4 (SD 8.9) n=46 SF-36 PCS final value: 40.5 (SD 11.4) n=46
		Aggregate	156 weeks	46	Completer analysis. To calculate means, LOCF was used.	36/38 (95%)	28/38 (74%)	24/38 (63%) 28/46	BASDAI final value: 2.7 (SD 2) n=46? BASFI final value: 3.1 (SD 2.5) BASMI final value: 2.8 (SD 2.2) SF-36 MCS final value: 48.8 (SD 10.4)

						Results			
Study characteristics						No (%) of responders			Other outcomes
Trial cohort and references of open-label studies	Population	Treatment & dose	Time point	No of patients	Imputation methods & withdrawal criteria	ASAS 20	ASAS 40	BASDAI 50	Other results ASAS 50, ASAS 70, BASDAI, BASFI, BASMI, mSASSS, MASES, SF-36 MCS, SF-36 PCS, EQ-5D
								(61%)	SF-36 PCS final value: 41.6 (SD 11.7)
ASSERT 2005[97, 222-227]	Ankylosing spondylitis	Infliximab (on placebo 0-24) 5 mg							
			Week 102	78 (remaining study patients may have taken high (unlicenced ose of infliximab)	Completer analysis		28/61 (46%)		BASMI change from baseline: -1 (IQR -2.0 to 0.0) SF-36 MCS change from baseline: 2.3 (IQR -3.6 to 11.9) SF-36 PCS change from baseline: 8.3 (IQR 2.5 to 17.7)
					ITT LOCF		33/78 (42%)		

One trial which was extended evaluated only spinal and sacroiliac joint inflammation (Lambert 2007) – results not shown.

11.8 Appendix 8 Adverse events

Table 141 Adverse events in RCT placebo phases

Trial name	**Population**	**Treatment arm**	**Dose**	**Timepoint (weeks)**	**No of pts randomised**	**SAEs**	**Serious infections**	**TB (incl TB reactivation)**	**Injection site reactions**	**Congestive heart failure**	**Malignancies**	**Non-melanoma skin cancer**	**Withdrawals due to Adverse events**
Haibel 2008[55]	nr-axSpA	Adalimumab	40mg	12	22	0	0			0	0	0	0
	nr-axSpA	placebo	0	12	24	0	0			0	0	0	0

Trial name	Population	Treatment arm	Dose	Timepoint (weeks)	No of pts randomised	SAEs	Serious infections	TB (incl TB reactivation)	Injection site reactions	Congestive heart failure	Malignancies	Non-melanoma skin cancer	Withdrawals due to Adverse events
Hu 2012[59]	AS AS	Adalimumab Placebo	40 mg 0	12 12	26 20								
Huang 2014[60]	AS AS	Adalimumab Placebo	40 mg 0	12 12	229 115	1 1	1 0	0 0		0 0	0 0	0 0	4 0
Lambert 2007[61]	AS AS	Adalimumab Placebo	40 mg 0	12 12	38 44								
ABILITY-1 (2013) (licensed population)[52]	nr-axSpA nr-axSpA	Adalimumab Placebo	40mg 0	12 12	95 97	3 1	0 0	0 0		0 0		1 1	
ATLAS (2006)[63]	AS AS	Adalimumab Placebo	40 mg 0	12 12	208 107								

Trial name	Population	Treatment arm	Dose	Timepoint (weeks)	No of pts randomised	SAEs	Serious infections	TB (incl TB reactivation)	Injection site reactions	Congestive heart failure	Malignancies	Non-melanoma skin cancer	Withdrawals due to Adverse events
RAPID-axSpA (2014)[46]	AS	Certolizumab pegol	200mg	12	65	Data only for whole group							
	AS	Certolizumab pegol	400mg	12	56								
	AS	Placebo	0	12	57								
	nr-axSpA	Certolizumab pegol	200mg	12	46								
	nr-axSpA	Certolizumab pegol	400mg	12	51								
	nr-axSpA	Placebo	0	12	50								
Barkham 2010[72]	AS	Etanercept	25mg twice weekly	12	20	0							0
	AS	Placebo	0	12	20	0							0
Davis 2003[47]	AS	Etanercept	25mg	12	138								

Trial name	Population	Treatment arm	Dose	Timepoint (weeks)	No of pts randomised	SAEs	Serious infections	TB (incl TB reactivation)	Injection site reactions	Congestive heart failure	Malignancies	Non-melanoma skin cancer	Withdrawals due to Adverse events
	AS	Placebo	0	12	139								
	AS	Etanercept	25mg	24	138		0	0	41				7
	AS	Placebo	0	24	139		1	0	13				1
Dougados 2011[74]	AS	Etanercept	50mg	12	39								
	AS	Placebo	0	12	43								
Dougados 2014[54]	nr-axSpA mixed	Etanercept	50mg	12	106	2			3		1		1
	nr-axSpA mixed	Placebo	0	12	109	1			0		0		0
	nr-axSpA	Etanercept	50mg	12	94								
	nr-axSpA	Placebo	0	12	95								

Trial name	Population	Treatment arm	Dose	Timepoint (weeks)	No of pts randomised	SAEs	Serious infections	TB (incl TB reactivation)	Injection site reactions	Congestive heart failure	Malignancies	Non-melanoma skin cancer	Withdrawals due to Adverse events
Gorman 2002[49]	AS AS	Etanercept Placebo	25mg 0	16 16	20 20	0 0			5 1				0 0
Calin 2004[48]	AS AS	Etanercept Placebo	25 mg 0	12 12	45 39	1 0	0 0		15 6				0 0
Van der Heijde 2006[51]	AS AS AS	Etanercept Etanercept Placebo	25mg 50mg 0	12 12 12	150 155 51		1 1 0	0 0 0	32 34 6		0 0 0		6 8 0
Giardina 2010[84]	AS AS	Etanercept Infliximab	50mg 5mg/kg	104 104	25 25		1 2	0 0	5 1	0 0	0 0		0 0
GO-RAISE 2008[86]	AS	Golimumab	50mg	16	138	5							

Trial name	Population	Treatment arm	Dose	Timepoint (weeks)	No of pts randomised	SAEs	Serious infections	TB (incl TB reactivation)	Injection site reactions	Congestive heart failure	Malignancies	Non-melanoma skin cancer	Withdrawals due to Adverse events
	AS AS	Golimumab placebo	100mg 0	16 16	140 78	7 4							
Bao 2014[53]	AS AS	Golimumab Placebo	50mg 0	14 14	108 105								
Tam 2014[107]	AS AS	Golimumab Placebo	50mg 0	24 24	20 21								0 1
Barkham 2009[56]	nr-axSpA nr-axSpA	Infliximab Placebo	5 mg/kg 0	16 16	20 20	0							1
Braun 2002[94]	AS AS	Infliximab Placebo	5mg/kg 0	12 12	34 35	3		1 0	0 0				4 0

Trial name	**Population**	**Treatment arm**	**Dose**	**Timepoint (weeks)**	**No of pts randomised**	**SAEs**	**Serious infections**	**TB (incl TB reactivation)**	**Injection site reactions**	**Congestive heart failure**	**Malignancies**	**Non-melanoma skin cancer**	**Withdrawals due to Adverse events**
Marzo-Ortega (2005)[50]	AS	Infliximab+methotrexate	5mg/kg	10	28								
	AS	Placebo+metotrexate	0	10	14								
	AS	Infliximab+methotrexate	5mg/kg	30	28	0			1				0
	AS	Placebo+metotrexate	0	30	14	0			0				0
Van den Bosch (2002)[96]	AS	Infliximab	5mg/kg	12	9	Unclear			Unclear				
	AS	Placebo	0	12	12	Unclear			Unclear				
ASSERT (2005)[97]	AS	Infliximab	5mg/kg	24	202	7	2	0	22		0		2
	AS	Placebo	0	24	75	2	0	0	7		0		1
Park 2013[105]	AS	Inflectra (CT-P13)	5mg/kg	14	125								

Trial name	Population	Treatment arm	Dose	Timepoint (weeks)	No of pts randomised	SAEs	Serious infections	TB (incl TB reactivation)	Injection site reactions	Congestive heart failure	Malignancies	Non-melanoma skin cancer	Withdrawals due to Adverse events
	AS	Infliximab	5mg/kg	14	125								
	AS	Inflectra (CT-P13)	5mg/kg	30	128	6		2	5				8
	AS	Infliximab	5mg/kg	30	122	8		1	6				5
	AS	Inflectra (CT-P13)	5mg/kg	54	125								
	AS	Infliximab	5mg/kg	54	125								

Blank fields indicate that data were not reported for that outcome

11.9 Appendix 9: Extended synthesis models

In this Appendix we describe in more detail the data and modelling approaches implemented in Section 6. Note that while this Appendix aims to provide a methodological description of methods, a full description of findings and its interpretations are in Section 6.

General aspects of implementation and software

The synthesis was conducted from a Bayesian perspective, using WinBUGS (a Markov Chain Monte Carlo simulation based software for Bayesian inference). For burn-in, we ran 100,000 simulations and another 100,000 were used in inferences. Convergence was assessed by running two chains and convergence was assumed if the Gelman-Rubin statistic was equal to 1. Goodness of fit was assessed using the Deviance Information Criterion (DIC).[160] Models with smaller DIC are better supported by the data. In the presence of autocorrelation, the MCMC simulation for inference was increased to 200,000 and a thin of 20 was applied (yielding a sample for inference of 10000 for each chain).

The main synthesis models will pool differences between treatment and control in change scores from baseline (BASDAI and BASFI). The treatment associated with the lowest (most negative) mean change score is expected to be best. However, it is important to quantify the uncertainty around the estimates and for this reason standard deviations will be reported alongside expected values. Where odds ratios are presented, median values instead of means were used to summarise inferences.

Where possible, meta-regression analyses were conducted to evaluate potential treatment effect modifiers. Meta-regression is a tool aimed at examining the impact of variables on effect size using regression-based techniques. In these explorations, the following baseline characteristics were considered: BASDAI score, BASFI score, age, gender, duration of symptoms (years) and C-reactive protein (CRP).

Relative effectiveness estimates for models assuming exchangeability across treatments (A5) are based on the predictive distribution, representing the distribution of the data averaged over all possible parameter values. This summary statistic best reflects the impact of uncertainty in the parameters of the model and is here judged as a more appropriate basis to be used in the decision model.[161]

11.9.1 Modelling approach A

Brief description of the data

Based on study populations and follow-up (i.e. around 12-week in duration), 16 of the RCTs are considered directly relevant to the decision problem for the AS population (studies 1 to 16 in Table 142). One of these studies did not report BASDAI or BASFI outcomes (study 3) and thus could not be included in analyses. The 15 remaining studies reported at least one outcome measure – BASDAI50 and/or change from baseline on BASDAI and BASFI scores.

Table 142: Evidence on BASDAI and BASFI related outcomes for the AS population

	Trial name	treat	N treat	N PLA	BASDAI50	change BASDAI	change BASFI
1	Hu 2012	1	26	20		X	X
2	Huang 2014	1	229	115	X	X	X
3	Lambert 2007	1	38	44			
4	ATLAS (2006)	1	208	107	X	X	
5	RAPID-axSpA (2014)	2	121	57	X	X	X
6	Barkham 2010	3	20	20	X	X*	X*
7	Davis 2003	3	138	139		X	X
8	Dougados 2011	3	39	43	X	X	X
9	Gorman 2002	3	20	20			X
10	Calin 2004	3	45	39		X	X
11	Van der Heijde 2006	3	305	51	X		
12	GO-RAISE 2008	4	138	78	X		X
13	Bao 2012	4	108	105	X		X
14	Braun 2002	5	34	35	X	X*	X*
15	Marzo-Ortega (2005)	5	28	14		X	X*
16	Van den Bosch (2002)	5	9	12		X*	X*

* Do not report any measure of dispersion (such as standard deviations)
treat: 1 =ADA, 2=CER (CER200 and/or CER400), 3=ETA (ETA25 and/or ETA50), 4=GOL50 , 5=INF

Note that some studies only report one of the BASDAI measures. For example, the golimumab trials (studies 12 and 13) only report BASDAI 50 and not the absolute change in this score.

This modelling approach directly evaluates relative treatment effects – i.e. log OR for BASDAI50 response and the difference between treatment and placebo in change in BASDAI and BASFI from baseline. The dataset analysed is shown in Table 143

Table 143. Modelling approach A: Data

Study, j	Treat, t	Outcome, o	y	se
1	1	1	--	--
2	1	1	1.61	0.28
3	1	1	--	--
4	1	1	1.47	0.30
5	2	1	1.79	0.42
6	3	1	2.30	1.13
7	3	1	--	--
8	3	1	1.04	0.48
9	3	1	--	--
10	3	1	--	--
11	3	1	1.78	0.37
12	4	1	1.47	0.36
13	4	1	2.34	0.50
14	5	1	2.45	0.69
15	5	1	--	--
16	5	1	--	--

1	1	2	-1.60	0.67
2	1	2	-1.40	0.22
3	1	2	--	--
4	1	2	-1.80	0.28
5	2	2	-1.45	0.36
6	3	2	-1.87	0.90*
7	3	2	-1.91	0.26
8	3	2	-1.20	0.44
9	3	2	--	--
10	3	2	-1.87	0.49
11	3	2	--	--
12	4	2	--	--
13	4	2	--	--
14	5	2	-2.60	0.69*
15	5	2	-1.73	0.70
16	5	2	-2.97	1.26*
1	1	3	-0.90	0.68
2	1	3	-1.28	0.20
3	1	3	--	--
4	1	3	--	--
5	2	3	-1.10	0.37
6	3	3	-1.56	0.93*
7	3	3	-1.34	0.29
8	3	3	-1.20	0.40
9	3	3	-2.20	0.92
10	3	3	-1.73	0.45
11	3	3	--	--
12	4	3	-1.50	0.27
13	4	3	-1.37	0.32
14	5	3	-2.00	0.71*
15	5	3	-1.82	1.00*
16	5	3	-3.21	1.28*

outcome: **1** logOR for BASDAI50, **2** difference between treatment and placebo on change in BASDAI from baseline, **3** difference between treatment and placebo on change in BASFI from baseline

* No standard deviation was reported in the original studies, the highest standard deviation from the other trials was used as a conservative estimate.

treat = treatment: 1 =ADA, 2=CER, 3=ETA, 4=GOL, 5=INF; **BASDAI**: results from individual studies on difference between treatment and placebo in change from baseline in BASDAI scores; **BASFI**: results from individual studies on difference between treatment and placebo in change from baseline in BASFI scores **se**: standard error associated with each outcome

Description of synthesis methods for modelling approach A

Consider we have available information on *J* trials comparing an individual treatment, *k* (out of the total number of treatments *T*) to placebo. Trials report one or more outcomes, *o*. Information on outcome *o* for treatment *k* in a study *j* is represented by y_{jko} and is used alongside the standard error for this measure, se^2_{jko}. In common with the approach implemented in Section 4, all outcomes are here assumed normally distributed, with mean θ_{jko}. We implemented alternative models that differ in the way treatment effects are considered; a summary of each is presented below. Note that at this stage each outcome was synthesised independently.

Model A1 (treatments: independent, studies: FE) – This model considers the *j* treatments to be independent, i.e. assumes the effects to differ between treatments, $d[k,o]$. This is a fixed effect model in that multiple studies evaluating the same treatment are considered to measure the same treatment effect.

The model used was:

Likelihood: $y_{jko} \sim \text{dnorm}(\theta_{jko}, se^2_{jko})$

Model: $\theta_{jko} = d[k,o]$

Priors: $d[k,o] \sim N(0,0.001)$

Model A2 (treatments: independent, studies: RE) – This model differs from A1 in that a random effect is assumed to describe the findings of multiple studies evaluating the same treatment.

The model used was:

Likelihood: $y_{jko} \sim \text{dnorm}(\theta_{jko}, se^2_{jko})$

Model: $\theta_{jko} \sim N(d[k,o], \sigma^2_o)$

Priors: $d[k,o] \sim N(0,0.001)$; $\sigma^2_o \sim dunif(0,10)$

The random effect is defined using a variance parameter for each outcome but common across treatments, σ^2_o.

Model A3 (treatments: equal, studies: FE) – This model differs from A1 in that treatments are not assumed to differ. The model thus evaluates a common relative effectiveness for all anti-TNFs, $d[o]$, for each outcome.

The model used was:

Likelihood: $y_{jko} \sim \text{dnorm}(\theta_{jko}, se^2_{jko})$

Model: $\theta_{jko} = d[o]$

Priors: $d[k,o] \sim N(0,0.001)$

Model A4 (treatments: equal, studies: RE) – This model differs from A3 in that a random effect is assumed to describe the findings of multiple studies evaluating the same treatment.

The model used was:

Likelihood: $y_{jko} \sim \text{dnorm}(\theta_{jko}, se_{jko}^2)$

Model: $\theta_{jko} \sim N(d[o], \sigma_o^2)$

Priors: $d[o] \sim N(0,0.001)$; $\sigma_o^2 \sim dunif(0,10)$

Model A5 (treatments: exchangeable, studies: FE) – This model differs from A1 in that a random effect is used to describe any differences between treatments (exchangeability is assumed). This model thus assumes the treatments to have a similar, but not equal, effectiveness – there are differences between the effectiveness of treatments that we may not be able to explain but that we should consider.

The model used was:

Likelihood: $y_{jko} \sim \text{dnorm}(\theta_{jko}, se_{jko}^2)$

Model: $\theta_{jko} = d[k, o]$

$d[k, o] \sim N(D[o], \gamma_o^2)$

Priors: $D[o] \sim N(0,0.001)$; $\gamma_1^2 \sim dunif(0,2)$; $\gamma_2^2, \gamma_3^2 \sim dunif(0,10)$

The parameter γ_o^2 is the variance parameter defining the random effect across treatment. The priors differ for outcome 1 as this is a log odds while outcomes 2 and 3 are assumed continuous measures.

Within this modelling approach we explored potential heterogeneity in treatment effects using meta-regression (i.e. potential treatment effect modifiers). We did so by extended the modelling approach in A1 to include treatment effect interactions with baseline characteristics (centered on their means where relevant). We have explored the inclusion of alternative covariates by evaluating the DIC associated with alternative models.

Results of modelling approach A

The results of each modelling approach are shown in below.

Table 144: Modelling approach A – results

	A1. Treat: indep Studies: FE (median, SD)	**A2. Treat: indep Studies: RE** (median, SD)	**A3. Treat: common Studies: FE** (median, SD)	**A4. Treat: common Studies: RE** (median, SD)	**A5. Treat: exchang Studies: FE** (median, SD)
Outcome 1: OR on BASDAI50					
Adalimumab	4.71 (1.00)	4.69 (6.11)			
Certolizumab	6.02 (3.33)	6.04 (22.87)			
Etanercept	4.73 (1.43)	4.72 (3.32)	5.21 (0.72)	5.30 (0.98)	5.34 (9.79)*
Golimumab	5.86 (1.81)	6.10 (7.45)			
Infliximab	11.9 (11.94)	12.10 (44.00)			
σ_1	--	0.31 (0.30)	--	0.15 (0.14)	--
D_1	--	--	--	--	1.69 (0.23)
γ_1	--	--	--	--	0.27 (0.28)
Outcome 2: change in BASDAI	(mean, SD)	(mean, SD)	(mean, SD)	(mean, SD)	(mean, SD)
Adalimumab	-1.56 (0.16)	-1.57 (0.27)			
Certolizumab	-1.45 (0.37)	-1.46 (0.51)			
Etanercept	-1.76 (0.20)	-1.73 (0.28)	-1.66 (0.11)	-1.67 (0.15)	-1.70 (0.87)*
Golimumab	NA	NA			
Infliximab	-2.28 (0.46)	-2.27 (-2.28)			
σ_2	--	0.25 (0.24)	--	0.25 (0.19)	--
D_2	--	--	--	--	-1.63 (0.57)
γ_2	--	--	--	--	0.43 (0.63)
Outcome 3: change in BASFI	(mean, SD)	(mean, SD)	(mean, SD)	(mean, SD)	(mean, SD)
Adalimumab	-1.22 (0.18)	-1.18 (0.29)			
Certolizumab	-1.10 (0.37)	-1.11 (0.47)			
Etanercept	-1.48 (0.19)	-1.50 (0.24)	-1.38 (0.11)	-1.39 (0.13)	-1.41 (0.49)*
Golimumab	-1.45 (0.20)	-1.44 (0.29)			
Infliximab	-2.16 (0.53)	-2.17 (0.56)			
σ_3	--	0.22 (0.19)	--	0.14 (0.12)	--
D_3	--	--	--	--	-1.40 (0.22)
γ_3	--	--	--	--	0.28 (0.33)
DIC	52.4	57.0	39.1	44.3	43.6

outcome: 1 logOR for BASDAI50, 2 difference between treatment and placebo on change in BASDAI from baseline, 3 difference between treatment and placebo on change in BASFI from baseline; $\boldsymbol{\sigma_o}$ is the variance parameter for outcome *o* of the random effect across studies; $\mathbf{D_o}$ is the mean of the random effect for outcome *o*; $\boldsymbol{\gamma_o}$ is the variance parameter for outcome *o* of the random effect across treatments.

* predictive distribution

From model A5, drug specific estimates can be retrieved (Table 145). Within this model drug specific inferences will borrow strength from the common class effect and estimates are thus shrunken towards the mean of this class effect (that is, estimates are closer to the value reported for the class in Table 144).

Table 145: Shrunken estimates of treatment effect from model A5.

Shrunken estimates of treatment effect for model A5	Model A5 Outcome 1: OR on BASDAI50 (median, SD)	Outcome 2: change in BASDAI (mean, SD)	Outcome 3: change in BASFI (mean, SD)
Adalimumab	5.05 (0.87)	-1.60 (0.15)	-1.31 (0.16)
Certolizumab	5.42 (1.71)	-1.59 (0.26)	-1.31 (0.23)
Etanercept	5.13 (1.08)	-1.72 (0.17)	-1.43 (0.15)
Golimumab	5.47 (1.25)	-1.69 (0.84)	-1.42 (0.16)
Infliximab	5.70 (3.30)	-1.88 (0.34)	-1.55 (0.33)

Explorations of heterogeneity suggested only gender to potentially modify the effect of anti-TNF treatment, specifically for change in BASDAI as outcome; however, when gender is used together with all covariates, such evidence on effect modification disappears (results not shown but available on request).

11.9.2 Modelling approach B

In the previous section the two outcomes based on BASDAI scores were synthesised separately; however, BASDAI50 is the probability of having a reduction in BASDAI score of 50%, and thus it should be possible to relate the proportion of BASDAI50 responders to the change in absolute BASDAI scores from baseline observed in each study. Within this section, we use this structural relation within the synthesis, allowing change scores from baseline to be informed not only from direct data on this quantity but also from data on BASDAI50.

Brief description of the data

The model implemented here pools the change in BASDAI score from baseline to evaluate the difference between treatment and placebo, using evidence reported in trials directly on the change scores for each arm and also data on BASDAI50. The data modelled within this approach are shown in Table 146.

Table 146. Data used in modelling approach B and C

s[]	t[]	n[]	r[]	b[]	sd[]	y[]	y.se[]	y.f[]	y.f.se[]
1	1	20	NA	6.2	1.1	-2	0.560	-1	0.34
1	2	26	NA	5.9	1.4	-3.6	0.377	-1.9	0.29
2	1	115	19	6.2	1.4	-1.4	0.177	-0.47	0.15
2	2	229	114	6	1.4	-2.8	0.126	-1.75	0.13
3	1	44	NA	6.5	1.6	NA	NA	NA	NA
3	2	38	NA	6.2	1.7	NA	NA	NA	NA
4	1	107	17	6.3	1.7	-0.8	0.2	NA	NA
4	2	208	94	6.3	1.7	-2.6	0.2	NA	NA
5	1	57	8	6.4	1.9	-1.0	0.3	-0.6	0.30
5	3	121	50	6.36	1.54	-2.45	0.206	-1.7	0.21
6	1	20	1	5.46	1.74	-0.1	0.632	0.21	0.71
6	4	20	7	6.05	1.71	-1.97	0.645	-1.35	0.56
7	1	139	NA	5.96	1.65	-0.45	0.18	-0.33	0.21
7	4	138	NA	5.81	1.76	-2.36	0.19	-1.67	0.20
8	1	43	10	5.8	1.5	-1.4	0.305	-1	0.27
8	4	39	18	6.4	1.2	-2.6	0.320	-2.2	0.29
9	1	20	NA	NA	NA	NA	NA	-0.1	0.49

9	4	20	NA	NA	NA	NA	NA	-2.3	0.36
10	1	39	NA	5.86	2.05	-0.85	0.35	-0.33	0.31
10	4	45	NA	6.1	1.87	-2.72	0.34	-2.06	0.33
11	1	51	10	6.11	1.37	NA	NA	NA	NA
11	4	305	180	6.09	1.69	NA	NA	NA	NA
12	1	78	12	6.6	1.49	NA	NA	0.1	0.19
12	5	138	61	6.6	1.49	NA	NA	-1.4	0.19
13	1	105	5	6.5	1.54	NA	NA	0.11	0.20
13	5	108	37	6.6	1.31	NA	NA	-1.26	0.25
14	1	35	3	6.3	1.4	-0.6	0.478	-0.1	0.55
14	6	34	18	6.5	1.2	-3.2	0.495	-2.1	0.44
15	1	14	NA	6.57	2.05	-1.38	0.564	0.1	0.88
15	6	28	NA	6.45	1.87	-3.11	0.42	-1.72	0.49
16	1	12	NA	5.27	2.05	-0.26	0.816	1.3	0.95
16	6	9	NA	5.89	1.87	-3.23	0.961	-1.91	0.86

outcome: 1 logOR for BASDAI50, 2 difference between treatment and placebo on change in BASDAI from baseline, 3 difference between treatment and placebo on change in BASFI from baseline

s[] = study, **t[]** = treatment: 1=PLA, 2 =ADA, 3=CER, 4=ETA, 5=GOL, 6=INF; **n[]** = total number of patients, **r[]** = number of patients showing a BASDAI50 response, **y[]**: vector of results from studies on change from baseline on BASDAI score; y.**se[]**: standard error associated with each y ; **y.f[]**: vector of results from studies on change from baseline on BASFI score; y.f.**se[]**: standard error associated with each y.f

Description of synthesis methods

Consider we have available information on *J* trials comparing an individual treatment, *k* (out of the total number of treatments *T*) to placebo. Study *j* may report y_{jk}, the mean change in BASDAI from baseline, alongside the standard error for this measure, se_{jk}. The likelihood for the data on change score was assumed normally distributed and was expressed as:

$$y_{jk} \sim N(\theta_{jk}, se_{jk}^2)$$

The mean of this distribution was the treatment effects, θ_{jk}, defined as the sum of the change score for the placebo arm plus the difference in change score for the treatments:

$$\theta_{jk} = \mu_j + \delta_{jk}.$$

Some studies also reported the number of responders to BASDAI 50 (a 50% reduction in BASDAI score), r_{jk} , out of the total number of individuals in the study, n_{jk}. The likelihood for the BASDAI50 data was binomially distributed and thus expressed as:

$$r_{jk} \sim Bin(p_{jk}, n_{jk})$$

Consider the BASDAI score at baseline for study j and treatment *k*, X_{jk}, as normally distributed, with a mean score at baseline of ν_{jk} and variability on BASDAI score at baseline represented by σ_{jk}^2:

$$X_{jk} \sim N(\nu_{jk}, \sigma_{jk}^2),$$

The probability parameter of the binomial distribution can be expressed as a function of the baseline and final BASDAI scores:

$$p_{jk} = P\left[\frac{Y_{jk}}{X_{jk}} < -0.5\right] = P\left[Y_{jk} + X_{jk}/2 < 0\right]$$

This can help us establish an algebraic relation between p_{jk} and the change score Y_{jk}, for a given baseline value, X_{jk}. This requires some assumptions over the distribution of scores, which are described next.

Across individuals, the BASDAI scores at baseline and the change score are assumed correlated, and are described using a bivariate normal distribution:

$$\begin{pmatrix} X_{1jk} \\ Y_{jk} \end{pmatrix} \sim N\left(\begin{pmatrix} \nu_{1jk} \\ \theta_{jk} \end{pmatrix}, \begin{pmatrix} \sigma_{jk}^2 & \rho\sigma_{jk}^2 \\ \rho\sigma_{jk}^2 & \sigma_{jk}^2 \end{pmatrix}\right)$$

For simplicity, the variability on BASDAI score at baseline, σ_{jk}^2, was assumed equal to that of the change score. The correlation parameter is represented by ρ.

We would like to further explore the following relationship:

$$p_{jk} = P\left[Y_{jk} + X_{jk}/2 < 0\right]$$

To do so, first consider expressing Y by conditioning on the baseline value, $X_{jk} = x$ (for simplicity we will drop the *jk* subscript in the next few formulas):

$$Y|X \sim N(\theta + \rho(x - \nu), (1 - \rho^2)\sigma^2)$$

So, we can standardize and relate this probability to a standard Normal distribution

$$p_{|X_1=x} = P\left(Y_{jk} + x/2 < 0_{|X_1=x}\right) = \Phi\left(\frac{-\left(\frac{x}{2} + \theta + \rho(x - \nu)\right)}{\sigma\sqrt{(1 - \rho^2)}}\right)$$

To obtain the joint distribution, one needs to average over $X_{jk} \sim N\left(\nu_{jk}, \sigma_{jk}^2\right)$, which means integrating over this distribution with respect to x:

$$p_{jk} = \int_{-\infty}^{+\infty} \Phi\left(\frac{-\left(\frac{x}{2} + \theta + \rho(x - \nu)\right)}{\sigma\sqrt{(1 - \rho^2)}}\right) f_X(x)dx$$

Note that one can express the expectation over the cdf of a normal distribution as:

$$E[\Phi(aX+b)] = \Phi\left(\frac{b+a\nu}{\sqrt{1-a^2\sigma^2}}\right) \text{ when } x\sim N(\upsilon,\sigma^2)$$

Here, $a = \frac{-(1/2+\rho)}{\sigma\sqrt{(1-\rho^2)}}$ and $b = \frac{-\theta+\rho\nu}{\sigma\sqrt{(1-\rho^2)}}$. Therefore:

$$p_{jk} = \Phi\left(\frac{-\theta+\rho\nu-(1/2+\rho)\nu}{\sigma\sqrt{(1-\rho^2)}\sqrt{1-\frac{(1/2-\rho)^2}{(1-\rho^2)}}}\right) = \Phi\left(-\frac{\theta+\nu/2}{\sigma\sqrt{5/4+\rho}}\right)$$

The relations established above thus allow the probability parameter from BASDAI50 data to be expressed algebraically as a function of the change score:

$$\text{probit}(p_{jk}) = \frac{-\theta_{jk}-\nu_{jk}/2}{\sigma_{jk}\sqrt{5/4+\rho}}$$

In computations, we used the mean score at baseline, $\nu_{jk,}$, and the associated standard deviation, σ_{jk}, as reported in the data (these were thus assumed known). The correlation between baseline and change score was estimated within the model by assuming this quantity to be independent of study but assumed to differ between placebo and anti-TNF treatments.

In what concerns the treatment effects, all trials in our evidence base compare against conventional care: $\delta_{jk} = d_k$ .Our preferred approach to model these was to assume a common class effect (i.e. exchangeable effects across treatments, analogous assumption to model A5 above). This means:

$$d_k \begin{cases} = 0 & if\ k = 1 \\ \sim N(D, \sigma_{re}^2) & if\ k \neq 1 \end{cases}$$

where k=1 is standard care.

The priors used to implement this model were:

$$D\sim N(0,0.001),\quad \mu_j\sim N(0,0.001),\quad \rho_{pla}\sim U(-1,1), \rho_{anti-TNF}\sim U(-1,1)$$

WinBUGS code for modelling approach B

model{

```
        for (i in 1:10) {
                y[i] ~ dnorm(theta[i], y.prec[i])          #change in score
                theta[i] <- mu[s[i]] + d[t[i]]
                }
        for (i in 11:18) {
                r[i] ~ dbin(p[i], n[i])
                aux[i] <- equals(t[i],1)+1
                probit(p[i]) <- -(b[i]*0.5 + theta[i])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))

                theta[i] <- mu[s[i]] + d[t[i]]
                }
        for (i in 19:28) {
                r[i] ~ dbin(p[i], n[i])
                y[i] ~ dnorm(theta[i], prec[i])            #change in score
                aux[i] <- equals(t[i],1)+1
                probit(p[i]) <- -(b[i]*0.5 + theta[i])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))

                theta[i] <- mu[s[i]] + d[t[i]]
        }
        for (j in 1:14) {
                mu[j] ~ dnorm(0,0.001)
                }
        d[1] <- 0
        for (k in 2:6) {
                d[k] ~ dnorm(re,intau)
        }
        re ~ dnorm(0, 0.01)
        intau <- 1/tau
        tau <- pow(sd,2)
        sd ~ dunif(0,2)
        re.pred ~ dnorm(re,intau)
        rho[1] ~ dunif(-1,1)
        rho[2] ~ dunif(-1,1)
}
```

Results of modelling approach B

The summary results regarding relative treatment effects from this modelling approach are reported in Table 147 for model B.

Table 147: Modelling approach B: results

	estimated Difference in	assumed* Probability of	Predicted Probability of	OR for

	change score from baseline (mean, SD)	**having a BASDAI50 response, placebo** (mean, SD)	**having a BASDAI50 response, anti-TNF** (mean, SD)	**BASDAI50 response, anti-TNF vs. placebo** (median, SD)
Anti-TNFs	-1.91 (0.48)**	0.10 (--)	0.40 (0.08)	5.94 (4.06)
Other model summaries				
D	-1.91 (0.28)	--	--	--
γ	0.30 (0.28)	--	--	--
$\rho_{placebo}$	0.26 (0.33)	--	--	--
$\rho_{anti-TNF}$	0.69 (0.26)	--	--	--
DIC	146.3	--	--	--

* This figure is based on a BASDAI baseline score of 6.11 (sd=1.56) and a placebo change score of -0.61 (sd=1.44), which represent the average across trials (weighted by number of patients), ** predictive distribution

Drug specific (shrunken) estimates from model B are shown in Table 148.

Table 148: Shrunken estimates of treatment effect from model B.

Shrunken estimates of treatment effect for model B	**change in BASDAI** (mean, SD)
Adalimumab	-1.77 (0.25)
Certolizumab	-2.01 (0.37)
Etanercept	-1.88 (0.18)
Golimumab	-1.92 (0.30)
Infliximab	-2.02 (0.32)

11.9.3 Modelling approach C

The models implemented here extend those in the previous section by adding the syntheses of changes in BASFI score. The data used is presented in Table 146.

Description of synthesis methods

Data on mean change in BASFI score reported in some of the studies available have been described as normally distributed (the likelihood):

$$y_{jk}^{BASFI} \sim N\left(\theta_{jk}^{BASFI}, \left(se_{jk}^{BASFI}\right)^2\right)$$

The treatment effects over BASFI θ_{jk}^{BASFI} were then defined as:

$$\theta_{jk}^{BASFI} = \mu_j^{BASFI} + \delta_{jk}^{BASFI}$$

Treatment effects on BASFI were assumed correlated to those on BASDAI across trials:

$$\begin{pmatrix}\delta_{jk}^{BASDAI}\\ \delta_{jk}^{BASFI}\end{pmatrix}\sim N\left(\begin{pmatrix}d_k^{BASDAI}\\ d_k^{BASFI}\end{pmatrix},\begin{pmatrix}\tau^2_{BASDAI} & \rho_m\tau^2_{BASDAI}\tau^2_{BASFI}\\ \rho_m\tau^2_{BASDAI}\tau^2_{BASFI} & \tau^2_{BASFI}\end{pmatrix}\right)$$

$$d_k^o\begin{cases}=0 & if\ k=1\\ \sim N(D_o,\sigma^2_{re,o}) & if\ k\neq 1\end{cases},\quad \text{with o=\{BASDAI, BASFI\} and k=1 is placebo.}$$

The additional priors used to implement this model were:

$$D_o\sim N(0,0.001),\ \sigma^2_{re}\sim U(0,2)\ \ \rho_m\sim U(-1,1)$$

The variation in treatment effects for both BASDAI and BASFI and the correlation parameter between these were estimated from the data. As in model B, we assumed exchangeability across the effects of the different treatments.

WinBUGS code for modelling approach C

```
model{
        for (i in 1:10) {
                y[i] ~ dnorm(theta[i,1], y.prec[i])                     #change in score
                y.f[i] ~ dnorm(theta[i,2], y.prec.f[i])                 #change in score BASFI
                }
        for (i in 11:14) {
                r[i] ~ dbin(p[i], n[i])
                aux[i] <- equals(t[i],1)+1
                probit(p[i]) <- -(b[i]*0.5 + theta[i,1])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))
                y.f[i] ~ dnorm(theta[i,2], y.prec.f[i])                 #change in score BASFI
                }
        for (i in 15:16) {
                r[i] ~ dbin(p[i], n[i])
                aux[i] <- equals(t[i],1)+1
                probit(p[i]) <- -(b[i]*0.5 + theta[i,1])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))
                }
        for (i in 17:26) {
                r[i] ~ dbin(p[i], n[i])
                y[i] ~ dnorm(theta[i,1], prec[i])               #change in score
                aux[i] <- equals(t[i],1)+1
                probit(p[i]) <- -(b[i]*0.5 + theta[i,1])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))
                y.f[i] ~ dnorm(theta[i,2], y.prec.f[i])                 #change in score BASFI
        }
        for (i in 27:28) {
                y.f[i] ~ dnorm(theta[i,2], y.prec.f[i])                 #change in score BASFI
        }
        for (i in 29:30) {
                r[i] ~ dbin(p[i], n[i])
                y[i] ~ dnorm(theta[i,1], prec[i])               #change in score
                aux[i] <- equals(t[i],1)+1
                probit(p[i]) <- -(b[i]*0.5 + theta[i,1])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))
```

```
        }
        for (i in 1:30) {
                theta[i,1:2] ~ dmnorm(delta[i,1:2],B[1:2,1:2])
                delta[i,1] <- mu1[s[i]] + d1[t[i]]
                delta[i,2] <- mu2[s[i]] + d2[t[i]]
        }
        d1[1] <- 0
        d2[1] <- 0
        for (k in 2:6) {
                d1[k] ~ dnorm(re1,intau)
                d2[k] ~ dnorm(re2,intau)
        }
        B[1,1]<- 1/(pow(sd[1],2)*(1-pow(cor,2)))
        B[2,2]<- 1/(pow(sd[2],2)*(1-pow(cor,2)))
        B[1,2]<- -cor/(sd[1]*sd[2]*(1-pow(cor,2)))
        B[2,1]<- B[1,2]
        sd[1] ~ dunif(0,5)
        sd[2] ~ dunif(0,5)
        cor~dunif(0,1)
        for (j in 1:15) {
                mu1[j] ~ dnorm(0,0.01)I(-5,5)
                mu2[j] ~ dnorm(0,0.01)I(-5,5)
                }
        re1 ~ dnorm(0, 0.01)I(-10,10)
        re.pred1 ~ dnorm(re1,intau)
        re2 ~ dnorm(0, 0.01)I(-10,10)
        re.pred2 ~ dnorm(re2,intau)
        intau <- 1/tau
        tau <- pow(sd.re,2)
        sd.re ~ dunif(0,2)
        rho[1] ~ dunif(0,1)
        rho[2] ~ dunif(0,1)
        for (k in 2:6) {
                d1.pred[k] ~ dnorm(re1,intau)
        }
}
```

Results of modelling approach C

The results on differences between treatment and placebo on change score form baseline are reported in Table 149, both for BASDAI and BASFI scores.

Table 149: Modelling approach C: results

estimated Difference in change score	assumed* Probability of having a	predicted Probability of having a	OR for BASDAI50

	from baseline (mean, SD)	**BASDAI50 response, placebo** (mean, SD)	**BASDAI50 response, anti-TNF** (mean, SD)	**response, anti-TNF vs. placebo** (median, SD)
Effect of anti-TNFs on BASDAI	-1.95 (0.30)	0.10 (--)	0.41 (0.05)	6.30 (1.56)
Effect of anti-TNFs on BASFI	-1.40 (0.28)	--	--	--
Other model summaries		--	--	--
D^{BASDAI}	-1.99 (0.20)	--	--	--
D^{BASFI}	-1.40 (0.16)			
γ_{BASDAI}	0.13 (0.10)	--	--	--
γ_{BASDAI}	0.11 (0.09)	--	--	--
$\rho_{placebo}$	0.42 (0.26)	--	--	--
$\rho_{anti-TNF}$	0.71 (0.23)	--	--	--
ρ_m	0.51 (0.29)	--	--	--
σ_{re}	0.16 (0.14)	--	--	--
DIC	181.9	--	--	--

* Based on a BASDAI baseline score of 6.11 (sd=1.56) and a placebo change score of -0.61 (sd=1.44), which represent the average across trials (weighted by number of patients)

Drug specific (shrunken) estimates from model C are shown in Table 14850.

Table 150: Shrunken estimates of treatment effect from model C.

Shrunken estimates of treatment effect for model C	**change in BASDAI** (mean, SD)	**change in BASFI** (mean, SD)
Adalimumab	-1.89 (0.22)	-1.34 (0.17)
Certolizumab	-2.02 (0.28)	-1.36 (0.21)
Etanercept	-1.94 (0.18)	-1.43 (0.16)
Golimumab	-1.98 (0.25)	-1.42 (0.17)
Infliximab	-2.03 (0.27)	-1.49 (0.25)

11.10 Appendix 10 Synthesis of evidence on the nr-axSpA population

This section analyses the evidence on the effectiveness of anti-TNFs on the nr-axSpA population.

Brief description of the data

On the nr-axSpA population, 5 RCTs were considered directly relevant to the decision problem (studies 17 to 21 in Table 14651). All studies reported BASFI outcomes and one study did not report BASDAI 50 (study 21).

Table 151: Evidence on BASDAI and BASFI related outcomes for the nr-axSpA population

	Trial name	**treat**	**N treat**	**N PLA**	**BASDAI50**	**change BASDAI**	**change BASFI**
17	Haibel 2008	ADA	22	24	x	x	x
18	ABILITY-1 (2013)	ADA	69	73	x	x	x
19	RAPID-axSpA (2014)	CER	46+51	50	x	x	x

20	Dougados 2014	ETA50	106	109	x	x	x
21	Barkham 2009	INF	20	20		x	x

The data on these five studies are shown in Table 152.

Table 152. Data on the nr-axSpA population

s[]	t[]	n[]	r[]	b[]	sd[]	y[]	y.se[]	y.f[]	y.f.se[]
1	1	24	5	6.20	0.59	-1.20	7.79	-0.80	6.87
1	2	22	11	6.50	0.69	-2.70	6.30	-2.40	7.24
2	1	73	10	6.38	0.44	-1.10	19.00	-0.63	22.78
2	2	69	27	6.43	0.42	-2.20	11.04	-1.28	16.91
3	1	50	8	6.40	0.44	-1.50	6.25	-0.40	6.25
3	3	97	47	6.55	0.43	-3.35	11.64	-2.30	12.21
4	1	109	26	6.00	0.28	-1.30	11.11	-0.80	25.00
4	4	106	46	6.00	0.31	-2.00	11.11	-1.40	25.00
5	1	20	NA	5.76	0.28	-0.75	3.42	-0.47	3.95
5	5	20	NA	5.85	0.31	-3.41	3.12	-2.70	3.59

s[] = study, **t[]** = treatment: 1=PLA, 2 =ADA, 3=CER, 4=ETA, 5=INF; **n[]** = total number of patients, **r[]** = number of patients showing a BASDAI50 response, **y[]**: vector of results from studies on change from baseline on BASDAI score; y.**se[]**: standard error associated with each y ; **y.f[]**: vector of results from studies on change from baseline on BASFI score; y.f.**se[]**: standard error associated with each y.f

Description of approaches to the synthesis

To synthesise these data we used the same implementation and software specifications as described in Appendix 9. Analyses explored two different scenarios to consider these data:

Scenario 1. data from nr-axSpA trials were considered in isolation

Scenario 2. data from AS population were also used, no difference between the populations was assumed.

All models implemented here jointly synthesise BASDAI and BASFI outcomes (our preferred modelling approach, C).

Results of the synthesis

Results of the analysis are in

Table 153.

Table 153: nr population: results

	estimated Difference in change score from baseline (mean, SD)	**assumed* Probability of having a BASDAI50 response, placebo** (mean, SD)	**predicted Probability of having a BASDAI50 response, anti-TNF** (mean, SD)	**OR for BASDAI50 response, anti-TNF vs. placebo** (median, SD)
Scenario 1. data from nr-axSpA trials				
Effect of anti-TNFs on BASDAI	-1.86 (0.79)	0.20 (--)	0.53 (0.13)	4.39 (6.59)
Effect of anti-TNFs on BASFI	-1.30 (0.84)	--	--	--
Other model summaries				
D^{BASDAI}	-1.86 (0.53)	--	--	--
D^{BASFI}	-1.30 (0.65)	--	--	--
γ_{BASDAI}	0.41 (0.43)	--	--	--
γ_{BASDAI}	0.68 (0.53)	--	--	--
$\rho_{placebo}$	0.60 (0.27)	--	--	--
$\rho_{anti-TNF}$	0.57 (0.28)	--	--	--
ρ_m	0.51 (0.29)	--	--	--
σ_{re}	0.55 (0.29)	--	--	--
DIC	88.6	--	--	--
Scenario 2. data from AS and nr-axSpA trials, no difference between the populations				
Effect of anti-TNFs on BASDAI	-1.97 (0.32)	0.20 (--)	0.55 (0.06)	4.94 (1.48)
Effect of anti-TNFs on BASFI	-1.37 (0.3)	--	--	--
Other model summaries				
D^{BASDAI}	-1.97 (0.20)	--	--	--
D^{BASFI}	-1.37 (0.18)	--	--	--
γ_{BASDAI}	0.12 (0.09)	--	--	--
γ_{BASDAI}	0.18 (0.11)	--	--	--
$\rho_{placebo}$	0.50 (0.26)	--	--	--
$\rho_{anti-TNF}$	0.74 (0.22)	--	--	--
ρ_m	0.54 (0.29)	--	--	--
σ_{re}	0.19 (0.16)	--	--	--
DIC	269.0	--	--	--

* Based on a BASDAI baseline score of [redacted] and a placebo change score of [redacted] which represent the results seen in the certolizumab trial (RAPID-axSpA)

11.11 Appendix 11 BASDAI and BASFI scores conditional on BASDAI response

In this section we use the results from the extended synthesis model (Appendices 9 and 10) to evaluate the conditional scores by simulating BASDAI and BASFI scores for two equivalent cohorts of patients one treated with an anti-TNF and the other with conventional therapy.

Description of methods

From the inferences obtained using the synthesis model above it is possible to derive the conditional change score in responders and non-responders using simulation. Whereas the synthesis focusses on the pooling of mean estimates of change scores and proportion of responders to BASDAI50, to derive conditional mean scores there is the need to consider the distributions at the individual patient level. Hence, conditional scores could not directly be derived from the synthesis, but through a simulation procedure based on the assumptions and results of the synthesis model.

The steps undertaken within the simulation procedure were:

(1st) Simulate baseline BASDAI scores, $x^{BASDAI*}$, from beliefs over its distribution, $X \sim N(\nu, \sigma)$

(2nd) Simulate $y^*_{k=1}$ from beliefs over the mean (μ) of this quantity considering correlation with $x^{BASDAI*}$

$$Y_{k=1|X=x} \sim N(\mu + \rho(x - \upsilon), (1 - {\rho_{pla}}^2)\sigma^2)$$

(3rd) Simulate $y^*_{k=2}$ (where k=2 represents treatment with anti-TNF) by considering

$$Y_{k\neq 1|X=x} \sim N(\mu + d + \rho(x - \upsilon), (1 - {\rho_{anti-TNF}}^2)\sigma^2)$$

(4th) Calculate final score for placebo and treatment separately, by summing $x^{BASDAI*}_{final} = y^{BASDAI*}_k + x^{BASDAI*}$

(5th) Compute response variables for both groups as $y^{BASDAI*}_k + x^*/2 \quad < 0$

Repeat steps 1 to 4 until the desired sample size is achieved, and calculate conditional scores based on response variable and change in scores.

To evaluate BASFI conditional on BASDAI scores one needs to firstly consider we have available information on the BASFI scores at baseline: $X^{BASFI} \sim N\left(\nu^{BASFI}, \left(se^{BASFI}\right)^2\right)$, and also on correlation with BASDAI scores, φ (at individual level). By considering $x^{BASDAI*}$, one can:

(6th) Simulate from the distribution of the baseline BASFI score conditional on the baseline BASDAI score being x^*:

$$x^{BASFI}{}_{|X^{BASDAI}=x} \sim N(\nu^{BASFI} + \frac{\sigma_{BASFI}}{\sigma_{BASDAI}}\varphi\left(x^{BASDAI*} - \nu^{BASDAI}\right), (1 - \varphi^2)\sigma^2_{BASFI})$$

Note the correlation parameter φ, which represents the individual level correlation between baseline BASFI and BASDAI scores.

(7th) Simulate the change from baseline on BASFI for placebo $y^{BASFI*}_{k=1}$ from belief over this quantity, consider this to be correlated with the $y^*_{k=1}$ simulated for BASDAI (use correlation parameter estimated within the synthesis)

$$y^{BASFI}_{k=1}{}_{|y^{BASDAI}_{k=1}=\mu*} \sim N(\mu^{BASFI} + \frac{\sigma_{BASFI}}{\sigma_{BASDAI}}\rho_m\left(\mu^{BASDAI*} - \mu^{BASDAI}\right), (1 - {\rho_m}^2)\sigma^2_{BASFI})$$

(8th) Simulate the change from baseline for anti-TNF treatment

$$\theta^{\text{BASFI}}{}_{|y^{BASDAI}=\mu*} \sim N(\mu^{\text{BASFI}} + \text{d} + \frac{\sigma_{BASFI}}{\sigma_{BASDAI}} \rho_m \left(x_{final}^{BASDAI*} - mean.x_{final}^{BASDAI*}\right), (1-\rho_m{}^2)\sigma_{BASFI}^2)$$

Note that d represents the mean of the predictive distribution from the synthesis model.

We used a simulation sample size of 10,000 patients. Given results depend on the baseline distributions of BASDAI and BASFI and on the change scores from baseline for placebo, we used the averages across trials (weighted by the number of patients in each trial) in AS. Baseline BASDAI scores were thus assumed normally distributed with mean 6.11 and standard deviation of 1.56; change from baseline for placebo was simulated from a normal distribution with mean -0.61 and standard deviation of 1.44. For BASFI, the baseline was assumed to have a mean of 5.27 and a standard deviation of 1.79 and change from baseline for placebo a mean of -0.19 and a standard deviation of 0.22. The correlation between baseline BASFI and BASDAI scores was valued at 0.7 (φ). Average scores from the RAPID-axSpa trial for certolizumab were used for the nr-axSpA analysis.

Results

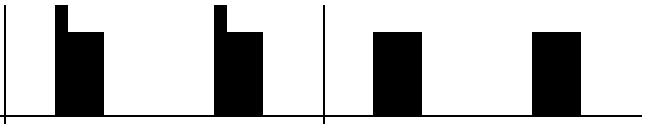
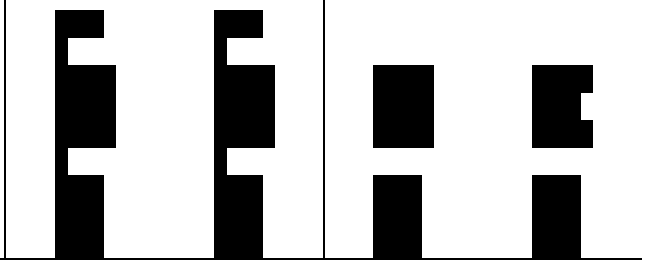
Results of the prediction of conditional scores using the synthesis model in the AS population are presented in Table 154 and for the nr-axSpA population in Table 155.

Table 154: Conditional scores predicted for the AS population using the synthesis model

	BASDAI		**BASFI**	
	control	*Treat*	*control*	*treat*
Scenario 1				
% responders to BASDAI50	0.10	0.42		
Change in score				
Responders	-2.70	-3.86	-1.41	-3.02
Non-responders	-0.45	-1.73	-0.17	-0.63
All	-0.66	-2.63	-0.29	-1.64
Baseline				
Responders	3.83	4.76	3.42	4.17
Non-responders	6.31	7.03	5.43	6.02
All	6.08	6.08	5.24	5.24

Table 155: Conditional scores predicted for the nr-axSpA population using results and assumptions of the synthesis model

	BASDAI		**BASFI**	
	control	*Treat*	*control*	*treat*
Scenario 1				
% responders to BASDAI50				
Change in score				
Responders				
Non-responders				
All				

Baseline Responders Non-responders All	
Scenario 2 **% responders to BASDAI50** **Change in score** Responders Non-responders All **Baseline** Responders Non-responders All	

* Based on a BASDAI baseline score [redacted], a placebo change in BASDAI score of [redacted] a BASFI baseline score of [redacted] and a placebo change in BASFI score of [redacted] which represent the results seen in the certolizumab trial (RAPID-axSpA) .

11.12 Appendix 12: Quality assessment of studies included in the cost effectiveness review*

Checklist used - Drummond M et al. Methods for the economic evaluation of health care programmes. 3rd ed. Oxford. Oxford University Press. 2005)[228]

	Ara 2007[152]	**Botteman 2007[153]**	**Kobelt 2007[151]**	**McLeod 2007[34]**	**Armstrong 2013[154]**
1. Was a well-defined question posed in answerable form?	Yes	Yes	Yes	Yes	Yes
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)?	Yes	Yes	No	Yes	Yes
3. Was the effectiveness of the programme or services established?	Yes (short-medium term)	Yes (short-medium term)	Yes (short term)	Yes (short-medium term)	Yes (short-medium term)
4. Were all the important and relevant costs and consequences for each alternative identified?	No	Yes	Yes	Yes	Yes (consequences) Cannot tell (costs)
5. Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)?	Cannot tell	Cannot tell	Cannot tell	Yes	Cannot tell
6. Were the cost and consequences valued credibly?	Cannot tell	Cannot tell	Cannot tell	Yes	Cannot tell
7. Were costs and consequences adjusted for differential timing?	Yes	Yes	Yes	Yes	Cannot tell
8. Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Yes	Yes	Yes	Yes
9. Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Yes	Yes	Yes	Yes
10. Did the presentation and discussion of study results include all issues of concern to users?	No	No	No	Yes	No

* = only stated publications were quality assessed and further materials (for example, Assessment Group reports from the NICE website) were not consulted

11.13 Appendix 13 Utility review

In accordance with the NICE reference case, utility values should be based on the EuroQoL – EQ5D instrument. Therefore a systematic review of utility studies was carried out to identify relevant studies which (i) directly estimate EQ-5D utility values; and (ii) establish the relationship between generic measures of utility (in particular, the EQ-5D) and measures of disease progression (including mapping studies). The review of utility studies focusses on anti-TNFs for ankylosing spondylitis (AS) and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (nr-axSpA).

Methods

Searches were undertaken in EMBASE and Ovid MEDLINE/Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations. A combination of disease terms and terms associated with the EQ-5D were used. Upon initial review, it was evident that the results of the search did not identify the studies found in the cost effectiveness review that also reported on the quality of life of AS patients (for example, Ara et al (2007)[152]). Therefore, a separate search in NHSEED, Medline and EMBASE for published modelling studies was also subsequently undertaken. No language and date limits were applied. Full details of the search strategy used are presented in Appendix 1.

Studies that reported utility values consistent with the NICE reference case were included in the review. That is, studies reporting utilities for AS or nr-AxSpa patients generated using:

- the EQ-5D
- HRQoL or changes in HRQoL measured directly by patients
- Changes in HRQoL should be valued using public preferences from a representative sample of the UK population using a choice-based method (or this could be reasonably assumed from the publication).

Where a mapping algorithm was reported, eligibility of studies was restricted to those that mapped from BASDAI and/or BASFI to EQ-5D.

Results

Identified studies

The combined search retrieved 210 citations. After screening titles and abstracts, 28 citations were retrieved for full review. The abstract by Pumford et al (2011)[229] was excluded as the full publication by Wade et al (2011)[230] reported on the same study. The abstract by Lee et al (2011)[231] was excluded as a more recent full publication of the study (Lee et al [2014][232]) reported that a non-UK valuation set was used. Joore et al (2010)[233] was also excluded as primary data were reported in van Tubergen et al

(2002)[234]. A further 3 studies were excluded due to the manuscripts being in a language other than English.

Kobelt and colleagues have reported costs/quality-of-life/cost effectiveness of AS patients in multiple references (for example; Kobelt et al (2004)[143], Kobelt et al (2006)[235], Kobelt et al (2007)[151] and Kobelt et al (2008)[236]). Kobelt et al (2004) and (2007) are relevant to a UK population and are preferred to the other Kobelt publications that are relevant to non-UK populations. Of these, Kobelt et al (2004) reports utility data collected and used in the analysis and is, therefore, included in this review.

In total, 12 studies were deemed to meet the NICE reference case and are summarised in Table 156.

The main reasons for excluding studies at the title/abstract and at full review stage were; 1) utilities were not reported [for example, Haywood et al (2010)[237]], 2) valuation set not reported or a non-UK valuation was used [for example, Kvamme et al (2010)[238]], 3) utilities were reported for a mixed population with different inflammatory arthropies or in a population not relevant to the decision problem [for example, Osnes-Ringen et al (2011)[239]].

Studies meeting the NICE reference case

The 12 studies meeting the reference case have been summarised in Table 156. The table includes a primary study to Boonen et al (2007)[240], reported in Boonen et al (2002/2003)[241, 242]. The study by Boonen et al (2007) has been retained as it reports utility values for patients with a BASDAI ≥4.

AS population

All studies included in Table 156 are of AS patients. Five studies reported utility values (or mapping algorithms) generated from data specifically collected from the UK population (Haywood et al (2002)[243], Healey et al (2013)[16], Kobelt et al (2004)[143], McLeod et al (2007)[34], Wade et al (2011)[230]). Four studies included interventions specific to this appraisal, all of these studies were of etanercept (Ara et al (2007)[152], Boonen et al (2008)[194], Braun et al (2007)[83], Wade et al (2011)[230]). Utility values reported ranged from values at baseline to 10 years follow-up.

NR population

Two citations were identified in the review that reported utilities for nr- axSpa patients (Dougados et al (2013)[77] and Lindstrom et al (2013)[244]). However, these studies did not explicitly report which population valuation sets were used and, therefore, were excluded from the review.

Mapping algorithms

Of the 12 studies in Table 156, 2 report mapping algorithms between disease specific measures and the EQ-5D (Ara et al (2007)[152] and McLeod et al (2007)[34]). Both have been reported as part of a cost-effectiveness analysis and provide limited information on methodology employed (for example covariates tested, correlation considerations and goodness of fit). McLeod et al (2007) reports on an algorithm generated using data from UK AS patients.

Table 156 - Summary of utility studies that meet the NICE reference case

Study	Population characteristics	Interventions	Utility assessment methods	Utilities reported Mean (SD) [95% CI]	Reviewer comments
Ara et al (2007)[152] The cost-effectiveness of etanercept in patients with severe ankylosing spondylitis in the UK. (mapping algorithm to EQ-5D values also reported)	AS, diagnosed using mNY criteria defined by a VAS for mean morning stiffness ≥30, and by at least two of the following: VAS for patient global assessment of disease activity ≥30, average of VAS for nocturnal and total pain ≥30 or BASFI ≥30, patients from 2 etanercept RCTs. European RCT - 356 patients randomised to receive placebo (n=51), etanercept 25mg twice weekly (n=150) and etanercept 50mg once weekly (n=155) for 12 weeks. Data from the etanercept arms were combined as no significant differences in outcomes were found. Mainly US RCT - 277 patients randomised to receive placebo (n=139), etanercept 25mg twice weekly (n=138) for 24 weeks plus a 3 year open-label extension. Age: 41 (European RCT), 42 (US RCT) Disease duration: 9.3 years	• Placebo • Etanercept 25mg twice-weekly • Etanercept 50mg once-weekly	EQ-5D • Completed by patients in 11 European countries (including the UK) • UK population valuation set is assumed to have been used as this is a UK study European RCT data were used to derive an algorithm between BASDAI/BASFI and EQ-5D. Methods were not reported	European RCT week 12 (observed) for patient with a BASDAI ≥4: • Anti-TNF responder: 0.79 (NR) • Anti-TNF non-responder: 0.48 (NR) • Placebo responder: 0.74 (NR) • Placebo non-responder: 0.46 (NR) US RCT week 24 (predicted using algorithm): • Anti-TNF responder: 0.80 (NR) • Anti-TNF non-responder: 0.46 (NR) • Placebo responder: 0.79 (NR) • Placebo non-responder: 0.42 (NR) Algorithm[%] (BASDAI/BASFI are on the 0-100 scale): Utility = 0.923 (0.0170) - 0.004 (0.0007) x BASFI - 0.004 (0.0008) x BASDAI R^2=0.52	Observed values may be generalisable to an AS population who have been treated with etanercept. However, it is not clear how generalisable the outputs are to a UK population. Responders categorised using BSR guidelines, i.e. BASDAI50. Baseline values not reported Generalisability of the algorithm is unclear as methods have not been reported. UK population valuation set is assumed to have been used.

Study	Population characteristics	Interventions	Utility assessment methods	Utilities reported Mean (SD) [95% CI]	Reviewer comments
	(European RCT), 10.3 years (US RCT) BASDAI: 6.1 (European RCT), 5.9 (US RCT) BASFI: 5.9 (European RCT), 5.4 (US RCT)				
Boonen et al (2002)[242] and (2003)[241] 2002 – Work status and productivity costs due to ankylosing spondylitis: comparison of three European countries 2003 - Costs of ankylosing spondylitis in three European countries: the patient's perspective	AS patients diagnosed using mNY criteria. • 130 patients from The Netherlands. Patients were sampled from the Dutch standard diagnosis register of rheumatic diseases Age: 46 Disease duration since diagnosis: 12 years BASDAI: 3.7 BASFI: 3.9 • 53 patients from France. Consecutive in- and out-patients at a hospital rheumatology department Age: 38 Disease duration since	NA	EQ-5D • Completed by patients in Europe (not including the UK) • It's assumed that the UK population valuation set was used as the authors reference Dolan et al (1997)[245] and Boonen et al (2003) say the 'York weighting' was used	Baseline: Netherlands = 0.69 (0.16) France = 0.63 (0.29) Belgium = 0.67 (0.14) Time averaged across 2 year follow-up period: Netherlands = 0.68 (0.16) France = 0.63 (0.23) Belgium = 0.67 (0.14) All patients = 0.67 (0.19)	Results may be generalisable to an AS population, however, generalisability to a UK population is unknown. A high proportion of missing data (84% were missing at least one bimonthly questionnaire). UK population valuation set is assumed to have been used.

Study	Population characteristics	Interventions	Utility assessment methods	Utilities reported Mean (SD) [95% CI]	Reviewer comments
	diagnosis: 9 years BASDAI: 2.8 BASFI: 2.5 • 26 patients from Belgium. Consecutive outpatients at a hospital rheumatology department Age: 42 Disease duration since diagnosis: 11 years BASDAI: 3.1 BASFI: 2.6				
Boonen et al (2007)[240] How do the EQ-5D, SF-6D and the well-being rating scale compare in patients with ankylosing spondylitis?	AS patients diagnosed using mNY criteria. • 134 patients from the prevalence-based OASIS cohort (Boonen et al [2002/2003][241, 242]. • 120 patients from an RCT comparing spa treatment (80) with usual care (40) (van Tuburgen et al [2002][234]).	• OASIS – NA (prevalence cohort) • RCT – spa treatment (3 weeks) and usual care	EQ-5D • Completed by patients in Europe (not including the UK) • UK population valuation set used Outputs from the EQ-5D rating scale and SF-6D are also reported in this study but are not summarised here.	Combined datasets (n = 254) = 0.64 (0.23) BASDAI <4 (n = 125) = 0.73 (0.16) BASDAI ≥4 (n=137) = 0.55 (0.26) BASFI <4 (n = 121) = 0.74 (0.16) BASFI ≥4 (n = 143) = 0.55 (0.25)	Results may be generalisable to an AS population, however, generalisability to a UK population is unknown. It is not clear if the utilities reported are baseline values (baseline and post intervention at 4 weeks EQ-5D results were included in the RCT). EQ-5D discriminates more between lower and higher BASDAI patients (and lower and higher BASFI patients)

Study	Population characteristics	Interventions	Utility assessment methods	Utilities reported Mean (SD) [95% CI]	Reviewer comments
	Both datasets were merged as authors found that QoL instruments provided similar results in the two populations. Age: 48 Disease duration since diagnosis: 13 years BASDAI: 4.2 BASFI: 4.2				than the SF-6D. The authors suggests there is a ceiling effect between EQ-5D values 0.6 – 0.8 (these patients showed a wide range of values on the SF-6D and rating scale).
Boonen et al (2008)[194] Rapid and sustained improvement in health-related quality of life and utility for 72 weeks in patients with ankylosing spondylitis receiving etanercept	257 AS patients, diagnosed using mNY criteria, who had completed 24 weeks of treatment in a previous RCT (277 patients enrolled) comparing etanercept with placebo. Patients were treated with etanercept in the open-label extension study. Age: 41 Disease duration: 10.8 years BASDAI: not reported BASFI: not reported	• Etanercept 25mg twice-weekly	EQ-5D • Completed by patients in 28 centres across Europe and North America • UK population valuation set was used	Baseline (n=232): • Previously treated with etanercept in the RCT (n=128): 0.69 (0.2) • Previously treated with placebo in the RCT (n=129): 0.49 (0.3) Figure 3(a) shows that patients who were previously on etanercept maintained their baseline utility up to week 72 (105 patients completed 72 weeks of treatment). Patients who were previously on placebo achieved a similar utility to those patients previously on etanercept by week 12 and	Results may be generalisable to an AS population, however, generalisability to a UK population is unknown. Negative utility values were imputed as 0 Patients eligible for the open-label study were those who completed the initial RCT, patients who discontinued due to lack of efficacy but completed follow-up evaluations and patients who discontinued due to adverse events which subsequently resolved. Figure 3(a) refers to

Study	Population characteristics	Interventions	Utility assessment methods	Utilities reported Mean (SD) [95% CI]	Reviewer comments
				maintained this to week 72 (115 patients completed 72 weeks of treatment).	'combined' EQ-5D scores – it is not clear what 'combine' denotes.
Braun et al (2007)[83] Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly	356 active AS patients diagnosed using mNY criteria defined by a VAS for mean morning stiffness ≥30, and by at least two of the following: VAS for patient global assessment of disease activity ≥30, average of VAS for nocturnal and total pain ≥30 or BASFI ≥30. Age: 40 Disease duration: 9 years BASDAI: 6.1 BASFI: 6.0	• Placebo • Etanercept 25mg twice-weekly (12 weeks) • Etanercept 50mg once-weekly (12 weeks)	EQ-5D • Completed by patients in 11 European countries (including the UK) • It's assumed that the UK population valuation set was used as the authors reference Dolan et al (1997)[245]	Mean increase between 0 to 12 weeks reported in figure 2 = Placebo patient's utility increase at 12 weeks: +0.13 Etanercept 25mg patient's utility increase at 12 weeks: +0.25 Etanercept 50mg patient's utility increase at 12 weeks: +0.3	Results may be generalisable to an AS population who have been treated with etanercept. However, it is not clear how generalisable the outputs are to a UK population. Baseline values not reported A rapid improvement in utilities seen within 2 weeks. 90% of patients completed 12 weeks of treatment UK population valuation set is assumed to have been used.
Gordeev et al (2010)[246] Role of contextual factors in health-related quality of life in ankylosing spondylitis	• 764 patients with AS, diagnosed using mNY criteria, in Canada and Australia were sent a questionnaire in the post. • 522 (68%) responded and were included in the	NA	EQ-5D • Completed by patients in Canada and Australia • UK population valuation set is used	Australian cohort (n=105): 0.68 (0.27) Canadian cohort (n=417): 0.62 (0.29)	This study may be generalisable to patients with AS. However, generalisability to a UK population is unknown. Contextual factors explained

Study	Population characteristics	Interventions	Utility assessment methods	Utilities reported Mean (SD) [95% CI]	Reviewer comments
	analysis Age: 43 (Australian), 53 (Canadian) Diagnosis duration: 13 years (Australian), 19 years (Canadian) BASDAI: 3.5 (Australian), 4.1 (Canadian) BASFI: 3.3 (Australian), 3.9 (Canadian)				37% of the variance in EQ-5D. Helplessness (measured using the Rheumatoid Attitudes Index Helplessness Subscale), employment and education were the most important contextual factors. Their role was independent of the strong effect of BASDAI and BASFI.
Haywood et al (2002)[243] Generic measures of health-related quality of life in ankylosing spondylitis: reliability, validity and responsiveness	• A random sample of 451 patients with AS, diagnosed using mNY criteria, were sent a postal questionnaire • 349 (77%) patients returned the questionnaire at baseline • 349 patients returned the questionnaire at baseline • 303 patients returned the questionnaire at 2 weeks • 289 patients returned the questionnaire at 6 months Age: 46 Symptom duration: 20 years BASDAI: not reported	NA	EQ-5D • Completed by patients in the UK • It's assumed that the UK population valuation set was used as the authors reference Kind et al (1998)[247] Outputs from the EQ-5D VAS and SF-12 are also reported in this study but are not summarised here.	Reliability analysis using data from patients whose health remained the same at 2 weeks (n=321): 0.53 (0.35) Longitudinal construct validity analysis at 6 months: AS • Patients whose AS health was better (n=57): improved by 0.30 (1.2) • Patients whose AS health stayed the same (n=120): -0.25 (1.5) • Patients whose AS health was worse (n=77): improved by -0.09 (1.6)	This study may be generalisable to UK patients with AS. UK population valuation set is assumed to have been used. BASDAI/BASFI values for this cohort are not reported.

Study	Population characteristics	Interventions	Utility assessment methods	Utilities reported Mean (SD) [95% CI]	Reviewer comments
	BASFI: not reported			General health • Patients whose general health was better (n=49): improved by 0.35 (1.3) • Patients whose AS health stayed the same (n=132): -0.21 (1.4) • Patients whose AS health was worse (n=67): -0.15 (1.7)	
Healey et al (2013)[16] Patients with well-established ankylosing spondylitis show limited deterioration in a ten-year prospective cohort study	• 269 patients with AS, diagnosed using mNY criteria, were invited to participate at a rheumatology centre • 159 patients participated at baseline • 69 patients participated at the 10 year assessment Age: 49 Disease duration: 16 years BASDAI: 4.1 BASFI: not reported	NA	EQ-5D • Completed by patients in the UK • It's assumed that the UK population valuation set was used as this is a UK study Outputs from the SF-12 are also reported in this study but are not summarised here.	Baseline assessment in 1998 (n=159): 0.64 (0.28) 10 year follow-up assessment: 0.61 (0.30)	This study may be generalisable to UK patients with AS. Only 69 patients participated in both assessments. A UK population valuation set is assumed to have been used.
Kobelt et al (2004)[143]	Clinical trial, hospital cohort and survey data for AS patients were utilised in this	NA	EQ-5D • Completed by patients	Survey mean: 0.67 (0.21)	This study may be generalisable to UK patients

Study	Population characteristics	Interventions	Utility assessment methods	Utilities reported Mean (SD) [95% CI]	Reviewer comments
The burden of ankylosing spondylitis and the cost-effectiveness of treatment with infliximab (Remicade®)	study. Utilities were estimated from a survey of 3000 patients. 1413 (57%) patients responded and were included in the analysis. Survey responders had the following characteristics: Age: 57 Disease duration: 30 years BASDAI: 4.2 BASFI: 4.5		in the UK • It's assumed that the UK population valuation set was used as the study references Dolan et al (1995)[248] and was conducted in the UK	BASDAI subgroups: • Patients with a BASDAI <3 (mean BASFI=2.4): 0.8 • Patients with a BASDAI 3-3.99 (mean BASFI=3.7): 0.7 • Patients with a BASDAI 4-4.99 (mean BASFI=4.5): 0.64 • Patients with a BASDAI 5-5.99 (mean BASFI=5.4): 0.60 • Patients with a BASDAI 6-6.99 (mean BASFI=6.4): 0.51 • Patients with a BASDAI >7 (mean BASFI=7.8): 0.39 BASFI subgroups: • Patients with a BASFI <3 (mean BASDAI=2.5): 0.8 • Patients with a BASFI 3-3.99 (mean BASDAI=3.8): 0.71 • Patients with a BASFI 4-4.99 (mean BASDAI=4.2): 0.67 • Patients with a BASFI 5-5.99 (mean BASDAI=4.7): 0.57	with AS. Patients from across the spectrum of possible BASDAI/BASFI values (0-10) responded to the survey Measures of uncertainty not reported UK population valuation set is assumed to have been used.

Study	Population characteristics	Interventions	Utility assessment methods	Utilities reported Mean (SD) [95% CI]	Reviewer comments
				• Patients with a BASFI 6-6.99 (mean BASDAI=5.5): 0.53 • Patients with a BASFI >7 (mean BASDAI=8.4): 0.47	
McLeod et al (2007)[34] Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation (mapping algorithm to EQ-5D values reported)	Utilities were estimated from a re-analysis of the Kobelt et al (2004)[143] survey data by the manufacturer of infliximab (n = 1144) Age: not reported Disease duration: not reported BASDAI: not reported BASFI: not reported	NA	EQ-5D • Completed by patients in the UK • It's assumed that the UK population valuation set was used as the study references Dolan et al (1995)[248] and was conducted in the UK Methods for mapping algorithm used by the Assessment group not reported.	Algorithm used in the Assessment Group (LRiG) model: Utility = 0.8772129 - 0.0384087 x BASDAI - 0.0322519 x BASFI - 0.0278913 x Male + 0.0016809 x Age Algorithms used in the manufacturer submissions are also reported but not reproduced here.	Generalisability of the algorithm is unclear as methods have not been reported. Report states that the manufacturer analysis is based on 1144 patients from Kobelt 2004. Utility values in Kobelt 2004 were calculated using data from 1413 patients. UK AS patients from across the spectrum of possible BASDAI/BASFI values (0-10) are likely to have been included in the analysis.
van Tubergen et al (2002)[234] Cost Effectiveness of Combined Spa–Exercise Therapy in Ankylosing Spondylitis: A Randomized	120 AS patients, diagnosed using mNY criteria. 111 included in the analysis. Age: 48 Disease duration: 11 years	• Spa treatment (3 weeks) • Usual care	EQ-5D • Completed by patients in Europe (not including the UK) • UK population valuation set is assumed to have been used as the study references Dolan	Spa treatment in Austria (n=36): • Baseline (2 weeks before treatment): 0.650 (0.22) • Change at 4 weeks: 0.02 (0.2)	Results may be generalisable to an AS population, however, generalisability to a UK population is unknown. Patients were allowed to continue taking their usual

Study	Population characteristics	Interventions	Utility assessment methods	Utilities reported Mean (SD) [95% CI]	Reviewer comments
Controlled Trial	BASDAI: not reported BASFI: 4.4		et al (1996)[249]. Outputs from the SF-6D are also reported in this study but are not summarised here.	• Change at 16 weeks: 0.04 (0.21) • Change at 28 weeks: -0.03 (0.23) • Change at 40 weeks: -0.01 (0.27) Spa treatment in The Netherlands (n=38): • Baseline (2 weeks before treatment): 0.64 (0.22) • Change at 4 weeks: 0.1 (0.24) • Change at 16 weeks: 0.12 (0.24) • Change at 28 weeks: 0.1 (0.21) • Change at 40 weeks: 0.03 (0.23) Usual care (n=37): • Baseline (2 weeks before treatment): 0.72 (0.1) • Change at 4 weeks: -0.06 (0.18) • Change at 16 weeks: -0.04 (0.19) • Change at 28 weeks: -0.08 (0.28) • Change at 40 weeks: -	medication throughout the study period. Medication could be changed if needed. This may bias the results. A UK population valuation set is assumed to have been used.

Study	Population characteristics	Interventions	Utility assessment methods	Utilities reported Mean (SD) [95% CI]	Reviewer comments
				0.03 (0.19)	
Wade et al (2011)[230] Baseline characteristics and patient reported outcome data of patients prescribed etanercept: web-based and telephone evaluation	43 patients prescribed etanercept for AS (diagnostic criteria not reported) RA, PsA and psoriasis patients were also included in the study. Age: 49 Disease duration: not reported BASDAI: not reported BASFI: not reported	Etanercept	EQ-5D • Completed by patients in the UK • UK population valuation set is assumed to have been used as this is a UK study	Baseline: 0.37 (0.37)	This study may be generalisable to UK patients with AS. 23% of AS patients were previously treated with a TNF alpha inhibitor. UK population valuation set is assumed to have been used. Differences in characteristics between telephone and web-based responders were observed for the entire sample (for all conditions).

AS = ankylosing spondylitis, LRiG =Liverpool Reviews and Implementation Group, mNY = modified New York criteria, NA = not applicable, OASIS = Outcome in Ankylosing Spondylitis International Study, PsA = psoriatic arthritis, RA = rheumatoid arthritis, RCT = randomised controlled trial, SSTAG = South Swedish Arthritis Treatment Group, UK = United Kingdom, * = median and, where included, the interquartile range, % = standard errors reported in brackets

11.14 Appendix 14: Comparison of parameter inputs across manufacturer models

Tables 157 and 158 provide an overview of the main parameter inputs applied in each of the manufacturer models for the AS and nr-axSpA populations.

Table 157 - Summary of main model inputs in manufacturer models - AS population

Parameter	MSD economic model (Infliximab, Golimumab)	AbbVie economic model (Adalimumab)	UCB economic model (Certolizumab)	Pfizer economic model (Etanercept)
Time horizon	Lifetime	40 years	Lifetime	Lifetime
Discount rate	3.5%	3.5%	3.5%	3.5%
Average age	39	42	41	41
Proportion male %	72	75	72	74
Average Weight	70	81.1	81.7	76.4
Baseline BASDAI	6.5	6.3	6.4	6.1
Baseline BASFI	5.0	5.3	5.7	5.9
Source of baseline characteristics	GO-RAISE	ATLAS	RAPID-axSpA trial	Study 314-EU
Mortality (SMR)	Male: 1.63 Female: 1.38	1.5	1.5	1.5
Response criteria	BASDAI50 response at week 12	ASAS20 response at week 12	ASAS20 response at week 24	BASDAI50 response at week 12
Proportion of responders %	Infliximab: 79.3 Golimumab: 48.5 Adalimumab: 47.0 Certolizumab: 53.0 Etanercept: 48.2 Placebo: 14.5	Infliximab: 72.4 Golimumab: 59.3 Adalimumab: 63.2 Certolizumab: 46.2 Etanercept: 60.7 Placebo: 27.2	Infliximab: 65.7 Golimumab: 54.1 Adalimumab: 56.2 Certolizumab: 55.7 Etanercept: 56.4 Placebo: -	Infliximab: 68 Golimumab: 61 Adalimumab: 54 Certolizumab: 47 Etanercept: 54 Placebo: 22
Placebo response	Loss or maintenance of placebo response not clearly reported.	BASDAI and BASFI return to baseline at week 12	No placebo response	BASDAI and BASFI return to baseline at 12 weeks
Annual long-term rate of anti-TNFs withdrawal	6.1% (GO-RAISE) Common rate for all anti-TNFs.	Time-dependent discontinuation; lognormal model fitted to Adalimumab week 12 responder data (ATLAS). Less than 15% projected to stay on treatment at year 40 Common rate for all anti-TNFs.	7% (NICE TA143) Common rate for all anti-TNFs.	Exponential model fitted to Etanercept data; model translates to 11% annual discontinuation for Etanercept. Hazard ratios applied for other anti-TNFs (Glintborg 2010)[108]
Natural history: annual rate of BASFI progression	0.07 points (Kobelt 2004)[143]	0.056 points (ATLAS)	0.07 points (Kobelt 2004)[143]	0.07 points (Kobelt 2004)[143]
AEs included; annual probability / rate	Serious AEs and ISRs included. Convent. care rates from GO-RAISE study. ORs from the NMA applied for each anti-TNF.	Only infectious AEs included; excess proportion for Adalimumab 29.7% annually (ATLAS trial). Same rate applied to all anti-TNFs.	No AEs included	Serious infections for Etanercept: 3.8% annually. Relative effects from a published NMA (Singh 2011)[127] applied for other anti-TNFs
HRQoL algorithm	0.877121 - 0.03841 *	0.899-0.031 *	2.126-0.132*BASFI-	0.887 - 0.006030 *

Parameter	MSD economic model (Infliximab, Golimumab)	AbbVie economic model (Adalimumab)	UCB economic model (Certolizumab)	Pfizer economic model (Etanercept)
(EQ-5D)	BASDAI - 0.03225 * BASFI - 0.02789 * male + 0.00168 * age (NICE TA143)	BASDAI-0.041 * BASFI (HUI3, data from ATLAS)	0.245*BASDAI (RAPID-axSpA study)	BASFI + 0.001030 * BASDAI + 0.000020 * BASFI^2 – 0.0000064 * BASDAI^2 (Study 314-EU)
Annual healthcare resource use costs	1902.49*exp(0.1832* BASFI) (NICE TA143)	£1124.619 × EXP(0.264× BASDAI) (OASIS)[157]	1909.33*exp(0.1832* BASFI) (NICE TA143)	BASDAI < 4: Annual cost: £151.96; 4 ≤ BASDAI < 6: Annual cost: £311.08; BASDAI ≥ 6: Annual cost: £1039.16 (Rafia 2012)[158]

Table 158 - Summary of main model inputs in manufacturer models - nr-axSpA population

Parameter	AbbVie economic model (Adalimumab)	UCB economic model (Certolizumab)	Pfizer economic model (Etanercept)
Time horizon	40 years	Lifetime	Lifetime
Discount rate	3.5%	3.5%	3.5%
Average age	38	37	32
Proportion male %	45	48	60
Average Weight	NR	82	74
Baseline BASDAI	6.4	6.5	6.0
Baseline BASFI	4.6	4.9	4.0
Source of baseline characteristics	ABILITY-1	RAPID-axSpA trial	Study 1031
Mortality (SMR)	1.0	1.5	1.0
Response criteria	ASAS40 response at week 12	ASAS20 response at week 12	BASDAI50 response at week 12
Proportion of responders %	Adalimumab: 55.9 Certolizumab: 58.8 Etanercept: NR Placebo: 22.2	Adalimumab: 56.3 Certolizumab: 59.0 Etanercept: 47.1 Placebo: -	Adalimumab: 44 Certolizumab: 59 Etanercept: 38 Placebo: 27
Placebo response	BASDAI and BASFI return to baseline at week 12	No placebo response	BASDAI and BASFI return to baseline at 12 weeks
Annual long-term rate of anti-TNFs withdrawal	Time-dependent discontinuation; lognormal model fitted to Adalimumab week 12 responder data (ABILITY-1). Less than 10% projected to stay on treatment at year 40 Common rate for all anti-TNFs.	7% (NICE TA143) Common rate for all anti-TNFs.	Exponential model fitted to Etanercept week 12 responder data; model translates to 5% annual discontinuation for Etanercept. Hazard ratios applied for other anti-TNFs (Glintborg 2010)[108]
Progression rate from nr-axSpA to AS	-	3.84% per year	-
Natural history: annual rate of BASFI progression	0.084 points (ABILITY-1)	0.07 points (Kobelt 2004)[143]	0.07 points (Kobelt 2004)[143]
AEs included; annual probability / rate	Only TB AEs and non-TB serious AEs included; excess rate for Adalimumab 7.3% for non TB serious AEs and 0.16% for TB AEs annually (ABILITY-1 trial). Same rate applied to all anti-TNFs.	No AEs included	No AEs included
HRQoL algorithm	0.922-0.039*BASDAI-0.041*BASFI (ABILITY-1)	2.1262-0.1323*BASFI-0.2450*BASDAI (RAPID-axSpA study)	0.919 - 0.00431 * BASFI + 0.000788 * BASDAI + 0.0000511 * BASFI^2 – 0.0000194 * BASDAI^2

Parameter	AbbVie economic model (Adalimumab)	UCB economic model (Certolizumab)	Pfizer economic model (Etanercept)
			– 0.00102 * Age + 0.0478 * Male – 0.0000754 * BASDAI*BASFI (Study 1031)
Annual healthcare resource use costs	£1124.62 × EXP(0.264× BASDAI) (OASIS)[157]	1909.33*exp(0.1832* BASFI) (NICE TA143)	BASDAI < 4: Annual cost: £151.96; 4 ≤ BASDAI < 6: Annual cost: £311.08; BASDAI ≥ 6: Annual cost: £1039.16 (Rafia 2012)[158]

Comparison of disease costs assumed for the AS and nr-axSpA populations

A variety of alternative regressions were applied across the submissions to estimate the annual disease costs associated with BASDAI and BASFI scores. MSD and UCB used the same exponential regression function estimated by LRiG as part of TA143 based on the OASIS study – uprated to current prices.

*Regression in NICE TA143 based on OASIS data and cost element uprated to current prices: £1902.492*EXP(0.1832*BASFI)*

AbbVie undertook their own re-analysis of the OASIS data set based on current prices. In their base-case an exponential model based on BASDAI was assumed. However, results from separate linear and exponential models were also presented.

Base-case regression used by AbbVie

*Exp BASDAI: £1124.619 * EXP(0.264 × BASDAI)*

Alternative regressions presented by AbbVie

Linear BASFI: £520.32102 +£804.64642 × BASFI

BASDAI: £118.47088 + £943.21394 × BASDAI

Exp BASFI: £1284.186 * EXP(0.213 × BASFI)

The submission by Pfizer was based on a recent UK study by Rafia et al (2012)[158]. Rather than employing a regression approach, the manufacturer used results based on a categorical analysis of the annual costs for BASDAI: BASDAI<4 = £151.96, 4<=BASDAI<6 = £311.08; BASDAI>=6 = £1039.16.

However, the paper by Rafia et al (2012) also specified a separate 2-part regression function which was not included within the Pfizer submission but is used in the subsequent comparisons of regressions to provide a more comparable approach to assessing the alternative costs sources used across the manufacturer submissions and the predictions across a range of different BASDAI and BASFI scores.

Two-part model in Rafia (2012):

1) Logistic regression model to derive probability of incurring costs:

2.71795 + 0.16716*BASFI + 0.37053*BASDAI - 0.02468* BASFI*BASDAI + 0.33778*Male - 0.04389*Age - 0.01373*Disease Duration

2) GLM to obtain 3-month costs:

6.79876 + 0.27548*BASFI + 0.13265*BASDAI - 0.01602* BASFI*BASDAI + 0.46458*Male - 0.01656*Age + 0.00381*Disease Duration

Figures 22 and 23 provide a comparison of the predictions from the alternative cost regressions using the separate sources identified across the manufacturer models. The baseline characteristics (BASDAI, BASFI, age and disease duration) are derived from a weighted average of the baseline characteristics of the clinical trials for the AS population from the manufacturer submissions.

In Figure 22, BASDAI scores are held constant at the mean value and the impact of varying BASFI across the range (0-10 scale) are reported. In Figure 2, BASFI scores are held constant at the mean value and the impact of varying BASDAI across the range (0-10 scale) are reported.

Figures 24 and 25 compare the alternative regression functions reported in the submission by AbbVie based on their re-analysis of the OASIS study.

Figure 22 Comparison of main manufacturer cost regressions – assuming constant BASDAI

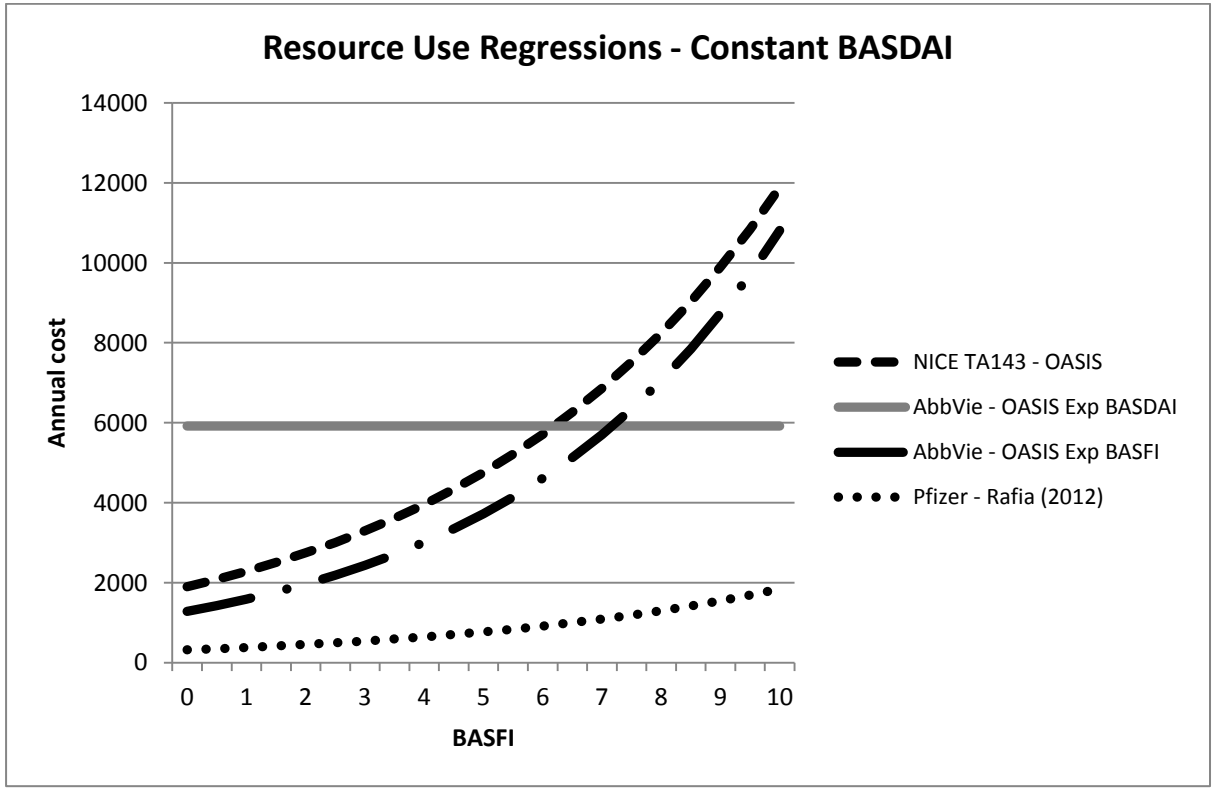


Figure 23 Comparison of main manufacturer cost regressions – assuming constant BASFI

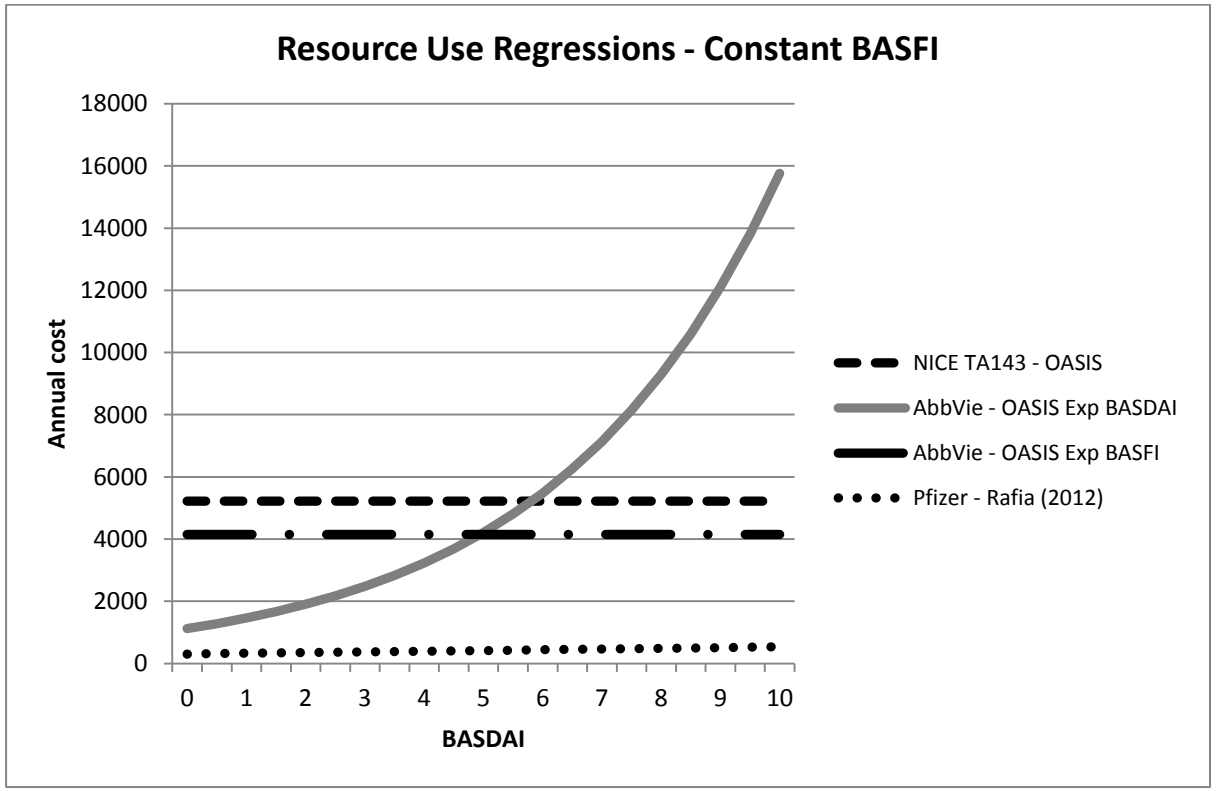


Figure 24 Comparison of AbbVie cost regressions – assuming constant BASDAI

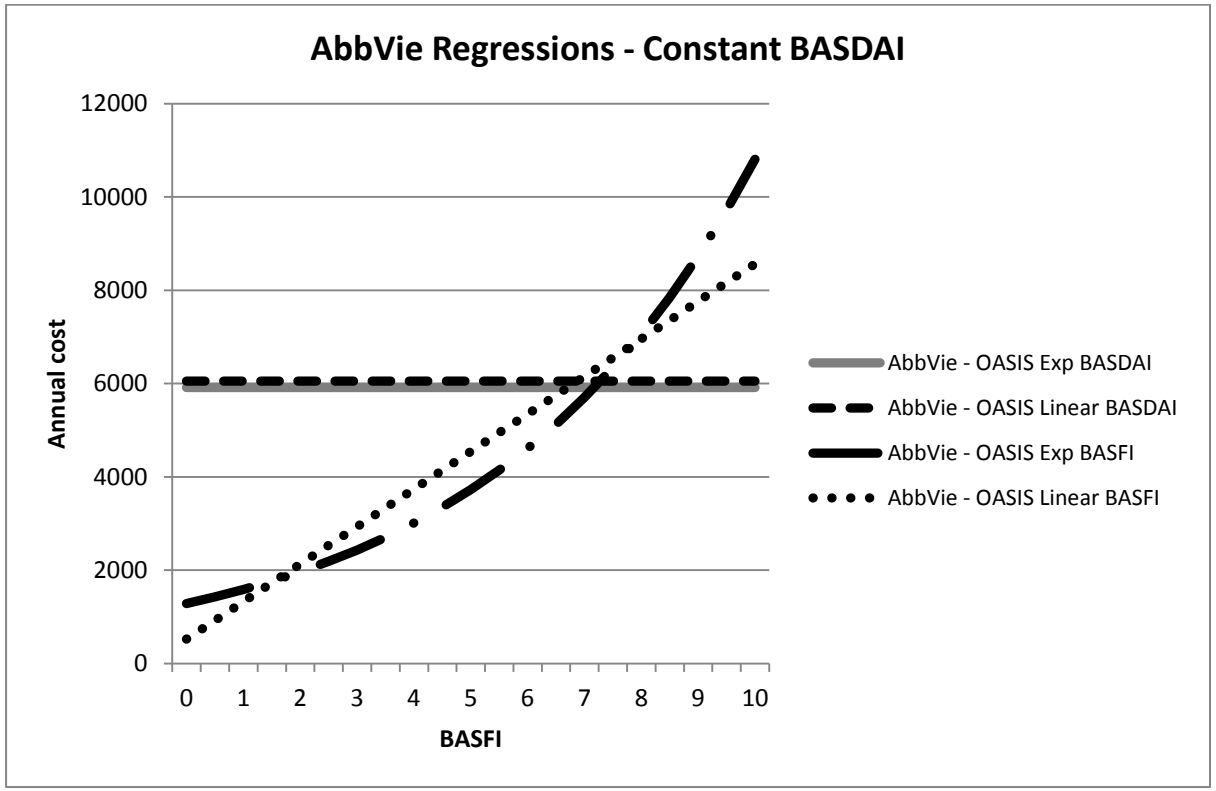


Figure 25 Comparison of AbbVie cost regressions – assuming constant BASFI

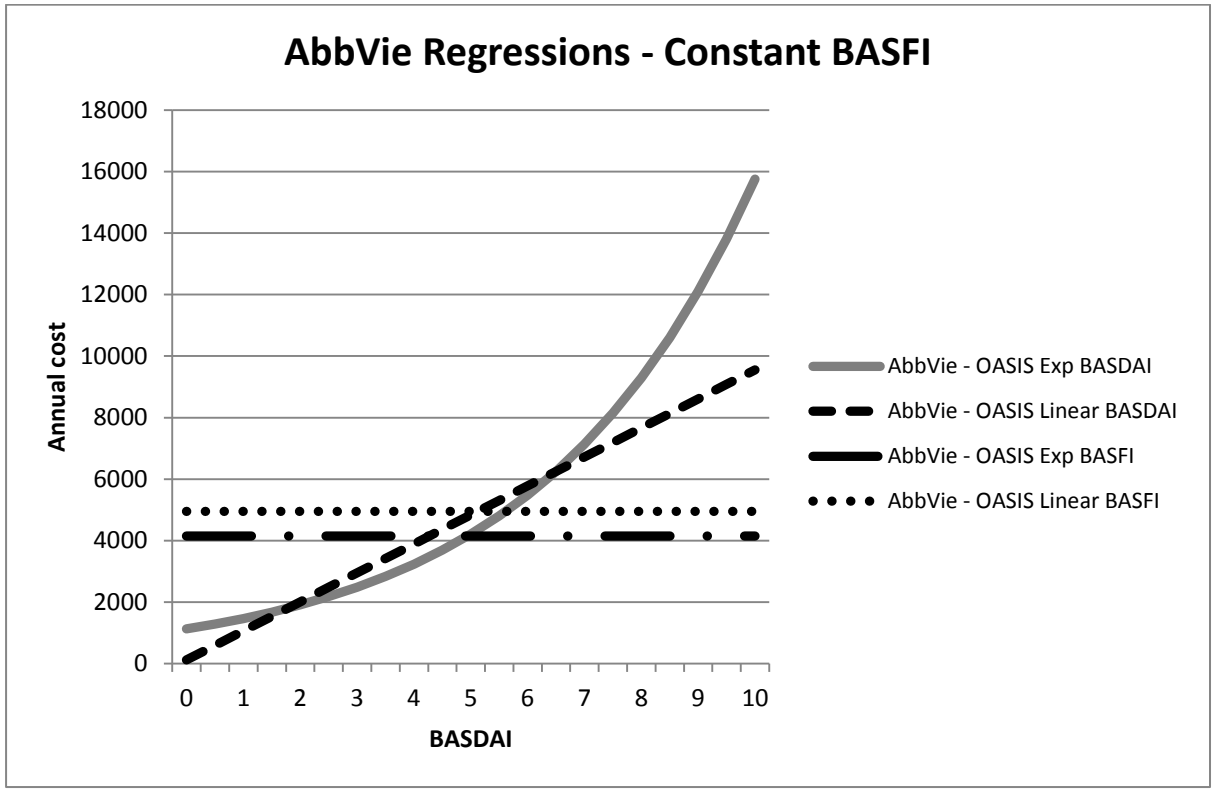


Table 159 - Cost inputs in manufacturer submissions (AS & nr-axSpA population)

Parameter	MSD economic model (Infliximab, Golimumab)	AbbVie economic model (Adalimumab)	UCB economic model (Certolizumab)	Pfizer economic model (Etanercept)
Administration costs	Subcutaneous therapies: no administration cost. Intravenous therapies: cost of £109 per administration (no reference provided)	Subcutaneous therapies: no administration cost. Intravenous therapies: cost of £99 per administration (no reference provided)	Subcutaneous therapies: £49 cost of nurse training for self-administration (PSSRU)[169] Intravenous therapies: cost of £398 per administration (PSSRU).	Subcutaneous therapies: £49 cost of nurse training for self-administration (PSSRU)[169] Intravenous therapies: cost of £302 per administration (NICE TA143).
Doses and unit costs	- Costs estimated in line with licensed doses. - PAS included for Certolizumab and Golimumab. - Infliximab dosage: Average weight of 70kg assumed (4 vials), subsequent administration every 7 weeks	- Costs estimated in line with licensed doses. - PAS included for Golimumab; not included for Certolizumab - Infliximab dosage: Average weight of 81.1kg assumed (5 vials), subsequent administration every 6 weeks	- Costs estimated in line with licensed doses. - PAS included for Certolizumab and Golimumab. - Infliximab dosage: Average weight of 81.7kg assumed (4.88 vials), subsequent administration every 7 weeks	- Costs estimated in line with licensed doses. - PAS included for Certolizumab and Golimumab - Infliximab dosage: Average weight of 76.4kg assumed (4 vials), subsequent administration every 6 weeks
Monitoring costs	Short term treatment costs applied in first cycle only for conventional care and anti-TNFs. Costs were informed by KOL interviews. Anti-TNFs: £873.2 Conventional care: £1,459.5	Initiation and quarterly monitoring costs included. Common for all anti-TNFs comparators (York Model TA199)[165] Initiation: £470.09 Monitoring: £110.98 per cycle	No monitoring costs included	No monitoring costs included in the base case

Parameter	MSD economic model (Infliximab, Golimumab)	AbbVie economic model (Adalimumab)	UCB economic model (Certolizumab)	Pfizer economic model (Etanercept)
Annual healthcare resource use costs	1902.49*exp(0.1832* BASFI) (NICE TA143)	£1124.619 × EXP(0.264× BASDAI) (OASIS)[157]	1909.33*exp(0.1832* BASFI) (NICE TA143)	BASDAI < 4: Annual cost: £151.96; BASDAI 4 ≤ BASDAI < 6: Annual cost: £311.08; BASDAI ≥ 6: Annual cost: £1039.16 (Rafia 2012)[158]

Table 160 - Withdrawal inputs in manufacturer submissions (AS & nr-axSpA population)

Parameter	MSD economic model (Infliximab, Golimumab)	AbbVie economic model (Adalimumab)	UCB economic model (Certolizumab)	Pfizer economic model (Etanercept)
Annual long-term rate of anti-TNF withdrawal– AS population	6.1% (GO-RAISE study, data of patients on treatment with golimumab from week 24 to week 256) Common rate for all anti-TNFs.	Time-dependent discontinuation rate; lognormal model fitted to Adalimumab week 12 responder data up to week 260 (ATLAS). Less than 15% of week-12 responders were projected to stay on treatment at year 40 for AS Common rate for all anti-TNFs.	7% (NICE TA143) Common rate for all anti-TNFs.	Exponential model fitted to Etanercept data; model translates to 11% annual discontinuation for Etanercept. Hazard ratios applied for other anti-TNFs (Glintborg 2010)[108] Annual discontinuation: Infliximab: 14.3% Golimumab: 12.3% Adalimumab: 12.3% Certolizumab: 12.3%
Annual long-term rate of anti-TNF withdrawal – nr-axSpA population	Not applicable.	Time-dependent discontinuation; lognormal model fitted to Adalimumab week 12 responder data up to week 156 (ABILITY-1). Less than 10% of week-12 responders were projected to stay on treatment at year 40 Common rate for all anti-TNFs.	7% (NICE TA143) Common rate for all anti-TNFs.	Exponential model fitted to Etanercept week 12 responder data; model translates to 5% annual discontinuation for Etanercept. Hazard ratios applied for other anti-TNFs (Glintborg 2010)[108] Annual discontinuation: Infliximab: 6.5% Golimumab: 5.6% Adalimumab: 5.6%

Parameter	MSD economic model (Infliximab, Golimumab)	AbbVie economic model (Adalimumab)	UCB economic model (Certolizumab)	Pfizer economic model (Etanercept)
				Certolizumab: 5.6%

Table 161 - Adverse events inputs in manufacturer submissions – AS population

Parameter	MSD economic model (Infliximab, Golimumab)	AbbVie economic model (Adalimumab)	UCB economic model (Certolizumab)	Pfizer economic model (Etanercept)
AEs included; annual probability	Serious AEs and ISRs included. Conventional care rates from GO-RAISE study at 24 weeks. OR of SAEs and ISRs from the NMA applied for each anti-TNF. Annual probability % of SAEs: Placebo: 7.6 Infliximab: 21.4 Golimumab: 5.4 Adalimumab: 6.8 Certolizumab: 13.4 Etanercept: 20.5 Annual probability % of ISRs: Placebo: 19.7 Infliximab: 24.3 Golimumab: 51.0 Adalimumab: 38.5 Certolizumab: 38.5 Etanercept: 52.6	Only infectious AEs included; excess proportion for Adalimumab was 29.7% annually (ATLAS trial) Same rate applied to all anti-TNFs.	No AEs included	Only serious infections included. Annual probability: 3.8% (Study 312) Relative effects for other anti-TNF agents were applied in the model, obtained from a published NMA (Singh 2011)[127]. Annual probability %: Infliximab: 4.1 Golimumab: 3.3 Adalimumab: 3.6 Certolizumab: 13.9 Etanercept: 3.8
Unit cost of AE	Cost per serious AE episode (weighted average): £214.26 anti-TNFs, £397.32 for conventional care	Cost per infectious AE episode: £45 (one GP visit assumed per infectious AE)	-	Cost per serious infection episode: £1,457 (weighted average) (NHS Reference costs)[166]

Parameter	MSD economic model (Infliximab, Golimumab)	AbbVie economic model (Adalimumab)	UCB economic model (Certolizumab)	Pfizer economic model (Etanercept)
	(GO-RAISE). Cost of injection site reaction £94.18 per episode			
Disutility of AE	Only disutility associated with SAEs applied; utility decrement of 0.01 applied for one cycle (NICE TA233)	No disutility applied	-	0.156 for 28 days

Table 162 - Adverse events inputs in manufacturer submissions – nr-axSpA population

Parameter	AbbVie economic model (Adalimumab)	UCB economic model (Certolizumab)	Pfizer economic model (Etanercept)
AEs included; annual probability	Only TB AEs and non-TB serious AEs included; excess proportion for Adalimumab 7.3% for non TB serious AEs and 0.16% for TB AEs annually (ABILITY-1 trial). Same rate applied to all anti-TNFs.	No AEs included	No AEs included
Unit cost of AE	- non-TB serious AEs: £4,216 per episode (NHS Reference costs)[166] - TB AE: £6,559.76 per episode (Botteman 2007)[153]	-	-
Disutility of AE	No disutility applied	-	-

11.15 Appendix 15: Full ICER tables for scenarios

Table 163 - Summary of cost-effectiveness scenarios – AS population

No.	Parameter/structural	Approach in scenario	Approach in base-case
1	Conventional care ('placebo') response	No response to conventional care assumed at 12 weeks	Response to conventional care included at 12 weeks
2.	Different baselines assumed for responders and non-responders and change in BASDAI/BASFI scores	Separate baselines based on pooled estimates provided by manufacturers. Changes in BASDAI/BASFI conditioned on response also based on pooled estimates provided by manufacturers	Separate baselines and changes in BASDAI/BASFI conditioned on responses estimated via extended synthesis model
3.	BASFI Progression	No effect of anti-TNFs on BASFI progression	Treatment effect applied from year 4 onwards
4.	BASFI progression	Treatment effect of anti-TNFs applied from start of model	Treatment effect applied from year 4 onwards
5.	Utilities	Linear BASDAI/BASFI model (based on Kobelt)	Non-linear BASDAI/BASFI model (Pfizer submission)

AS Scenario Results – Rebound equal to gain

Table 164 - AS – Scenario 1 (rebound equal to gain)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	7.262	-	111,702	-	-	-	-
Certolizumab Pegol PAS	7.952	0.691	125,734	14,033	20,319	0.462	0.861
Golimumab	7.952	0.691	127,531	15,829	22,920	0.313	0.764
Adalimumab	7.952	0.691	127,594	15,893	23,013	0.308	0.761
Etanercept	7.952	0.691	127,879	16,178	23,425	0.292	0.741
Certolizumab Pegol	7.952	0.691	129,308	17,607	25,495	0.188	0.651
Infliximab	7.952	0.691	141,750	30,048	43,510	0.000	0.063

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 165 - AS – Scenario 2 (rebound equal to gain)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	7.036	-	112,417	-	-	-	-
Certolizumab Pegol PAS	8.364	1.327	127,716	15,300	11,527	0.962	0.996
Golimumab	8.364	1.327	129,386	16,970	12,785	0.919	0.994
Adalimumab	8.364	1.327	129,473	17,057	12,851	0.918	0.994
Etanercept	8.364	1.327	129,862	17,445	13,143	0.903	0.994
Certolizumab Pegol	8.364	1.327	131,290	18,873	14,220	0.844	0.989
Infliximab	8.364	1.327	147,853	35,437	26,699	0.095	0.668

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 166 - AS – Scenario 3 (rebound equal to gain)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	7.253	-	109,379	-	-	-	-
Certolizumab Pegol PAS	8.128	0.875	127,455	18,075	20,655	0.462	0.843
Golimumab	8.128	0.875	129,140	19,760	22,581	0.348	0.775
Adalimumab	8.128	0.875	129,224	19,845	22,677	0.341	0.771
Etanercept	8.128	0.875	129,600	20,220	23,106	0.319	0.760
Certolizumab Pegol	8.128	0.875	131,028	21,649	24,739	0.234	0.698
Infliximab	8.128	0.875	147,118	37,739	43,125	0.001	0.063

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 167 - AS – Scenario 4 (rebound equal to gain)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE	Probability of CE

						£20K	**£30K**
Conventional Therapy	7.239	-	111,036	-	-	-	-
Certolizumab Pegol PAS	8.201	0.962	128,804	17,767	18,466	0.589	0.929
Golimumab	8.201	0.962	130,485	19,448	20,213	0.462	0.878
Adalimumab	8.201	0.962	130,570	19,533	20,301	0.453	0.875
Etanercept	8.201	0.962	130,949	19,912	20,695	0.429	0.862
Certolizumab Pegol	8.201	0.962	132,377	21,341	22,180	0.345	0.808
Infliximab	8.201	0.962	148,597	37,560	39,037	0.005	0.124

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 168 - AS – Scenario 5 (rebound equal to gain)

	Total QALYs	**Incremental QALYs**	**Total costs (£)**	**Incremental costs (£)**	**ICER (£)**	**Probability of CE £20K**	**Probability of CE £30K**
Conventional Therapy	10.272	-	111,187	-	-	-	-
Certolizumab Pegol PAS	11.043	0.771	129,139	17,953	23,290	0.217	0.891
Golimumab	11.043	0.771	130,819	19,632	25,469	0.099	0.755
Adalimumab	11.043	0.771	130,904	19,717	25,579	0.094	0.750
Etanercept	11.043	0.771	131,285	20,098	26,073	0.074	0.724
Certolizumab Pegol	11.043	0.771	132,713	21,526	27,926	0.048	0.593
Infliximab	11.043	0.771	148,974	37,787	49,021	0.000	0.003

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

AS Scenario Results – Rebound to conventional care

Table 169 - AS – Scenario 1 (rebound to conventional care)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	7.295	-	112,675	-	-	-	-
Certolizumab Pegol PAS	7.762	0.467	128,654	15,979	34,229	0.038	0.385
Golimumab	7.762	0.467	130,446	17,771	38,068	0.014	0.257
Adalimumab	7.762	0.467	130,511	17,836	38,207	0.013	0.256
Etanercept	7.762	0.467	130,799	18,124	38,824	0.010	0.245
Certolizumab Pegol	7.762	0.467	132,228	19,553	41,885	0.004	0.161
Infliximab	7.762	0.467	144,800	32,125	68,815	0.000	0.000

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 170 - AS – Scenario 2 (rebound to conventional care)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	7.054	-	112,115	-	-	-	-
Certolizumab Pegol PAS	7.742	0.687	129,659	17,543	25,530	0.162	0.706
Golimumab	7.742	0.687	131,346	19,231	27,986	0.086	0.587
Adalimumab	7.742	0.687	131,430	19,315	28,107	0.082	0.586
Etanercept	7.742	0.687	131,804	19,689	28,652	0.068	0.556
Certolizumab Pegol	7.742	0.687	133,232	21,117	30,731	0.042	0.450
Infliximab	7.742	0.687	149,253	37,138	54,045	0.000	0.004

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 171 - AS – Scenario 3 (rebound to conventional care)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	7.252	-	110,930	-	-	-	-
Certolizumab Pegol PAS	7.818	0.566	131,610	20,679	36,518	0.021	0.339
Golimumab	7.818	0.566	133,289	22,359	39,483	0.009	0.249
Adalimumab	7.818	0.566	133,374	22,444	39,634	0.008	0.245
Etanercept	7.818	0.566	133,755	22,824	40,306	0.006	0.230
Certolizumab Pegol	7.818	0.566	135,183	24,253	42,828	0.003	0.166
Infliximab	7.818	0.566	151,457	40,526	71,565	0.000	0.000

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 172 - AS – Scenario 4 (rebound to conventional care)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	7.268	-	108,817	-	-	-	-
Certolizumab Pegol PAS	7.894	0.626	128,999	20,182	32,222	0.047	0.429
Golimumab	7.894	0.626	130,683	21,866	34,910	0.022	0.341
Adalimumab	7.894	0.626	130,767	21,951	35,045	0.020	0.339
Etanercept	7.894	0.626	131,144	22,327	35,647	0.016	0.310
Certolizumab Pegol	7.894	0.626	132,573	23,756	37,928	0.008	0.234
Infliximab	7.894	0.626	148,706	39,889	63,684	0.000	0.000

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 173 - AS – Scenario 5 (rebound to conventional care)

	Total QALYs	**Incremental QALYs**	**Total costs (£)**	**Incremental costs (£)**	**ICER (£)**	**Probability of CE £20K**	**Probability of CE £30K**
Conventional Therapy	10.272	-	112,648	-	-	-	-
Certolizumab Pegol PAS	10.967	0.695	133,103	20,455	29,414	0.012	0.511
Golimumab	10.967	0.695	134,781	22,133	31,827	0.005	0.340
Adalimumab	10.967	0.695	134,866	22,218	31,950	0.005	0.333
Etanercept	10.967	0.695	135,248	22,600	32,499	0.004	0.300
Certolizumab Pegol	10.967	0.695	136,677	24,028	34,554	0.002	0.165
Infliximab	10.967	0.695	152,997	40,349	58,022	0.000	0.000

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 174 - Summary of cost-effectiveness scenarios – nr-axSpA population

No.	**Parameter/structural**	**Approach in scenario**	**Approach in base-case**
1	Conventional care ('placebo') response	No response to conventional care assumed at 12 weeks	Response to conventional care included at 12 weeks
2.	Different baselines assumed for responders and non-responders and change in BASDAI/BASFI scores	Separate baselines based on pooled estimates provided by manufacturers. Changes in BASDAI/BASFI conditioned on response also based on pooled estimates provided by manufacturers	Separate baselines and changes in BASDAI/BASFI conditioned on responses estimated via extended synthesis model
3.	BASFI Progression	No effect of anti-TNFs on BASFI progression	Treatment effect applied from year 4 onwards
4.	BASFI progression	Treatment effect of anti-TNFs applied from start of model	Treatment effect applied from year 4 onwards
5.	Utilities	Linear BASDAI/BASFI model (based on Kobelt)	Non-linear BASDAI/BASFI model (Pfizer submission)
6.	Treatment effect of anti-TNFs	Trials in nr-axSpA and AS populations combined	Only trials in nr-axSpA included

Nr-axSpA Scenario Results – Rebound equal to gain

Table 175 - Nr-axSpA – Scenario 1 (rebound equal to gain)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	10.036	-	87,879	-	-	-	-
Certolizumab Pegol PAS	10.621	0.585	108,266	20,387	34,841	0.040	0.384
Adalimumab	10.621	0.585	110,046	22,167	37,884	0.015	0.248
Etanercept	10.621	0.585	110,411	22,532	38,507	0.013	0.235
Certolizumab Pegol	10.621	0.585	111,839	23,960	40,949	0.008	0.167

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 176 - Nr-axSpA – Scenario 2 (rebound equal to gain)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	9.321	-	95,037	-	-	-	-
Certolizumab Pegol PAS	10.238	0.917	118,411	23,375	25,482	0.290	0.665
Adalimumab	10.238	0.917	120,081	25,044	27,302	0.219	0.622
Etanercept	10.238	0.917	120,556	25,520	27,821	0.200	0.603
Certolizumab Pegol	10.238	0.917	121,985	26,948	29,378	0.160	0.555

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 177 - Nr-axSpA – Scenario 3 (rebound equal to gain)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	9.891	-	91,479	-	-	-	-
Certolizumab Pegol PAS	11.262	1.370	130,734	39,254	28,643	0.138	0.576
Adalimumab	11.262	1.370	132,141	40,662	29,670	0.102	0.528
Etanercept	11.262	1.370	132,879	41,399	30,208	0.093	0.505
Certolizumab Pegol	11.262	1.370	134,306	42,827	31,250	0.076	0.460

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 178 - Nr-axSpA – Scenario 4 (rebound equal to gain)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	9.923	-	90,625	-	-	-	-
Certolizumab Pegol PAS	11.338	1.415	129,492	38,867	27,471	0.154	0.627
Adalimumab	11.338	1.415	130,899	40,274	28,466	0.127	0.574
Etanercept	11.338	1.415	131,637	41,012	28,988	0.116	0.549
Certolizumab Pegol	11.338	1.415	133,064	42,440	29,996	0.087	0.501

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 179 - Nr-axSpA – Scenario 5 (rebound equal to gain)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	10.973	-	89,400	-	-	-	-
Certolizumab Pegol PAS	12.527	1.554	128,760	39,361	25,324	0.120	0.781
Adalimumab	12.527	1.554	130,165	40,765	26,227	0.086	0.725
Etanercept	12.527	1.554	130,905	41,506	26,704	0.071	0.692
Certolizumab Pegol	12.527	1.554	132,333	42,933	27,622	0.053	0.629

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 180 - Nr-axSpA – Scenario 6 (rebound equal to gain)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	9.944	-	88,563	-	-	-	-
Certolizumab Pegol PAS	11.382	1.437	129,592	41,030	28,282	0.068	0.612
Adalimumab	11.382	1.437	130,978	42,415	29,228	0.040	0.570
Etanercept	11.382	1.437	131,737	43,175	29,753	0.032	0.546
Certolizumab Pegol	11.382	1.437	133,165	44,602	30,732	0.020	0.483

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Nr-axSpA Scenario Results – Rebound to conventional care

Table 181 - Nr-axSpA – Scenario 1 (rebound to conventional care)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	10.007	-	88,711	-	-	-	-
Certolizumab Pegol PAS	10.524	0.517	109,867	21,156	40,928	0.018	0.236
Adalimumab	10.524	0.517	111,644	22,932	44,365	0.002	0.143
Etanercept	10.524	0.517	112,012	23,301	45,078	0.002	0.130
Certolizumab Pegol	10.524	0.517	113,441	24,729	47,842	0.001	0.090

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 182 - Nr-axSpA – Scenario 2 (rebound to conventional care)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	9.277	-	95,300	-	-	-	-
Certolizumab Pegol PAS	10.088	0.811	119,550	24,249	29,884	0.168	0.506
Adalimumab	10.088	0.811	121,219	25,919	31,942	0.124	0.454
Etanercept	10.088	0.811	121,695	26,394	32,528	0.108	0.425
Certolizumab Pegol	10.088	0.811	123,123	27,823	34,288	0.086	0.383

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 183 - Nr-axSpA – Scenario 3 (rebound to conventional care)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	9.891	-	91,602	-	-	-	-
Certolizumab Pegol PAS	11.066	1.175	132,047	40,445	34,416	0.052	0.396
Adalimumab	11.066	1.175	133,456	41,854	35,615	0.036	0.348
Etanercept	11.066	1.175	134,192	42,590	36,241	0.031	0.330
Certolizumab Pegol	11.066	1.175	135,620	44,017	37,456	0.026	0.290

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 184 - Nr-axSpA – Scenario 4 (rebound to conventional care)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	9.948	-	90,402	-	-	-	-
Certolizumab Pegol PAS	11.223	1.275	131,015	40,613	31,841	0.063	0.456
Adalimumab	11.223	1.275	132,416	42,014	32,940	0.047	0.415
Etanercept	11.223	1.275	133,160	42,758	33,523	0.040	0.395
Certolizumab Pegol	11.223	1.275	134,587	44,185	34,642	0.027	0.337

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 185 - Nr-axSpA – Scenario 5 (rebound to conventional care)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	10.975	-	90,413	-	-	-	-
Certolizumab Pegol PAS	12.462	1.487	130,404	39,991	26,900	0.069	0.678
Adalimumab	12.462	1.487	131,817	41,404	27,850	0.050	0.599
Etanercept	12.462	1.487	132,549	42,136	28,343	0.042	0.572
Certolizumab Pegol	12.462	1.487	133,976	43,563	29,303	0.028	0.498

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 186 - Nr-axSpA – Scenario 6 (rebound to conventional care)

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	9.953	-	89,196	-	-	-	-
Certolizumab Pegol PAS	11.228	1.275	131,515	42,319	33,184	0.013	0.398
Adalimumab	11.228	1.275	132,901	43,704	34,270	0.007	0.353
Etanercept	11.228	1.275	133,661	44,464	34,866	0.002	0.332
Certolizumab Pegol	11.228	1.275	135,088	45,891	35,985	0.001	0.284

Additional validation scenarios assuming same baselines for responders and non-responders

Table 187 - AS – rebound equal to gain

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	7.262	-	111,636	-	-	-	-
Certolizumab Pegol PAS	8.317	1.054	126,238	14,601	13,851	0.803	0.975
Golimumab	8.317	1.054	127,917	16,281	15,444	0.732	0.958
Adalimumab	8.317	1.054	128,002	16,366	15,525	0.730	0.958
Etanercept	8.317	1.054	128,383	16,746	15,886	0.708	0.952
Certolizumab Pegol	8.317	1.054	129,811	18,175	17,241	0.645	0.931
Infliximab	8.317	1.054	146,079	34,443	32,673	0.044	0.376

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 188 - AS –rebound to conventional care

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	7.274	-	109,511	-	-	-	-
Certolizumab Pegol PAS	7.958	0.684	127,164	17,654	25,809	0.277	0.632
Golimumab	7.958	0.684	128,850	19,339	28,273	0.183	0.554
Adalimumab	7.958	0.684	128,934	19,423	28,396	0.178	0.550
Etanercept	7.958	0.684	129,309	19,799	28,945	0.165	0.534
Certolizumab Pegol	7.958	0.684	130,738	21,227	31,034	0.107	0.473
Infliximab	7.958	0.684	146,808	37,298	54,528	0.000	0.010

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 189 - Nr-axSpA – rebound equal to gain

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Therapy	9.977	-	88,692	-	-	-	-
Certolizumab Pegol PAS	11.551	1.574	125,205	36,513	23,199	0.390	0.759
Adalimumab	11.551	1.574	126,606	37,914	24,089	0.341	0.733
Etanercept	11.551	1.574	127,350	38,658	24,562	0.319	0.720
Certolizumab Pegol	11.551	1.574	128,777	40,085	25,469	0.272	0.702

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

Table 190 - Nr-axSpA – rebound to conventional care

	Total QALYs	Incremental QALYs	Total costs (£)	Incremental costs (£)	ICER (£)	Probability of CE £20K	Probability of CE £30K
Conventional Care	10.030	-	88,389	-	-	-	-
Certolizumab Pegol PAS	11.391	1.361	126,116	37,727	27,721	0.218	0.617
Adalimumab	11.391	1.361	127,525	39,136	28,756	0.176	0.586
Etanercept	11.391	1.361	128,261	39,872	29,297	0.160	0.574
Certolizumab Pegol	11.391	1.361	129,689	41,299	30,345	0.133	0.537

Probability of CE £20/30K = probability that the TNF-alpha inhibitor, when compared to conventional care, is a cost-effective option at the stated threshold

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