NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (including a review of TA143 and TA233)

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using adalimumab, certolizumab pegol, etanercept, golimumab and infliximab in the NHS in England. The Appraisal Committee has considered the evidence submitted and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the Committee papers).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using adalimumab, certolizumab pegol, etanercept, golimumab and infliximab in the NHS in England.

For further details, see the Guides to the technology appraisal process.

The key dates for this appraisal are:

Closing date for comments: 19 June 2015

Second Appraisal Committee meeting: 30 June 2015

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

1.1 Adalimumab, certolizumab pegol, etanercept and golimumab are recommended within their marketing authorisations, as treatment options for active ankylosing spondylitis.

Golimumab is recommended only when the company provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, in accordance with the patient access scheme.

1.2 Infliximab is not recommended within its marketing authorisation for the treatment of ankylosing spondylitis

1.3 Adalimumab, certolizumab pegol and etanercept are recommended within their marketing authorisations, as treatment options for non-radiographic axial spondyloarthritis.

1.4 The choice of treatment should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available, and may include consideration of associated conditions. If more than 1 treatment is suitable, the least expensive should be chosen.

1.5 The response to adalimumab, certolizumab pegol, etanercept or golimumab treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response, defined as:

- reduction of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units and
- reduction of the spinal pain visual analogue scale (VAS) by 2 cm or more.

For people who cannot tolerate adalimumab, certolizumab pegol, etanercept or golimumab and who stop taking it before response can be assessed at 12 weeks, another TNF-alpha inhibitor is recommended within its marketing authorisation.

1.6 Treatment with another TNF-alpha inhibitor is not recommended for people whose disease has not responded to treatment with the first TNF-alpha inhibitor, or those who had an initial response which was then lost.

1.7 When using BASDAI and spinal pain VAS scores, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the questionnaires, and make any adjustments they consider appropriate.

1.8 People whose treatment with a TNF-alpha inhibitor is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 Clinical need and practice

2.1 Ankylosing spondylitis and non-radiographic axial spondyloarthritis are part of a group of clinically heterogeneous inflammatory rheumatologic diseases known as spondyloarthritis. Spondyloarthritis can be categorised as having either predominantly axial (sacroiliac joints or spine) or peripheral

involvement. In people with axial spondyloarthritis, the predominant symptom is back pain with inflammation of the sacroiliac joints (sacroiliitis) or the spine or both. The onset of symptoms typically occurs in the third decade of life. Damage is progressive and irreversible and there is increased risk of spinal fracture later in life. There may also be peripheral joint involvement or extra articular manifestations such as uveitis, inflammatory bowel disease and psoriasis.

2.2 Disease is classified as ankylosing spondylitis if changes to the sacroiliac joints or the spine, or both, can be seen on X-ray. These include erosions, sclerosis (thickening of the bone), and partial or total ankylosis (fusion of joints). The prevalence of ankylosing spondylitis is thought to range from 0.05% to 0.23% and it is about 3 times more common in men than in women.

2.3 Not everyone with symptoms of axial spondyloarthritis will have changes that can be seen on X-ray. Disease is then classified as axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (non-radiographic axial spondyloarthritis). Sacroiliitis or inflammation of the spine may be visible on MRI. Limited epidemiological data are available for non-radiographic axial spondyloarthritis, but it affects about equal numbers of men and women.

2.4 Conventional therapy for ankylosing spondylitis and non-radiographic axial spondyloarthritis includes non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy. Tumour necrosis factor alpha (TNF-alpha) inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) are typically used when the disease has not responded adequately to conventional therapy.

2.5 In clinical trials of ankylosing spondylitis and non-radiographic axial spondyloarthritis, 3 key disease components are assessed: disease activity, physical function and structural damage. A number of assessment tools have been developed to measure these:

- Disease activity is most commonly assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). BASDAI is a validated, composite index that records patients' responses to 6 questions relating to 5 major symptoms: fatigue, axial pain, peripheral pain, stiffness and enthesitis. Responses are recorded on 10 cm visual analogue scales (VAS). Another instrument commonly used to assess disease activity is the Bath Ankylosing Spondylitis Metrology Index (BASMI). This uses clinical measurements such as the amount of movement achieved when the patient rotates their head (cervical rotation) or reaches towards the floor (lumbar side flexion).
- Physical function is often assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI). BASFI is a patient-assessed, validated, composite index made up of 10 questions that address function and the patient's ability to manage their disease. As with BASDAI, responses are recorded on a 10 cm VAS.
- Structural damage and disease progression are usually evaluated by radiography, using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS).

2.6 Studies of the natural history of ankylosing spondylitis and non-radiographic axial spondyloarthritis show that disease activity (measured by BASDAI) is fairly stable over time and does not change. Physical function (assessed by BASFI) does deteriorate (‘progress’) over time, but the rate of progression is not constant or predictable. Because BASFI is a measure of both disease activity

and bone formation, changes in BASFI scores over time are driven by progression of spinal damage as assessed by mSASSS.

2.7 The Assessment of SpondyloArthritis international Society (ASAS) has developed a set of response criteria that are commonly used in ankylosing spondylitis clinical trials. The ASAS criteria relate to improvement across a set of 4 domains:

- patient global assessment (measured on a 10 cm VAS)
- physical function (measured using BASFI)
- inflammation (using the mean of 2 questions from BASDAI relating to severity and duration of morning stiffness)
- spinal pain (measured on a 10 cm VAS).

An ASAS 20 response (a common primary efficacy outcome in clinical trials) is defined as an improvement of greater than 20% and an absolute change of 1 or more points on the 0–10 cm VAS in at least 3 of the 4 domains. In the fourth domain there must be no worsening by a similar amount. Other definitions of ASAS response (ASAS 40, 50 and 70, based on improvements of 40%, 50% and 70%, respectively) and an improvement of 50% or more in BASDAI score (BASDAI 50) are also used to measure outcomes in clinical studies.

3 The technologies

3.1 Adalimumab (Humira, AbbVie), certolizumab pegol (Cimzia, UCB Pharma), etanercept (Enbrel, Pfizer), golimumab (Simponi, Merck Sharp & Dohme), and infliximab (Remicade, Merck Sharp & Dohme; Inflectra, Hospira; Remsima, Celltrion) inhibit the pro-inflammatory cytokine, tumour necrosis factor alpha (TNF-alpha). TNF-alpha inhibitors may modify the inflammatory process of the disease. Adalimumab, certolizumab pegol, golimumab and infliximab are monoclonal antibodies, and etanercept is a

recombinant human tumour necrosis factor receptor (TNF-receptor) fusion protein.

3.2 Adalimumab, etanercept, golimumab and infliximab have marketing authorisations in the UK for the treatment of adults with severe active ankylosing spondylitis that has responded inadequately to conventional therapy. Certolizumab pegol has a marketing authorisation in the UK for the treatment of 'adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to, nonsteroidal anti-inflammatory drugs (NSAIDs)'.

3.3 Adalimumab, certolizumab pegol and etanercept are also licensed for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (non-radiographic axial spondyloarthritis) but with objective signs of inflammation by elevated C-reactive protein and/or magnetic resonance imaging, whose disease has responded inadequately to, or who cannot tolerate, NSAIDs. Golimumab and infliximab do not currently have a marketing authorisation in the UK for non-radiographic axial spondyloarthritis.

Adalimumab

3.4 Adalimumab is administered by subcutaneous injection. The recommended dose regimen for patients with ankylosing spondylitis, and for patients with non-radiographic axial spondyloarthritis, is 40 mg (given as 1 injection) every other week. The summary of product characteristics recommends that continued adalimumab therapy should be carefully reconsidered in patients whose disease does not respond within 12 weeks after starting treatment.

3.5 The summary of product characteristics lists the following adverse reactions for adalimumab: infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache, musculoskeletal pain, hepatitis B reactivation, various malignancies and serious haematological, neurological and autoimmune reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.6 The price of adalimumab is £352.14 for a 40 mg pre-filled pen or pre-filled syringe, or a 40 mg/0.8 ml vial (excluding VAT; 'British National Formulary' [BNF] edition 68). The annual cost of treatment with adalimumab is estimated at £9156, assuming the patient has 40 mg every other week (see section 3.4). Costs may vary in different settings because of negotiated procurement discounts.

Certolizumab pegol

3.7 Certolizumab pegol is administered by subcutaneous injection. The recommended induction dosage for patients with ankylosing spondylitis, and for patients with non-radiographic axial spondyloarthritis, is 400 mg (given as 2 injections of 200 mg each) at weeks 0, 2 and 4. The recommended maintenance dose regimen is 200 mg every other week or 400 mg every 4 weeks. The summary of product characteristics recommends that continued certolizumab pegol therapy should be carefully reconsidered if there is no evidence of therapeutic benefit within 12 weeks of starting treatment.

3.8 The summary of product characteristics lists the following adverse reactions for certolizumab pegol: infections (including sepsis, pneumonia, tuberculosis, invasive fungal and opportunistic infections), blood and lymphatic system malignancies (including lymphoma and leukaemia), autoimmune conditions (including

lupus-like syndrome), injection site reactions (erythema, itching, haematoma, pain or swelling), and hepatitis B reactivation. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.9 The price of certolizumab pegol is £357.50 for a 200 mg pre-filled syringe (excluding VAT; BNF edition 68). Assuming the recommended dosage is followed (see section 3.7), the annual cost for first year of treatment with certolizumab pegol is estimated at £10,368. Costs may vary in different settings because of negotiated procurement discounts.

Etanercept

3.10 Etanercept is administered by subcutaneous injection. The recommended dosage for patients with ankylosing spondylitis, and for patients with non-radiographic axial spondyloarthritis, is 25 mg administered twice weekly or 50 mg administered once weekly. The summary of product characteristics recommends that continued etanercept therapy should be carefully reconsidered in patients whose disease does not respond within 12 weeks of starting treatment.

3.11 The summary of product characteristics lists the following adverse reactions for etanercept: infections (including upper respiratory infections, bronchitis, bladder infections and skin infections, as well as serious infections such as sepsis), injection site reactions (such as pain, swelling, itching, reddening and bleeding at the puncture site), allergic reactions, development of auto-antibodies, itching, fever, various malignancies and serious haematological, neurological and autoimmune reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.12 The price of etanercept is £89.38 for a 25 mg pre-filled syringe or a 25 mg vial containing powder for reconstitution (with solvent), and £178.75 for a 50 mg pre-filled pen or pre-filled syringe (excluding VAT; BNF edition 68). The annual cost of treatment with etanercept, using either twice weekly or once weekly dosage frequency (see section 3.10), is estimated at £9296. Costs may vary in different settings because of negotiated procurement discounts.

Golimumab

3.13 Golimumab is administered by subcutaneous injection. The recommended dose regimen for patients with ankylosing spondylitis is 50 mg once a month, on the same date each month. The summary of product characteristics recommends that continued golimumab therapy should be carefully reconsidered if there is no evidence of therapeutic benefit within 12–14 weeks of starting treatment (that is, after 3–4 doses). For patients with a body weight greater than 100 kg whose disease does not respond adequately after 4 doses (50 mg each), the summary of product characteristics states that increasing the dosage of golimumab to 100 mg once a month may be considered. If there is still no evidence of therapeutic benefit after 3–4 additional doses of 100 mg, continued golimumab therapy should be carefully reconsidered.

3.14 The summary of product characteristics lists the following adverse reactions for golimumab: infections (including sepsis, pneumonia, tuberculosis, and invasive fungal and opportunistic infections), demyelinating disorders, lymphoma, hepatitis B reactivation, congestive heart failure, autoimmune processes (lupus-like syndrome) and haematologic reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.15 The price of golimumab is £762.97 for a 50 mg pre-filled pen or pre-filled syringe and £1525.94 for a 100 mg pre-filled pen (excluding VAT; BNF edition 68). Merck Sharp & Dohme has agreed a patient access scheme with the Department of Health. This will make the 100 mg dose of golimumab available to the NHS at the same cost as the 50 mg dose. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. Assuming the patient has 50 mg every month, the annual cost of treatment with golimumab is estimated at £9156. Because of the patient access scheme, this cost would remain the same for patients with a body weight greater than 100 kg whose disease does not respond adequately to the 50 mg per month dosage and who subsequently have monthly doses of 100 mg (see section 3.13).

Infliximab

3.16 Infliximab is administered by intravenous infusion. The recommended dosage for patients with ankylosing spondylitis is a 5 mg/kg infusion at weeks 0, 2 and 6, then every 6–8 weeks. The summary of product characteristics states that if there is no response by 6 weeks (that is, after 2 doses), no additional treatment with infliximab should be given.

3.17 The summary of product characteristics lists the following adverse reactions for infliximab: infections (including upper respiratory tract infections, sepsis, opportunistic infections and tuberculosis), hepatitis B reactivation, congestive heart failure, serum sickness (delayed hypersensitivity reactions), haematologic reactions, systemic lupus erythematosus/lupus-like syndrome, demyelinating disorders, hepatobiliary events, lymphoma, hepatosplenic T-cell lymphoma, and serious infusion reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.18 The price of infliximab is £419.62 for a 100 mg vial containing powder for reconstitution (excluding VAT; BNF edition 68). For a patient with a body weight of 73 kg, the annual cost for first year of treatment with infliximab therapy (including 3 induction doses) is estimated at between £16,785 and £13,428 (depending on whether the maintenance infusions are repeated every 6 or 8 weeks). Costs may vary in different settings because of negotiated procurement discounts.

3.19 Biosimilar versions of infliximab (Inflectra, Hospira; Remsima, Celltrion) have a marketing authorisation in the UK for the same indications. The therapeutic indications, dosage and method of administration for Remsima and Inflectra are identical to those for Remicade. Adverse reactions are similar too. The price of Remsima is £377.66 for a 100 mg vial (price confirmed by Celltrion Healthcare and Napp Pharmaceuticals). For a patient with a body weight of 73 kg, the annual cost for first year of treatment with Remsima therapy is estimated at between £15,106 and £12,085 (depending on whether the maintenance infusions are repeated every 6 or 8 weeks). Inflectra did not have an approved list price in the UK at the time of the appraisal.

4 Evidence and interpretation

The Appraisal Committee (section 8) considered evidence from a number of sources (section 9).

Clinical effectiveness

4.1 The Assessment Group conducted a systematic review and identified 24 relevant randomised controlled trials (RCTs): 19 recruited people with ankylosing spondylitis, 4 recruited people with axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (non-radiographic axial spondyloarthritis), and 1 recruited both populations. All except 2 of the trials were placebo-

controlled. Of the 24 RCTs, 17 had open-label extension studies, with 11 studies having a total duration of at least a year.

4.2 Patients whose disease responded inadequately to, or who could not tolerate non-steroidal anti-inflammatory drugs (NSAIDs), were included in 12 RCTs. However, in 7 of these 12 RCTs, between 80 and 100% of patients had NSAIDs during the trial. In the trials that did not require failure of NSAIDs as an inclusion criterion, a similar proportion of patients had NSAIDs during the trial. A BASDAI score of greater than or equal to 4 was used as an inclusion criterion in most trials; however, the Assessment Group commented that average baseline Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores were high, mostly between 5.5 and 6.6 (on a scale from 0–10, 10 being most severe). Bath Ankylosing Spondylitis Functional Index (BASFI) scores and the level of C-reactive protein at baseline also varied across the RCTs, and so did the thresholds used to define elevated C-reactive protein in the trials in non-radiographic axial spondyloarthritis. The Assessment Group noted that higher C-reactive protein levels are associated with an increased likelihood of an improvement of 50% or more in BASDAI score (BASDAI 50) response.

4.3 Of the 20 RCTs in ankylosing spondylitis, 4 were for adalimumab, 1 for certolizumab pegol, 7 for etanercept, 3 for golimumab and 5 for infliximab. Most were conducted in Europe or North America; 4 were conducted in China. Among patients in the included RCTs, 65% to 97% were male, the average age ranged from 27 to 48, and the average duration of disease was 6.8 to 19 years.

4.4 Of the 5 RCTs in non-radiographic axial spondyloarthritis, 2 were for adalimumab, 1 for certolizumab pegol and 1 for etanercept. The Assessment Group also included a trial for infliximab, even though infliximab does not have a marketing authorisation in the UK for non-radiographic axial spondyloarthritis. The Assessment Group

stated that this was to inform the relative efficacy of TNF-alpha inhibitors in this indication because the dose used in the identified trial was the same as that licensed for ankylosing spondylitis. Three RCTs were multicentre conducted worldwide, 1 was conducted in Germany and 1 was UK based. Among patients in the included RCTs, 45% to 75% were male, the average age ranged from 28.2 to 38.3 years, and the average duration of disease was 2.4 to 17.2 years. The Assessment Group noted substantial heterogeneity in the baseline characteristics across the trials, such as variations in C-reactive protein levels and the proportion of patients with MRI changes.

4.5 The Assessment Group synthesised the data on clinical effectiveness using a Bayesian meta-analysis. For both indications, it included RCTs reporting results between 10 and 16 weeks after starting treatment. The Assessment Group excluded 2 studies because they were redundant in a class effect model (a study by Giardina et al.) or did not include any of the relevant comparators needed for meta-analysis (PLANETAS). The Assessment Group analysed the TNF-alpha inhibitors both individually and as a group, assuming a class effect. The Assessment Group chose to use a fixed-effect model for both analyses (this assumes that all the studies estimated exactly the same treatment effect and that the variability between individual study results occurred by chance). Peripheral symptoms were not included as outcomes in the meta-analysis (with the exception of enthesitis) because few data were available.

Ankylosing spondylitis

4.6 The results of the meta-analysis showed a consistent beneficial effect across all 5 TNF-alpha inhibitors at 10–16 weeks, compared with placebo. The pooled relative risk (RR) of an ASAS 20 (a common primary efficacy outcome in clinical trials) response

ranged from 1.80 (certolizumab pegol) to 2.45 (infliximab). For an ASAS 40 (based on improvements of 40% response), the RRs ranged from 2.53 (certolizumab pegol) to 3.42 (adalimumab). For BASDAI 50 the RRs of a response were 3.16 with adalimumab, 3.17 with etanercept, 3.57 with golimumab, 3.60 with certolizumab pegol, and 4.86 with infliximab. The additional reduction in BASDAI and BASFI scores achieved with adalimumab, certolizumab pegol, etanercept and infliximab compared with placebo were all statistically significant and clinically important. Additional reductions in BASDAI scores compared with placebo were 1.46 units with certolizumab pegol, 1.55 units with adalimumab, 1.75 units with etanercept and 2.28 units with infliximab. Additional BASFI reductions were 1.1 units with certolizumab pegol, 1.25 units with adalimumab, 1.43 units with etanercept, 1.45 units with golimumab and 2.16 units with infliximab.

4.7 When TNF-alpha inhibitors were considered as a class, with 1 treatment effect, the meta-analysis showed statistically significant improvements compared with placebo at 10–16 weeks for all outcomes (Table 1). The Assessment Group reported little evidence of statistical heterogeneity for the key outcomes (ASAS outcomes, BASFI, BASDAI and BASDAI 50) but substantial heterogeneity for other outcomes.

Table 1. Estimated class effect of TNF-alpha inhibitors compared with placebo in ankylosing spondylitis: meta-analysis of outcomes at 10–16 weeks (main analysis)

	Outcome	95% CI
ASAS 20 (RR)	2.21	2.01 to 2.43
ASAS 40 (RR)	3.06	2.52 to 3.76
BASDAI 50 (RR)	3.37	2.75 to 4.16
BASDAI (additional change from baseline)[1]	−1.66	−1.88 to −1.43
BASFI (additional change from baseline)[1]	−1.38	−1.59 to −1.18
BASMI (additional change from baseline)[1]	−0.27	−0.36 to −0.18

	Outcome	95% CI
SF-36 PCS (additional change from baseline)[2]	4.40	3.60 to 5.21
SF-36 MCS (additional change from baseline)[2]	1.93	0.12 to 3.72
MASES	−0.54	−0.89 to −0.19
[1] Negative changes in BASDAI, BASFI and BASMI represent improvement (that is, a health benefit) [2] Positive changes in SF-36 represent improvement (that is, a health benefit)		
ASAS, Assessment in SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CI, confidence interval; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; RR, relative risk; SF-36 MCS, Short Form 36 mental component summary; SF-36 PCS Short Form 36 physical component summary		

4.8 The meta-analysis showed no statistically significant differences between the 5 TNF-alpha inhibitors for efficacy outcomes at 10–16 weeks. The Assessment Group noted that the meta-analysis results for infliximab at 10–16 weeks appeared slightly better than results for the other TNF-alpha inhibitors (although the credible intervals are wide). They suggested that this apparent superiority could be due to infliximab producing a more rapid clinical improvement than the other treatments (but having similar effectiveness in the long term). This conclusion was based on results from a trial by Giardina et al. that compared infliximab with etanercept. In the Giardina et al. trial, the BASDAI and BASFI outcomes at week 12 favoured treatment with infliximab, but by week 48 the results for infliximab and etanercept were almost identical.

4.9 Analysis of long-term efficacy results from open-label extension studies showed that, after approximately 2 years of treatment, ankylosing spondylitis continues to respond well to TNF-alpha inhibitors in around half of people with the disease. Mean changes from baseline for BASDAI, BASFI and BASMI (if reported) were generally maintained at clinically meaningful levels during long-term follow-up. However, the Assessment Group stated that the

open-label extension studies produced less reliable data than the RCTs. Results may not reflect clinical practice, because some people continued treatment even though their disease did not respond to therapy (contrary to the UK marketing authorisations), and some people took the higher dose of golimumab (100 mg) without fulfilling the marketing authorisation requirements for this dose (body weight of more than 100 kg). The Assessment Group also suggested that differences in outcomes may be due to differences in follow-up protocols rather than true treatment effects. The Assessment Group concluded that the long-term benefit of TNF-alpha inhibitors appear similar across treatments.

4.10 The impact of TNF-alpha inhibitors on spinal damage (that is, radiographic progression assessed by mSASSS) is unclear. There are some data that suggest a benefit from TNF-alpha inhibitors after approximately 4 years of treatment. The Assessment Group suggested that the uncertainty may be due to lack of long-term follow-up data and the insensitivity of X-rays as a tool for evaluating disease progression in ankylosing spondylitis.

4.11 The Assessment Group used results from 11 patient registry studies (identified in a separate screening of the systematic review results) to assess the efficacy of sequential treatment with TNF-alpha inhibitors in ankylosing spondylitis. Most of the studies provided data on infliximab, etanercept and adalimumab; less evidence was available for certolizumab pegol and golimumab. The proportion of patients who continued to take their first TNF-alpha inhibitor was around 70–80% after 1 year, 65–75% after 2 years, 70% after 3 years and 55% after 5 years. Only 3 studies provided efficacy results for people who had switched to a second or third TNF-alpha inhibitor; results showed approximately a 30% proportional reduction (10% absolute reduction) in the number of people with a BASDAI 50 response to sequential TNF-alpha

inhibitors (Table 2). In addition, improvements in BASDAI and BASFI reported after a second and third TNF-alpha inhibitor were not as good the improvements achieved with the first TNF-alpha inhibitor, as observed in the largest registry (DANBIO) (Table 2). Despite a reduction in efficacy with sequential treatment, the Assessment Group highlighted that, on average, people having a third TNF-alpha inhibitor continued treatment for as long as people having their second (Table 2).

Table 2. Efficacy of sequential TNF-alpha inhibitors in ankylosing spondylitis, based on results from the DANBIO registry

	1st TNF-alpha inhibitor (n=1436)	2nd TNF-alpha inhibitor (n=432)	3rd TNF-alpha inhibitor (n=137)
BASDAI 50 at 3 months	54%	37%	30%
BASDAI: median change after 3 months of treatment	−3.1	−2.0	−1.3
BASFI: median change after 3 months of treatment	−2.2	−1.6	−1.3
Median time to drug discontinuation (95% CI)	3.1 years (2.6 to 3.7)	1.6 years (1.0 to 2.2)	1.8 years (0.9 to 2.7)
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CI, Confidence Interval			

4.12 The Assessment Group concluded that, despite a decrease in response rates, sequential treatment with TNF-alpha inhibitors can be beneficial for people with ankylosing spondylitis.

Non-radiographic axial spondyloarthritis

4.13 Outcomes for 3 of the 4 treatments in the meta-analysis (certolizumab pegol, etanercept and infliximab) were based on results from single trials of each drug. The RRs, compared with placebo, of an ASAS 20 response were similar for adalimumab, certolizumab pegol and etanercept (ASAS 20 was not reported in the trial of infliximab), ranging from 1.46 to 1.92. The RRs of a

BASDAI 50 response (compared with placebo) was 1.92 with etanercept, 2.52 with adalimumab and 2.80 with certolizumab pegol. A greater variation in results was observed in the ASAS 40 response and reductions in BASDAI and BASFI. For ASAS 40 the RRs ranged from 2.07 (etanercept) to 3.63 (infliximab). Additional reductions in BASDAI compared with placebo were 0.70 units with etanercept, 1.23 with adalimumab, 1.85 with certolizumab pegol, and 2.67 units with infliximab. Additional BASFI reductions were 0.60 units with etanercept, 0.90 units with adalimumab, 1.90 units with certolizumab pegol and 2.24 units with infliximab. Infliximab appeared to be the most effective, but this trial was judged to have a high risk of bias.

4.14 When TNF-alpha inhibitors were considered as a class, with 1 treatment effect, the meta-analysis showed statistically significant improvements compared with placebo at 10–16 weeks for all outcomes (Table 3). The Assessment Group reported that statistical heterogeneity was apparent in the analyses, and therefore the reliability of the pooled estimates, and their true relevance to people seen in clinical practice, is questionable. Estimates of the class effect of TNF-alpha inhibitors were consistently smaller in non-radiographic axial spondyloarthritis compared against those observed in ankylosing spondylitis trials (most noticeably for BASFI and BASDAI 50).

Table 3. Estimated class effect of TNF-alpha inhibitors compared with placebo in non-radiographic axial spondyloarthritis: meta-analysis of outcomes at 10–16 weeks (main analysis)

	Outcome	95% CI
ASAS 20 (RR)	1.65	1.37 to 2.04
ASAS 40 (RR)	2.74	2.08 to 3.62
BASDAI 50 (RR)	2.31	1.76 to 3.10
BASDAI (additional reduction from baseline)	−1.32	−1.74 to −0.90
BASFI (additional reduction from baseline)	−0.99	−1.34 to −0.64
BASMI (additional reduction from baseline)	−0.15	−0.32 to 0.02
SF-36 PCS (additional reduction from baseline)	4.41	3.04 to 5.81
SF-36 MCS (additional reduction from baseline)	2.33	0.07 to 4.62
ASAS, Assessment in SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CI, Confidence Interval; RR, relative risk; SF-36 MCS, Short Form 36 mental component summary; SF-36 PCS Short Form 36 physical component summary		

4.15 The Assessment Group did indirect comparisons of the TNF-alpha inhibitors. There were no statistically significant differences between the 5 TNF-alpha inhibitors for efficacy outcomes at 10–16 weeks.

4.16 Analysis of long-term efficacy results from open-label extension studies showed that, after 1 year of treatment, non-radiographic axial spondyloarthritis continues to respond well to TNF-alpha inhibitors in around half of people with the disease. This level of response is maintained up to 2 years with certolizumab pegol and up to 3 years with adalimumab. Mean change from baseline for BASDAI, BASFI and Bath Ankylosing Spondylitis Metrology Index (BASMI) (if reported) were generally maintained at clinically meaningful levels during long-term follow-up (data available up to 1 year). However, the open-label extension studies produced less reliable data than the RCTs. Results may not reflect clinical

practice, because some people continued treatment even though their disease did not respond to therapy (contrary to the UK marketing authorisations). The Assessment Group concluded that the long-term benefits of TNF-alpha inhibitors appear similar across treatments.

4.17 The Assessment Group reported issues with 2 of the trials in non-radiographic axial spondyloarthritis (ABILITY-1 for adalimumab and Rapid-axSpA for certolizumab pegol), which were highlighted by the US Food and Drug Administration. These 2 trials included large proportions of people with ankylosing spondylitis. This led to an overestimation of the treatment benefit observed with TNF-alpha inhibitors in 1 of the trials (ABILITY 1) but not the other (Rapid-axSpA). This difference further emphasised the heterogeneity across the trials in non-radiographic axial spondyloarthritis.

4.18 The Assessment Group did not identify any efficacy data for people with non-radiographic axial spondyloarthritis who had switched to a second or third TNF-alpha inhibitor.

Adverse events

4.19 The identified RCTs did not allow for a meaningful analysis of adverse events because of limitations in the number and size of RCTs and the short duration of the placebo-controlled periods. The Assessment Group evaluated adverse event rates from a Cochrane Review and from network meta-analysis of 9 biologic interventions (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tocilizumab) in adults with any disease, except HIV/AIDS. The Cochrane Review included 160 RCTs (including 48,676 people); 115 of these RCTs (72%) included the TNF-alpha inhibitors under consideration in this appraisal.

4.20 Analysis of the Cochrane Review showed that, as a group, TNF-alpha inhibitors are associated with significantly higher rates of serious infections, tuberculosis reactivation, non-melanoma skin cancer, total adverse events, and withdrawals due to adverse events, when compared with control treatments in the short-term (median treatment duration of the RCTs was 6 months).

4.21 When individual TNF-alpha inhibitors were analysed separately, only infliximab and certolizumab pegol were associated with statistically significant increases in adverse events compared with control treatments:

- infliximab was associated with higher rates of total adverse events (number needed to harm [NNH] 13, 95% credible interval [CrI] 8 to 505) and withdrawals due to adverse events (NNH 10, 95% CrI 5 to 30)
- certolizumab pegol was associated with higher rates of serious infections (NNH 12, 95% CrI 4 to 79) and serious adverse events (NNH 18, 95% CrI 9 to 162).

4.22 Cancer risk was not analysed as part of the Cochrane Review. Because TNF-alpha inhibitors are known to have a possible association with cancer, the Assessment Group identified an individual patient-data meta-analysis (including 22,904 people from 74 RCTs) that assessed the cancer risk associated with 3 of the TNF-alpha inhibitors under consideration in this appraisal (adalimumab, etanercept and infliximab). When considering the class effect of the 3 TNF-alpha inhibitors, there was no increase in risk of cancers excluding non-melanoma skin cancer (RR 0.99, 95% confidence interval [CI] 0.61 to 1.68). However TNF-alpha inhibitors were associated with a doubling in the risk of non-melanoma skin cancer (RR 2.02, 95% CI 1.11 to 3.95).

Evidence from patient experts

4.23 Patient experts discussed the 2 conditions together, reporting that the key symptom is inflammatory back pain which becomes increasingly severe over time. Up to 25% of people with ankylosing spondylitis or non-radiographic axial spondyloarthritis eventually develop complete fusion of the spine, which leads to substantial disability. Patient experts noted that, because the conditions present at an early age when people are beginning their career (average age of onset is 24 years), disease progression leads to substantial loss in work productivity. One third of people give up work before normal retirement age and another 15% reduce or change their work because of their disease. Being unable to work has important consequences both for the individual and for their family; people with ankylosing spondylitis or non-radiographic axial spondyloarthritis are more likely to divorce or to never marry and women are less likely to have children. Many people with the conditions report depression and fatigue. Patient experts reported that, in addition to local spinal symptoms, 50% of people suffer from associated disorders elsewhere. For example, 40% experience eye inflammation, 16% develop psoriasis and 10% have inflammatory bowel disease. Patient experts also highlighted the issue of underdiagnosis – symptoms are often present for 7–10 years before a diagnosis is made.

4.24 Comments from patient experts indicated the outcome most important to people with axial spondyloarthritis was the prevention of further damage to their spine and joints. A reduction in pain and fatigue was also important. The patient experts stated that people having TNF-alpha inhibitors have reported substantial improvements in pain and stiffness, leading to improvements in mobility and an improved quality of life. People reported that they were able to independently manage activities of daily living that

were previously problematic. However, patient experts estimated that 2 in 10 cases of axial spondyloarthritis do not respond to treatment with a TNF-alpha inhibitor. Based on previous NICE guidance, these people would not be offered an alternative TNF-alpha inhibitor. This knowledge leads to high levels of anxiety in people with axial spondyloarthritis. The option to switch to a second TNF-alpha inhibitor would reduce fears and anxiety. There is also anecdotal evidence suggesting that a second or third TNF-alpha inhibitor can be clinically effective if the first has failed.

4.25 The patient experts reported that when people were asked about infliximab specifically, some people preferred its mode of administration (an infusion administered by a healthcare professional) to the method of self-injection. This might benefit people with memory problems, learning disabilities, dexterity problems, or a fear of needles. However, some people were worried about the potential for postponed appointments (leading to a return of symptoms) and the need to take time off work and the need to travel for treatment with infliximab.

Cost effectiveness

Published evidence

4.26 The Assessment Group's systematic review of cost-effectiveness evidence identified 5 published economic evaluations of TNF-alpha inhibitors in patients with ankylosing spondylitis. No published economic evaluations were identified for patients with non-radiographic axial spondyloarthritis. The Assessment Group considered that the published models lacked evidence-based justifications for parameter estimates and structural assumptions.

Company submissions

4.27 For ankylosing spondylitis, the companies compared the 5 TNF-alpha inhibitors that have a marketing authorisation for this

indication (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) with each other, and with conventional care. For non-radiographic axial spondyloarthritis, the companies compared the 3 TNF-alpha inhibitors that have a marketing authorisation in this indication (adalimumab, certolizumab pegol and etanercept) with each other and with conventional therapy (with the exception of Abbvie, which did not include etanercept in its model). All evaluations adopted an NHS perspective. Costs and benefits in all cases were discounted at 3.5%.

4.28 The companies used a lifetime horizon for their models, except Abbvie (adalimumab) which used a 40-year time horizon. Based on recommendations in NICE's technology appraisal guidance on adalimumab, etanercept and infliximab for ankylosing spondylitis, all models included response criteria to decide whether TNF-alpha inhibitors were continued or withdrawn. The criteria were ASAS 20, ASAS 40 or BASDAI 50 at week 12, with the exception of company UCB which used response criteria at week 24. In common with previously published models, the models were based on the estimation of BASDAI and BASFI scores over time. All models assumed that, after initial improvements in BASDAI for people whose disease responds to treatment, BASDAI scores remain relatively constant over the longer term. However, there were differences in assumptions about long-term disease progression (that is, changes in physical function measured by BASFI) and the rebound effect after treatment withdrawal (in patients whose disease initially responded but then stopped responding to therapy). The models assumed 1 of 2 scenarios; 'optimistic' or 'pessimistic'. The optimistic scenario assumed an ongoing benefit of TNF-alpha inhibitors after withdrawal (known as 'rebound equal to gain' or 'rebound to baseline'). In this scenario, physical function (measured by BASFI) deteriorates ('rebounds') to the patient's baseline level. The pessimistic scenario assumed a greater

deterioration in physical function after treatment withdrawal, to the level that it would have been if the disease had not initially responded to therapy (known as ‘rebound to natural history’ or ‘rebound to conventional care’). In both scenarios, the subsequent trajectory of disease progression after rebound (measured by BASFI) mirrors the natural history of the disease. Differences in assumptions are presented in in Table 4 and Table 5, along with other key structural assumptions.

Table 4. Model structure and key assumptions: ankylosing spondylitis

Parameter	Infliximab, Golimumab (MSD)	Adalimumab (Abbvie)	Certolizumab pegol (UCB)	Etanercept (Pfizer)
Model type	Decision tree followed by Markov model	Markov model	Decision tree followed by Markov model	Patient-level simulation model
Response criteria (12 or 24 weeks)	BASDAI 50 response	ASAS 20 response	ASAS 20 response	BASDAI 50 response
Response criteria justification	GO-RAISE outcome	ATLAS primary endpoint	RAPID-axSpA primary	NICE definition of response (TA143)
Annual rate of withdrawal (long-term)	6.1% (GO-RAISE)	<15% on treatment at year 40 (ATLAS)	7% (NICE TA143)	11% for etanercept
BASFI progression: TNF-alpha inhibitor responders	Constant after week 108; 0.035 after week 256	Constant after week 260	Constant after week 24	Constant after week 48
BASFI progression: TNF-alpha inhibitor non-responders	0.07	0.056	0.07	0.07
BASFI progression: Conventional care	0.07 after week 24	0.056	0.07	0.07 after week 12
Rebound assumption	Rebound to baseline (6 months)	Rebound to baseline (immediately)	Rebound to conventional therapy (6 months)	Rebound to baseline (6 months)

ASAS, Assessment in SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; MSD, Merck, Sharp & Dohme

Table 5. Model structure and key assumptions: non-radiographic axial spondyloarthritis

Parameter	Adalimumab (Abbvie)	Certolizumab pegol (UCB)	Etanercept (Pfizer)
Model type	Markov model	Markov model	Patient-level simulation model
Response criteria (12 or 24 weeks)	ASAS 40 response	ASAS 20 response	BASDAI 50 response
Response criteria justification	ABILITY-1 primary endpoint	RAPID-axSpA primary endpoint	NICE definition of response (TA143)
Annual rate of withdrawal (long-term)	<10% on treatment at year 40 (ATLAS)	7% (NICE technology appraisal guidance on adalimumab, etanercept and infliximab for ankylosing spondylitis)	5% for etanercept
BASFI progression: TNF-alpha inhibitor responders	Constant after week 140	Constant after week 12	Constant after week 48
BASFI progression: TNF-alpha inhibitor non-responders	0.084 (ABILITY-1 study)	0.07 (Kobelt 2007)	Constant/0.07 (Kobelt 2007)
BASFI progression: Conventional care	0.084	0.07	0.07 after week 12
Rebound assumption	Rebound to baseline (immediately)	Rebound to conventional therapy (6 months)	Rebound to baseline (6 months)

ASAS, Assessment in SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index

Comparison of company models

4.29 A comparison of the ICER estimates compared with conventional therapy submitted by each company is provided in Table 6 (ankylosing spondylitis) and Table 7 (non-radiographic axial spondyloarthritis).

Table 6. Ankylosing spondylitis: comparisons of company ICER estimates (per QALY gained) compared with conventional therapy

	Abbvie (adalimumab)	UCB (certolizumab pegol)	Pfizer (etanercept)	MSD (golimumab, infliximab)
Conventional care	-	-	-	-
Adalimumab	16,391	19,932	20,909	19,275
Certolizumab pegol	17,067[1]	16,647[2]	19,586[2]	19,401[2]
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

[1] Based on list price for certolizumab pegol

[2] Based on patient access scheme for certolizumab pegol

MSD, Merck, Sharp & Dohme

Table 7. Non-radiographic axial spondyloarthritis: comparisons of company ICER estimates (per QALY gained) compared with conventional therapy

	Abbvie (adalimumab)	UCB (certolizumab pegol)	Pfizer (etanercept)
Conventional care	-	-	-
Adalimumab	13,228	30,370	23,242
Certolizumab pegol	12,866[1]	15,615[2]	23,575[2]
Etanercept	Not Assessed	50,692	23,195

[1] Based on list price for certolizumab pegol

[2] Based on patient access scheme for certolizumab pegol

4.30 The Assessment Group commented that, in general, the companies submitted good quality models. Despite the different model structures and assumptions used across the company submissions, similar ICERs were reported for each of the TNF-alpha inhibitors compared with conventional care in ankylosing spondylitis. There were greater differences between company submissions in the ICERs reported for non-radiographic axial spondyloarthritis' . The Assessment Group suggested that the

variation in ICER estimates reported across the submissions (both within and between populations) might be explained by differences in the following parameters and underlying assumptions:

- the response criteria and time when response was measured
- the magnitude of improvement in outcomes and the time when these were assumed to 'level off' (that is, plateau)
- the underlying rate of disease progression, measured by change in BASFI scores, without treatment ('natural history' of disease) and the impact of TNF-alpha inhibitors on this rate
- disease progression after treatment stopped (the 'rebound' assumption) and the timing of this.

4.31 Although there was consistency across the companies' ICER estimates for the ankylosing spondylitis population, the Assessment Group considered them (and the ICERs reported for people with non-radiographic axial spondyloarthritis) to be both speculative and uncertain. The uncertainty is due to unresolved issues with parameter estimates and structural assumptions used in published cost-effectiveness evaluations (highlighted in the Assessment Group's review). For example, several company models used data from open-label extension studies without any formal consideration of the selection bias inherent in these studies. The Assessment Group was also concerned about the appropriateness of the sources of natural history data, and subsequent assumptions made about the trajectories of BASDAI and BASFI progression. Related to this are assumptions about the effect of TNF-alpha inhibitors on disease progression, and a lack of consensus on whether TNF-alpha inhibitors are primarily symptom-control treatments or whether they are also disease modifiers. The Assessment Group noted that identical assumptions with respect to the impact of treatment on progression were applied across both populations, without consideration of how generalisable these assumptions

were. Finally, the Assessment Group suggested that BASDAI and BASFI may not be the most appropriate conceptual basis for modelling progression of these diseases. But, in the absence of data linking other disease measures to costs and utilities, it concluded that there were no other options.

Sequential treatment

4.32 The Assessment Group did not believe that the company submissions provided a robust basis for informing the cost effectiveness of intermittent and sequential use of TNF-alpha inhibitors. Only Pfizer submitted evidence for the cost effectiveness of sequential treatment. In their base case analysis, only people who stopped treatment due to adverse events were eligible to receive a second TNF-alpha inhibitor. The model assumed that the second treatment had equal efficacy to the first. In a sensitivity analysis, people who stopped treatment due to loss of response also switched to a second TNF-alpha inhibitor, which was assumed to have a reduced effect. In the sensitivity analysis, pairwise comparison of the TNF-alpha inhibitors with conventional care showed that the ICERs for treatment with a second TNF-alpha inhibitor were approximately £1000 higher than the ICERs of a first treatment (for all treatments except infliximab) in both ankylosing spondylitis and non-radiographic axial spondyloarthritis. Excluding infliximab, the ICERs of the other TNF-alpha inhibitors in ankylosing spondylitis were similar (ranging from £21,990 to £22,417 per QALY). The ICER for infliximab as a second treatment was £35,840 per QALY (lower than the ICER for infliximab as a first treatment). The ICERs of the 3 treatments for non-radiographic axial spondyloarthritis ranged from £23,925 to £23,998 per QALY. The company used evidence from the DANBIO patient registry to estimate the efficacy of the second TNF-alpha inhibitor. The Assessment Group commented that registries are unreliable because of their selection bias, and the company also stated that

the results of this analysis should be interpreted with caution due to the lack of robust clinical data demonstrating the efficacy of sequential treatment.

Assessment Group's model

4.33 The Assessment Group developed a de novo economic model to assess the cost effectiveness of all 5 TNF-alpha inhibitors that have a marketing authorisation for ankylosing spondylitis and the 3 that are licensed for non-radiographic axial spondyloarthritis. The Assessment Group developed a cohort model in the form of a modified decision tree. The model used a lifetime horizon, assuming that patients enter the model at the age of 40 years and have an average body weight of 73 kg. BASDAI 50 response at 12 weeks determined whether patients continued having a TNF-alpha inhibitor or withdrew from treatment. For those who responded, there was an ongoing risk of withdrawal of treatment at any time point. Patients who withdrew from treatment (at 12 weeks or later) were assumed to move on to conventional care. The analysis was done from the perspective of the NHS and personal social services, and costs and health effects were discounted at an annual rate of 3.5%. The mean costs and QALYs reported are derived from probabilistic sensitivity analysis (that is, produced by varying the input parameters simultaneously with values from a probability distribution).

4.34 To address some of the uncertainties identified in published economic evaluations and company submissions, and to generate more appropriate parameter estimates (and associated uncertainties) for its de novo model, the Assessment Group performed an extended evidence synthesis of the available clinical data. The evidence synthesis was used to estimate baseline BASDAI/BASFI scores, the effect of treatment on these scores, and the probability of a response (BASDAI 50) at 12 weeks. The

Assessment Group also used a new approach to model long-term disease progression and the impact of treatment on the natural history of disease, by relating the assumptions more explicitly to the existing clinical data for TNF-alpha inhibitors. Specifically, the Assessment Group accounted for the independent effects of symptomatic improvements (that is, reduction in disease activity according to BASDAI) on BASFI scores. They also considered the effect of changes in radiographic progression (measured by the Modified Stoke Ankylosing Spondylitis Spinal Score [mSASSS]) on BASFI. As a result of these analyses, the model assumed that patients who continued to have and respond to a TNF-alpha inhibitor after week 12 experienced a slower progression rate (according to BASFI scores) compared with the natural history of the disease (this effect was delayed until year 4). For responders who subsequently stop taking TNF-alpha inhibitors, there is some form of rebound in BASFI and BASDAI scores (this is also relevant for patients who stop at 12 weeks). Because trial data could not accurately characterise the extent of this rebound, the Assessment Group presented 2 scenarios in their base case; 1 assuming rebound to baseline and 1 assuming rebound to natural history (representing the best-case and worst-case scenarios, respectively). The Assessment Group's model used different baseline BASDAI/BASFI scores for responders and non-responders. Therefore, in the rebound to baseline scenario, responders and non-responders revert to different baseline scores after treatment is stopped. This assumption is based on results from the extended synthesis which estimated that non-responders had higher baseline BASDAI and BASFI scores than responders (that is, response is unlikely to be independent of baseline patient characteristics).

4.35 Health-related quality of life was estimated using BASDAI and BASFI data, using the approach submitted by Pfizer. Separate

algorithms were used for each population, using data from the 1031 study and the 314-EU study (both mapped to EQ-5D).

4.36 The only adverse event costs included in the model were serious infections and tuberculosis reactivation. All other costs were assumed to vary according to the BASFI score (data were derived from the OASIS database). The Assessment Group's model used both the list price for certolizumab and the patient access scheme, so that the list price ICERs could be considered until the patient access scheme is agreed by the Department of Health.

4.37 The Assessment Group did 6 sensitivity analyses:

- **Scenario 1** assumed no placebo effect; that is, no patients having conventional care had a BASDAI 50 response at week 12. By contrast, the base-case model incorporated a probability of response to conventional care at 12 weeks.
- **Scenario 2** reduced the difference in baseline BASDAI/BASFI scores between responders and non-responders. As in the base case, a difference still exists (conditional on response). But while the base case used estimates from the Assessment Group's extended synthesis, the sensitivity analysis was informed by data from company submissions. This scenario also used data pooled from company submissions (instead of the extended synthesis) to estimate the change in BASDAI and BASFI scores for responders and non-responders.
- **Scenario 3** assumed that TNF-alpha inhibitors have no effect on BASFI progression (in the base case, BASFI progression is slowed in responders).
- **Scenario 4** assumed that the treatment effect of TNF-alpha inhibitors (measured by BASFI) was reached immediately. By contrast, in the base case model, disease modification was delayed until year 4.

- **Scenario 5** mapped utilities using a linear model (consistent with previous NICE technology appraisal guidance on adalimumab, etanercept and infliximab and on golimumab for treating ankylosing spondylitis). The base case used a non-linear mapping algorithm.
- **Scenario 6** used results from ankylosing spondylitis trials in the model for non-radiographic axial spondyloarthritis.

4.38 In both the base case model and the sensitivity analyses, the Assessment Group assumed a class effect of TNF-alpha inhibitors (that is, the QALYs gained are the same for each) based on their review of the clinical evidence. Therefore, the difference in the ICERs between the individual TNF-alpha inhibitors is driven entirely by different acquisition and administration costs. In a fully incremental comparison of cost effectiveness, using the class effect assumption, the TNF-alpha inhibitor with the lowest cost would dominate the other treatments (that is, provide the same QALYs at a lower cost). Therefore, the Assessment Group presented pairwise ICERs comparing each TNF-alpha inhibitor with conventional therapy.

Results for patients with ankylosing spondylitis

4.39 In the rebound to baseline scenario (Table 8), pair-wise comparison of the TNF-alpha inhibitors with conventional care showed that 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% and 9%, respectively). The ICER for infliximab using the biosimilar price was £36,751 per QALY. Excluding infliximab, the ICERs of the other TNF-alpha inhibitors were similar, ranging from £21,079 (golimumab) to £23,133 (certolizumab pegol). At a maximum acceptable ICER of £20,000 per QALY gained, golimumab had a 43% probability of being cost-effective compared with conventional therapy. Its probability of being cost-

effective compared with conventional therapy at a maximum acceptable ICER of £30,000 per QALY gained was approximately 84%.

Table 8. Base case results for ankylosing spondylitis: rebound to baseline

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional therapy	110,821	7.245	-	-	-
Golimumab	130,173	8.163	19,352	0.918	21,079
Adalimumab	130,257	8.163	19,436	0.918	21,170
Etanercept	130,630	8.163	19,810	0.918	21,577
Certolizumab	132,059	8.163	21,238	0.918	23,133
Infliximab	148,073	8.163	37,252	0.918	40,576
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

4.40 In the rebound to natural history scenario (Table 9), the ICERs for the TNF-alpha inhibitors varied between £36,554 (golimumab) and £66,529 (infliximab) per additional QALY gained, compared with conventional care. The ICER using the biosimilar price for infliximab was £60,222 per QALY. At a maximum acceptable ICER of £20,000 per QALY gained, golimumab had only a 2% probability of being cost-effective compared with conventional therapy. This probability rose to 30% at a maximum acceptable ICER of £30,000 per QALY gained. As before, infliximab had the lowest probability of being cost-effective (0% likelihood, at both thresholds).

Table 9. Base case results for ankylosing spondylitis: rebound to natural history

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional therapy	109,933	7.265	-	-	-
Golimumab	131,960	7.867	22,027	0.603	36,554
Adalimumab	132,045	7.867	22,111	0.603	36,695
Etanercept	132,423	7.867	22,489	0.603	37,322
Certolizumab	133,851	7.867	23,918	0.603	39,693
Infliximab	150,022	7.867	40,088	0.603	66,529
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

4.41 The ICER estimates appeared to remain relatively stable (compared with the base-case results) across most of the 6 sensitivity analyses. The exception to this was scenario 2, which used company data to inform the baseline BASDAI/BASFI scores (conditional on response) and to estimate the change in BASDAI and BASFI scores for responders and non-responders. When the company data were used, the ICER estimates became more favourable towards the TNF-alpha inhibitors (Table 10), driven by smaller differences between the baseline scores of responders and non-responders.

Table 10. Results of the Assessment Group's sensitivity analysis (scenario 2) for ankylosing spondylitis

	Incremental cost-effectiveness ratio (ICER)	
	Rebound to baseline	Rebound to natural history
Golimumab	16,451	28,892
Adalimumab	16,535	29,018
Etanercept	16,907	29,580
Certolizumab pegol	18,309	31,733
Infliximab	34,246	55,842

Results for patients with non-radiographic axial spondyloarthritis

4.42 In the rebound-to-baseline scenario (Table 11), the ICERs of the alternative TNF-alpha inhibitors ranged from £29,253 (adalimumab) to £30,807 (certolizumab) per QALY, compared with conventional care. At a maximum acceptable ICER of £20,000 per QALY gained, adalimumab had a 11% probability of being cost-effective compared with conventional therapy, which rose to 55% at a maximum acceptable ICER of £30,000 per QALY gained.

Table 11. Base case results for non-radiographic axial spondyloarthritis: rebound to baseline

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional therapy	89,493	9.956	-	-	-
Adalimumab	130,316	11.351	40,823	1.395	29,253
Etanercept	131,057	11.351	41,563	1.395	29,784
Certolizumab	132,484	11.351	42,991	1.395	30,807
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

4.43 In the rebound-to-natural-history scenario (Table 12), the ICER of the alternative TNF-alpha inhibitors varied between £33,639 (adalimumab) to £35,365 per additional QALY (certolizumab). At a maximum acceptable ICER of £20,000 per QALY gained, adalimumab had a 5% probability of being cost-effective compared with conventional therapy. Its probability of being cost-effective compared with conventional therapy at a maximum acceptable ICER of £30,000 per QALY gained was approximately 39%.

Table 12. Base case results for non-radiographic axial spondyloarthritis: rebound to natural history

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional therapy	89,395	9.880	-	-	-
Adalimumab	131,740	11.139	42,346	1.259	33,639
Etanercept	132,486	11.139	43,091	1.259	34,232
Certolizumab	133,913	11.139	44,518	1.259	35,365
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

4.44 The ICER estimates remained relatively stable (compared to the base case results) across the 6 sensitivity analyses. Scenario 2 showed the largest variation compared to the base case analysis. ICER estimates became more favourable towards the TNF-alpha inhibitors (Table 13), driven by smaller differences between the baseline scores of responders and non-responders.

Table 13. Results of the Assessment Group's sensitivity analysis (scenario 2) for non-radiographic axial spondyloarthritis

	Incremental cost-effectiveness ratio (ICER)	
	Rebound to baseline	Rebound to natural history
Adalimumab	22,593	26,287
Etanercept	23,036	26,784
Certolizumab pegol	23,886	27,754

4.45 The Assessment Group listed the following as the main limitations in its model:

- BASDAI and BASFI may not be the most appropriate tools for modelling disease progression, but they were used due to lack of data linking costs and QALYs to other disease measures
- uncertainty remains in long-term projections of BASDAI and BASFI scores
- there are potential benefits that have not been formally captured and quantified, such as potential impact on productivity costs

and benefits that TNF-alpha inhibitors may confer for extra-articular manifestations

- the model could not address important clinical questions on the sequential use of TNF-alpha inhibitors
- the model is based on an assumption that 12-week continuation rules are adhered to in clinical practice, which does not necessarily reflect how TNF-alpha inhibitors are currently used within the NHS.

4.46 The Assessment Group acknowledged that BASDAI and BASFI may not be the most appropriate measures to use in the model. However, it considered that its approach captured the potential impact of TNF-alpha inhibitors on long-term disease progression (BASFI changes) more explicitly than existing models. The de novo model included changes in different clinical/biological processes (in addition to disease activity according to BASDAI) that independently affect BASFI. The Assessment Group considered that the effect of symptomatic improvements (that is, changes in BASDAI scores) on BASFI was captured in the conditional scores applied to responders. In addition, because long-term BASDAI was assumed to be constant after the short-term response period, long-term changes in BASFI were modelled as a function of mSASSS scores.

Consideration of the evidence

4.47 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of TNF-alpha inhibitors, having considered evidence on the nature of ankylosing spondylitis and non-radiographic axial spondyloarthritis and the value placed on the benefits of TNF-alpha inhibitors by people with the conditions, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical management

4.48 The Committee discussed the diagnosis of ankylosing spondylitis or non-radiographic axial spondyloarthritis. It heard that differentiation between the 2 conditions is based on radiological changes on X-rays. The Committee understood that to diagnose ankylosing spondylitis, definitive radiographic change on X-ray is needed. The Committee heard from the clinical experts that diagnosing non-radiographic axial spondyloarthritis is more complex. People who have clinical signs and symptoms of axial spondyloarthritis together with MRI changes showing inflammation are the easiest to diagnose, although sometimes repeat MRI scanning may be needed to detect changes. A smaller number do not have MRI changes but have other objective markers of inflammation (that is, elevated levels of C-reactive protein). In general, clinicians are much less confident of the diagnosis based on symptoms alone, in the absence of MRI or C-reactive protein changes. Clinical and patient experts explained the importance of early diagnosis and treatment in order to prevent or delay progressive and irreversible damage, which could ultimately cause people to need a wheelchair or be unable to get out of bed due to the severity of their physical disability. They noted that delayed diagnosis is common, and that the mean time from the development of symptoms to diagnosis in the UK is approximately 8.4 years. The Committee heard that reasons for delayed diagnosis include a low awareness of the conditions in the general population; a presenting symptom that is non-specific (back pain); lack of a clear clinical pathway for these conditions; and lack of follow-up for people who do not present with X-ray changes. The Committee also heard that although MRI scanning shows inflammation before it becomes visible on X-ray, accurate diagnosis with MRI needs particular scanning techniques and appropriate specialist interpretation.

4.49 The Committee explored the differences, and potential relationship between ankylosing spondylitis and non-radiographic axial spondyloarthritis. It heard from the patient and clinical experts that these are 2 distinguishable conditions within a spectrum of disease. Clinical experts suggested that some people with non-radiographic axial spondyloarthritis will develop ankylosing spondylitis (about 10% over 2 years and 50% over 10 years). The Committee heard that it is difficult to predict which people with non-radiographic axial spondyloarthritis will progress, and at what rate it would happen.

4.50 The Committee discussed the impact on quality-of-life of both conditions. The Committee understood that these are chronic, progressive conditions associated with pain, stiffness and increasing spinal and other joint damage. It noted that there may be extra-articular manifestations of disease such as uveitis, psoriasis, bowel disease and cardiovascular problems, as well as symptoms such as depression, fatigue and lack of sleep. The Committee was aware that these conditions have a significant impact on a person's mobility, social life, employment, mental health and overall quality of life. The Committee understood that the families of people with these conditions may also be substantially impacted.

4.51 The Committee discussed the current management of ankylosing spondylitis. The Committee heard that symptoms will not be controlled by NSAIDs in 40% of people with ankylosing spondylitis, and others will be not be able to tolerate NSAIDs. The Committee noted that adalimumab, etanercept and golimumab were recommended by NICE as treatment options for people with severe, active ankylosing spondylitis whose condition has responded inadequately to conventional therapy (NICE technology appraisal guidance on adalimumab, etanercept and infliximab and golimumab for treating ankylosing spondylitis). The Committee understood that access to other TNF-alpha inhibitors, such as

certolizumab pegol and infliximab, would allow patients and clinicians a greater choice of treatment options. The Committee heard from patient experts that TNF-alpha inhibitors had completely changed some people's lives by restoring mobility and reducing pain, and could allow people to continue working and fulfilling parental and carer duties. A patient expert stated that his TNF-alpha inhibitor treatment had also stopped flare-ups of uveitis (an extra-articular manifestation of ankylosing spondylitis). The Committee heard from the clinical experts that individual TNF-alpha inhibitors have different effects on extra-articular manifestations and therefore the choice of TNF-alpha inhibitor in clinical practice is based on individual patient characteristics. The Committee understood the importance of TNF-alpha inhibitors in treating ankylosing spondylitis.

4.52 The Committee considered the use of TNF-alpha inhibitors in people with non-radiographic axial spondyloarthritis. The patient and clinical experts emphasised that there is a misconception that this condition is less severe than ankylosing spondylitis. They explained that both conditions result in the same level of pain, reduced function and poor quality of life. People severely affected by the condition found it hard to understand why they had to wait for changes to be visible on X-rays before being eligible for treatment with TNF-alpha inhibitors.The Committee noted that adalimumab, etanercept and certolizumab pegol have UK marketing authorisations for use in people with non-radiographic axial spondyloarthritis. However it heard that there was extreme variability in access to TNF-alpha inhibitors across the country for people with this condition, and that access was based on individual funding requests. The Committee understood that there was clinical support for the use of TNF-alpha inhibitors in people with non-radiographic axial spondyloarthritis, whose disease is not controlled by or who cannot tolerate NSAIDs. The clinical experts stated that

early treatment with TNF-alpha inhibitors could prevent spinal damage in these people. The Committee heard that some people may be more likely to benefit from TNF-alpha inhibitors than others. The clinical experts referred to the diagnosis of non-radiographic axial spondyloarthritis, and further divided people with symptoms of the condition into 3 groups: people with MRI changes; those with no MRI changes but elevated C-reactive protein levels; and those without MRI changes and without elevated C-reactive protein. The experts suggested that people with symptoms of non-radiographic axial spondyloarthritis, but without objective signs of inflammation (for whom TNF-alpha inhibitors are not indicated according to their UK marketing authorisations), are less likely to benefit from TNF-alpha inhibitor treatment.

4.53 The Committee discussed the response criteria used to determine whether TNF-alpha inhibitor treatment is continued in clinical practice. It heard from clinical experts that in UK clinical practice, response to TNF-alpha inhibitor treatment is usually assessed after 3 months. They defined an adequate response to treatment as an improvement in BASDAI score of at least 50%, or of at least 2 units. The experts explained that some people will not show a response to treatment until 6 months, but that most responses are achieved within 3 months. The Committee heard from the patient expert that his disease responded to treatment after only 8 weeks. The Committee heard from the clinical experts that the probability of response to TNF-alpha inhibitors is higher in clinical practice than in clinical trials (approximately 80% response rate in practice compared to 50–60% in clinical trials). The clinical experts suggested that this could, in part, be due to the more restrictive definition of response used in clinical trials compared with clinical practice. They also stated that the improvement of 2 units in the BASDAI score as used in clinical practice represented a meaningful

and clinically significant benefit, independent of the baseline BASDAI score.

4.54 The Committee heard from the clinical experts that people who cannot tolerate a first TNF-alpha inhibitor, which makes them unable to take it for long enough to assess response, are no less likely to respond to an alternative agent. People whose condition does not respond to a first TNF-alpha inhibitor, or in whom an initial response is lost, are also likely to gain benefit from an alternative TNF-alpha inhibitor. This is because of differences in the mechanism of action between the agents or because specific antibodies have developed against the first agent. The Committee noted that switching between TNF-alpha inhibitors was not recommended in NICE's previous technology appraisal guidance on adalimumab, etanercept and infliximab and golimumab for treating ankylosing spondylitis, except when intolerance to the first agent occurs in the first 3 months of treatment before the assessment of response. With respect to treatment switching after failure of a first TNF-alpha inhibitor, the patient expert commented that stopping TNF-alpha inhibitor treatment after loss of response would mean returning to reliance on NSAID therapy and the associated long-term adverse effects. The patient experts also emphasised that patients currently feel anxiety, knowing that they will not have the opportunity to try an alternative TNF-alpha inhibitor if their disease fails to respond to the first TNF-alpha inhibitor or it stops working after an initial response.

Clinical effectiveness

4.55 The Committee considered the clinical effectiveness evidence for each condition separately. The Committee agreed that the trials in ankylosing spondylitis were generalisable to clinical practice in the UK but noted substantial heterogeneity in the baseline characteristics across the trials of non-radiographic axial

spondyloarthritis (such as variation in levels of C-reactive protein and the proportion of patients with MRI changes). The Committee heard from the clinical experts that these patient populations generally reflected the patients seen in UK clinical practice (although with some reservations about the inclusion of people without objective signs of inflammation, for whom TNF-alpha inhibitors are not indicated according to their UK marketing authorisations), and concluded that the trials were generalisable to the NHS.

4.56 The Committee discussed the results of the Assessment Group's meta-analysis for each condition. The Committee noted that all the TNF-alpha inhibitors showed a benefit compared with placebo at 10–16 weeks in both conditions. The Committee noted that infliximab appeared to be more effective at 12 weeks than other TNF-alpha inhibitors in ankylosing spondylitis, but were unsure whether the superior benefit of infliximab was sustained long-term. The Committee considered the results of the Giardina et al. trial (see section 4.8) and agreed that, on balance, there was not enough evidence to indicate that infliximab was more effective in the longer term than the other TNF-alpha inhibitors. The Committee concluded that TNF-alpha inhibitors were clinically effective compared with placebo and given the lack of difference in effect between them they should be considered as a class, with broadly similar, even if not completely identical effects.

4.57 The Committee questioned whether the efficacy of TNF-alpha inhibitors was the same in both conditions. The Committee noted that the class effect results for TNF-alpha inhibitors were less favourable in non-radiographic axial spondyloarthritis, compared with ankylosing spondylitis (with the exception of outcomes measured on the health-related quality of life instrument: SF-36). The Committee heard from the clinical experts that they would not

expect a differential response to treatment in the 2 conditions. Clinical experts stated that their limited clinical experience of TNF-alpha inhibitors in non-radiographic axial spondyloarthritis suggested that the magnitude of response was the same for both groups of patients. The Committee noted comments from the Assessment Group that heterogeneity across the trials of non-radiographic axial spondyloarthritis may have confounded the outcomes for TNF-alpha inhibitors. The Committee heard from the clinical experts that these trials included people who were less likely to benefit from TNF-alpha inhibitors (people without objective signs of inflammation such as MRI changes and elevated C-reactive protein, for whom TNF-alpha inhibitors are not indicated according to their UK marketing authorisations; see section 4.48, 4.52 and 4.55). The Committee noted that clear guidelines for the diagnosis of non-radiographic axial spondyloarthritis would be helpful, to identify patients who are more or less likely to benefit from TNF-alpha inhibitor treatment. The Committee agreed that the clinical trials may have underestimated the benefit of TNF-alpha inhibitors in non-radiographic axial spondyloarthritis. The Committee concluded that people with non-radiographic axial spondyloarthritis are likely to achieve a similar benefit from TNF-alpha inhibitors as people with ankylosing spondylitis.

4.58 The Committee discussed whether there were any differences between the TNF-alpha inhibitors and heard from clinical experts that TNF-alpha inhibitors are well tolerated in both conditions, and that people rarely stop treatment due to adverse events. The Committee noted comments from experts that there are differences between the TNF-alpha inhibitors in their effects on extra-articular manifestations. The Committee heard from the clinical experts that in clinical practice the choice of TNF-alpha inhibitor is based on individual patient characteristics. The Committee concluded that TNF-alpha inhibitors are relatively well tolerated and that the

clinical characteristics of the patient, particularly any extra-articular manifestations of the disease, would need to be considered when choosing a TNF-alpha inhibitor.

4.59 The Committee considered the clinical evidence for treatment with a second or third TNF-alpha inhibitor for a person whose disease does not respond to treatment, or for someone who experiences a loss of response (sequential treatment). The Committee noted the absence of randomised controlled trial data, but noted the data from the DANBIO registry for ankylosing spondylitis and agreed that, despite a decrease in response rates for each subsequent treatment, sequential treatment with TNF-alpha inhibitors can be beneficial in ankylosing spondylitis. However, the Committee was concerned that this evidence was based on registry data alone and was uncertain about the true magnitude of the benefit of sequential treatment in ankylosing spondylitis. The Committee noted that there were no efficacy data for people with non-radiographic axial spondyloarthritis who had switched to a second or third TNF-alpha inhibitor but heard from clinical experts that the efficacy of a second TNF-alpha inhibitor in this condition would be expected to be similar to the efficacy of a second TNF-alpha inhibitor in ankylosing spondylitis. The Committee concluded that sequential treatment with TNF-alpha inhibitors is likely to be beneficial, but that clinical data are limited.

Cost effectiveness

4.60 The Committee considered the evidence for the cost effectiveness of TNF-alpha inhibitors in ankylosing spondylitis and non-radiographic axial spondyloarthritis. It noted that although the models from the companies and the Assessment Group all used changes in BASDAI and BASFI scores to model costs and utilities, the underlying assumptions in each model were very different. The Committee noted that the Assessment Group divided the models

into 3 key stages: the probability of initial response, the size of initial response for responders and non-responders, and the long-term trajectory of BASDAI and BASFI scores (conditional on response status). The Committee noted the Assessment Group's criticism that some of the company models combined the latter 2 stages. The Committee decided to focus on the Assessment Group's model for decision-making purposes.

4.61 The Committee explored the uncertainties relating to key assumptions in the Assessment Group's cost-effectiveness analysis. The Committee discussed the first key stage of the model: the probability of initial response (defined as a 50% improvement in BASDAI score). The Committee heard that in the Assessment Group's model, responders had lower baseline BASDAI and BASFI scores compared with non-responders (a difference that was reduced in scenario 2). The Committee noted that this assumption implied that people with more severe disease did not benefit as much from TNF-alpha inhibitors as people with less severe disease, because someone with more severe disease (higher baseline scores) must have larger absolute improvements than someone with less severe disease to achieve a BASDAI 50 response. It concluded, based on discussion with clinical and patient experts, that there was no evidence to suggest that people with severe disease were less likely to experience clinically meaningful benefit than those with less severe disease.

4.62 The Committee discussed the long-term effect of TNF-alpha inhibitors on disease progression (assessed using BASFI) in people whose disease responds to treatment. The Committee heard that most company submissions assumed that TNF-alpha inhibitors completely prevent long term disease progression (measured by BASFI). It heard that some company submissions also presented more optimistic scenarios in which physical function

continued to improve beyond the initial response period, implying further improvement beyond 12 weeks, which subsequently plateaued. The Committee noted that the assumption of no deterioration (measured by BASFI) during treatment was based on small, single-arm follow-up trials that were subject to selection bias and were therefore unreliable. It heard from clinical experts that their impression was that physical function (measured by BASFI) continues to deteriorate during treatment with a TNF-alpha inhibitor, but that treatment slows the rate of deterioration. The clinical experts disagreed with the Assessment Group's assumption that a TNF-alpha inhibitor's effect on progression is delayed until year 4, and the Committee agreed that it was not clinically plausible for disease progression to slow at a specific time point during treatment. The Committee concluded that the precise effect of TNF-alpha inhibitors on the long term BASFI trajectory was uncertain. It agreed that it was biologically plausible for physical function (measured by BASFI) to continue deteriorating during TNF-alpha inhibitor treatment, but at a slower rate compared with the natural history of the disease.

4.63 The Committee considered what happens when a patient stops TNF-alpha inhibitor treatment. Considering the impact of stopping treatment on BASFI scores, the Committee noted that 2 rebound scenarios had been presented by the companies and the Assessment Group. In the rebound to baseline scenario, the BASFI score returns to the patient's baseline score. The alternative scenario (rebound to natural history) assumes a greater deterioration in physical function (measured by BASFI) after treatment stops, to the level that it would have been if the disease had not initially responded to therapy. The Committee heard from the clinical experts that in clinical practice patients would most likely rebound close to their baseline scores, rather than deteriorate to a poorer state of health than they were at baseline. The Committee

concluded that the rebound to baseline scenario was the most plausible assumption.

4.64 The Committee noted that the ICERs produced by the Assessment Group's base case model for ankylosing spondylitis appeared to be consistent with the results of the company models, despite differences in the assumptions used. The Committee also noted that the ICERs for golimumab all included the discount agreed in the patient access scheme. The Committee noted that the ICERs for adalimumab, certolizumab pegol, etanercept and golimumab compared with conventional care ranged from approximately £21,100 per QALY gained for golimumab to £23,100 per QALY gained for certolizumab pegol in the Assessment Group's base case (assuming rebound to baseline). The Committee noted that ICERs were substantially reduced when the difference in baseline scores between responders and non-responders was reduced (in the Assessment Group's sensitivity analysis scenario 2) with ICERs ranging from approximately £16,500 for golimumab to £18,300 for certolizumab pegol, per QALY gained. The Committee considered that these ICERs were all within the range considered to be a cost-effective use of NHS resources and concluded that adalimumab, certolizumab pegol, etanercept and golimumab could be recommended as options for treating adults with ankylosing spondylitis whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.

4.65 The Committee noted that the ICERs for infliximab for ankylosing spondylitis were approximately £40,600 and £36,800 per QALY gained compared with conventional care, using the original and biosimilar prices respectively, in the Assessment Group's base case. All the company submissions also resulted in high ICERs for infliximab, ranging from approximately £37,700 to £44,400 per QALY. For scenario 2 in the Assessment Group's sensitivity

analyses (that used baseline BASDAI scores for responders and non-responders from trial data rather than the synthesis model) the ICER for infliximab was approximately £34,200 per QALY gained compared with conventional care. The Committee noted that the ICERs for infliximab were higher than the other TNF-alpha inhibitors, largely due to the higher administration costs of infliximab, and concluded that the ICERs for infliximab were not within the range considered to be a cost-effective use of NHS resources. Therefore, infliximab could not be recommended for use in ankylosing spondylitis.

4.66 The Committee considered the cost-effectiveness results for the TNF-alpha inhibitors in non-radiographic axial spondyloarthritis. It noted that the ICERs produced by the Assessment Group's model, and 1 of the company models, were higher than the corresponding ICERs for ankylosing spondylitis. The Committee noted that the Assessment Group's base case for the rebound to baseline scenario included ICERs ranging from approximately £29,300 for adalimumab to £30,800 for certolizumab pegol per QALY gained, compared with conventional care. For scenario 2 the ICERs were lower, ranging from £22,600 for adalimumab to £23,900 for certolizumab pegol, per QALY gained. The Committee referred to the clinical discussions, where it had concluded that the benefit of TNF- alpha inhibitors was potentially underestimated in the clinical trials due to heterogeneous patient characteristics. It also noted that the Assessment Group's assumption of a slower disease progression rate (measured by BASFI) in this condition compared with ankylosing spondylitis was not confirmed by the clinical experts, and that this would in part have driven the increase in ICERs compared with ankylosing spondylitis. Considering both of these issues, the Committee considered that the most plausible ICERs were likely to be below those presented by the Assessment Group and agreed that the ICERs for adalimumab, certolizumab

pegol and etanercept were within the range that would be considered a cost-effective use of NHS resources. The Committee concluded that adalimumab, certolizumab pegol and etanercept could be recommended as options for treating adults with non-radiographic axial spondyloarthritis whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.

4.67 The Committee noted that the Assessment Group was unable to use the 2-point BASDAI change in the definition of response in their model (because of lack of data) and therefore used only BASDAI 50 to define response. The Committee noted the earlier discussions about what is used to define response in clinical practice. The Committee heard that clinical experts considered it unreasonable to restrict the definition of adequate response in clinical practice to a 50% improvement in BASDAI, because this means that someone with more severe disease (a higher baseline BASDAI score) must experience a greater absolute improvement in BASDAI than someone with less severe disease to qualify for continued treatment. The Committee noted that the clinical experts had stated that a 2 unit improvement in BASDAI represents a significant and clinically meaningful change. Therefore, the Committee concluded that the decision to continue treatment in clinical practice should be based on the broader definition of response to treatment outlined in British Society of Rheumatology (BSR) guidelines and the previous technology appraisal: a reduction of the BASDAI to 50% of the baseline value, or a reduction of 2 units or more, together with a reduction of the spinal pain VAS by 2 cm or more. If an adequate response is not achieved 12 weeks after treatment initiation, treatment should be discontinued.

4.68 The Committee also discussed the possibility of using an alternative TNF-alpha inhibitor for people who cannot tolerate a first

TNF-alpha inhibitor. It concluded that it would be appropriate to use an alternative TNF-alpha inhibitor (within its marketing authorisation) if this intolerance was evident before the first clinical-effectiveness assessment at 12 weeks after starting treatment.

4.69 The Committee discussed whether it was appropriate to consider treatment with a second or third TNF-alpha inhibitor for a person whose disease does not respond to treatment, or for someone who experiences a loss of response. The Committee noted that results from registries in ankylosing spondylitis showed approximately a 30% reduction in response rate with each subsequent TNF-alpha inhibitor (10% absolute reduction). It heard from the Assessment Group that this implies that the ICER would be correspondingly higher, but that the Assessment Group had not modelled sequential use. The Committee noted that one company had explored the issue of sequential use and, even taking into account reduced efficacy of subsequent TNF-alpha inhibitors in previous treatment failures, there was only an estimated £1000 increase in the ICER per QALY gained with subsequent treatment. The Committee noted that the Assessment Group did not consider this analysis valid. The Committee also noted the limited clinical-effectiveness data for sequential TNF-alpha inhibitor use and concluded that it had insufficient cost-effectiveness evidence to allow it to recommend sequential use of TNF-alpha inhibitors as a cost-effective use of NHS resources.

4.70 The Committee was aware that, in principle, potential differences between the TNF-alpha inhibitors in their effects on extra-articular manifestations may have cost implications, but noted that there was insufficient evidence to incorporate extra-articular manifestations into the cost-effectiveness analysis. However, the Committee concluded that because the TNF-alpha inhibitors had been considered as a class, the choice of treatment for both

conditions should be based on clinical appropriateness, which may include consideration of associated conditions. If different TNF-alpha inhibitors are equally suitable, the product with the lowest acquisition and administration costs should be used.

4.71 The Committee discussed patient preferences for particular drugs, which may be influenced by the route and the frequency of their administration. The Committee considered NICE's principles on social value judgements; in particular, the principle to consider individual choice and respect for autonomy, but not with the effect of promoting the use of interventions that are not cost-effective. Because 4 cost-effective treatment options (adalimumab, certolizumab pegol, etanercept and golimumab) are recommended for the treatment of ankylosing spondylitis, and because the available evidence persuaded the Committee that infliximab was not cost-effective in treating this condition, it concluded that it could not recommend the use of infliximab simply on the basis of another treatment choice.

4.72 The Committee considered whether its recommendations were associated with any potential issues related to equality. It concluded that when using BASDAI and spinal pain VAS scores to confirm the presence of sustained active spinal disease, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the questionnaire and make any adjustments they consider appropriate.

Summary of Appraisal Committee's key conclusions

TA	Appraisal title: TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial	Section

	spondyloarthritis (including a review of TA143 and TA233)	
Key conclusions		
Adalimumab, certolizumab pegol, etanercept and golimumab are recommended within their marketing authorisations, as treatment options for active ankylosing spondylitis.		1.1
Adalimumab, certolizumab pegol and etanercept are recommended within their marketing authorisations, as treatment options for non-radiographic axial spondyloarthritis.		1.3
The choice of treatment should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available, and may include consideration of associated conditions. If more than 1 treatment is suitable, the least expensive should be chosen.		1.4, 4.58, 4.70
The response to adalimumab, certolizumab pegol, etanercept or golimumab treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response, as defined in 1.5.		1.5, 4.53
For people who experience intolerance to adalimumab, certolizumab pegol, etanercept or golimumab before response can be assessed at 12 weeks, an alternative TNF-alpha inhibitor is recommended within its marketing authorisation.		1.5, 4.54
Treatment with a second TNF-alpha inhibitor is not recommended for people whose disease has not responded to treatment with a first TNF-alpha inhibitor, or those who had an initial response which was then lost. The Committee noted the		1.6, 4.69

limited clinical-effectiveness data available for sequential TNF-alpha inhibitor use and concluded that it had insufficient cost-effectiveness evidence to allow it to recommend sequential use of TNF-alpha inhibitors as a cost effective use of NHS resources. Infliximab is not recommended for the treatment of ankylosing spondylitis. The Committee noted that the ICERs for infliximab were higher than the other TNF-alpha inhibitors, largely due to the higher administration costs of infliximab, and concluded that the ICERs for infliximab were not within the range considered to be a cost-effective use of NHS resources.		1.2, 4.65
Current practice		
Clinical need of patients, including the availability of alternative treatments	Ankylosing spondylitis and non-radiographic axial spondyloarthritis result in the same level of pain, reduced function and poor quality of life. Early treatment is important in order to prevent or delay progressive and irreversible damage, which could ultimately cause someone to need a wheelchair or be unable to get out of bed.	4.48, 4.49, 4.50
	Adalimumab, etanercept and certolizumab pegol have UK marketing authorisations for use in people with non-radiographic axial spondyloarthritis whose condition has responded inadequately, or who are intolerant, to conventional therapy with non-steroidal anti-inflammatory drugs	4.52

	(NSAIDs). However there is extreme variability in access to TNF-alpha inhibitors across the country for people with this condition. Nearly half (40%) of people with ankylosing spondylitis will not be able to control their symptoms with NSAIDs, and others will be not be able to tolerate to them. Adalimumab, etanercept and golimumab are recommended by NICE as treatment options for people with ankylosing spondylitis whose condition has responded inadequately, or who are intolerant, to NSAIDs. The Committee heard that access to other TNF-alpha inhibitors, such as certolizumab pegol and infliximab, would allow patients and clinicians a greater choice of treatment options.	4.51
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related	Patient experts reported that use of TNF-alpha inhibitors to treat both conditions had completely changed some people's lives by restoring mobility and reducing pain, and allowing people to continue working and fulfil parental and carer duties. The Committee was aware that potential differences between the	4.51 4.70

benefits?	TNF-alpha inhibitors in their effects on extra-articular manifestations may have cost implications, but noted that there was insufficient evidence to incorporate extra-articular manifestations into the cost-effectiveness analysis.	
What is the position of the treatment in the pathway of care for the condition?	The Committee understood that if response to conventional therapy (NSAIDs) was inadequate, or the treatments were not tolerated, patients may be eligible for TNF-alpha inhibitor treatment.	4.51, 4.52
Adverse reactions	The Committee heard from clinical experts that TNF-alpha inhibitors are well tolerated in both conditions, and that people rarely stop treatment due to adverse events. It concluded that the clinical characteristics of the patient would need to be considered when choosing a TNF-alpha inhibitor.	4.58
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Assessment Group identified 24 relevant randomised controlled trials (RCTs): 19 recruited people with ankylosing spondylitis, 4 recruited people with axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (non-	4.1

	radiographic axial spondyloarthritis), and 1 recruited both populations. All except 2 of the trials were placebo-controlled. Of the 24 RCTs, 17 had open-label extension studies, with 11 studies having a total duration of at least a year.	
Relevance to general clinical practice in the NHS	These trial populations generally reflected the patients seen in UK clinical practice, although with some reservations about the inclusion of people without objective signs of inflammation (for whom TNF-alpha inhibitors are not indicated according to their UK marketing authorisations), and concluded that the trials were generalisable to the NHS.	4.52, 4.55
Uncertainties generated by the evidence	Infliximab appeared to be more effective at 12 weeks than other TNF-alpha inhibitors in ankylosing spondylitis, but the Committee agreed that there was not enough evidence to indicate that the superior benefit of infliximab was sustained long-term. Given the lack of difference in effect between TNF-alpha inhibitors they were considered as a class with broadly similar, even if not completely identical, effects. In the network meta-analysis, the	4.56 4.57

	class-effect results for TNF-alpha inhibitors were less favourable in non-radiographic axial spondyloarthritis, compared with ankylosing spondylitis. However the Committee heard that the clinical experts would not expect a differential response to treatment in the 2 conditions. The Committee noted that heterogeneity across the trials of non-radiographic axial spondyloarthritis may have confounded the outcomes for TNF-alpha inhibitors and that the trials included people who were less likely to benefit from TNF-alpha inhibitors (people without objective signs of inflammation, for whom TNF-alpha inhibitors are not indicated according to their UK marketing authorisations). The Committee agreed that clinical trials may have underestimated the benefit of TNF-alpha inhibitors in non-radiographic axial spondyloarthritis and concluded that people with this condition may achieve a similar benefit from TNF-alpha inhibitors as people with ankylosing spondylitis.	
Are there any clinically relevant subgroups for which there is evidence of differential	There are no clinically relevant subgroups for which there is evidence of differential effectiveness.	

effectiveness?		
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The network meta-analysis of randomised controlled trial data showed that TNF-alpha inhibitors are clinically effective compared with placebo at 10–16 weeks in both conditions (within their marketing authorisations).	4.56
	No randomised controlled trial data were available to assess the effect of sequential treatment with TNF-alpha inhibitors. Registry data showed that, despite a decrease in response rates for each subsequent treatment, sequential treatment with TNF-alpha inhibitors can be beneficial in ankylosing spondylitis. Clinical experts agreed. There were no registry data for people with non-radiographic axial spondyloarthritis who had switched to a second or third TNF-alpha inhibitor, but clinical experts stated that the efficacy of a second TNF-alpha inhibitor in this condition would be considered similar to the efficacy of a second TNF-alpha inhibitor in ankylosing spondylitis. The Committee concluded that sequential treatment with TNF-alpha inhibitors is likely to be beneficial, but that clinical data are	4.54, 4.59

	limited.	
How has the new clinical evidence that has emerged since the original appraisal (TA143 and TA233) influenced the current (preliminary) recommendations?	Since the publication of TA143, certolizumab pegol has received a marketing authorisation in the UK for ankylosing spondylitis and for non-radiographic axial spondyloarthritis. Adalimumab and etanercept also now have marketing authorisations for non-radiographic axial spondyloarthritis. All are recommended within their marketing authorisations as treatment options for ankylosing spondylitis or non-radiographic axial spondyloarthritis.	1.1, 1.3, 3.2, 3.3
Evidence for cost effectiveness		
Availability and nature of evidence	Although the models from the companies and the Assessment Group all used changes in BASDAI and BASFI scores to model costs and utilities, the underlying assumptions in each model were very different. The Assessment Group divided the models into 3 key stages: the probability of initial response, the size of initial response for responders and non-responders, and the long-term trajectory of BASDAI and BASFI scores (conditional on response status). The Committee noted the Assessment Group's criticism that	4.60

	some of the company models combined the latter 2 stages. The Committee decided to use the Assessment Group's model for its decision making.	
Uncertainties around and plausibility of assumptions and inputs in the economic model	In the Assessment Group's model, responders had lower baseline BASDAI and BASFI scores compared with non-responders (a difference that was reduced in scenario 2), implying that people with more severe disease did not benefit as much from TNF-alpha inhibitors as people with less severe disease. The Committee concluded that there was no evidence to suggest that people with severe disease were less likely to experience clinically meaningful benefit than those with less severe disease. The Committee agreed with the Assessment Group's assumption that physical function (measured by BASFI) continues deteriorating during TNF-alpha inhibitor treatment, but at a slower rate compared with the natural history of the disease. However, it disagreed with the Assessment Group's assumption that a TNF-alpha inhibitor's effect on progression is delayed until year 4.	4.61 4.62

	The Assessment Group presented 2 alternative base case cost-effectiveness analyses to reflect their uncertainty about what happens when a patient stops TNF-alpha inhibitor treatment (the 'rebound' assumption). The Committee concluded that rebound to baseline was the most plausible assumption and considered the ICERs from this analysis. Sequential use of TNF-alpha inhibitors was not modelled and there was uncertainty about the cost-effectiveness of sequential use.	4.63 4.69
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee was aware that potential differences between the TNF-alpha inhibitors in their effects on extra-articular manifestations may have cost implications, but noted that there was insufficient evidence to incorporate extra-articular manifestations into the cost-effectiveness analysis. However, the Committee concluded that because the TNF-alpha inhibitors had been considered as a class, the choice of treatment for both conditions should be based on clinical appropriateness, which may include consideration of	4.70

	associated conditions.	
Are there specific groups of people for whom the technology is particularly cost effective?	There are no specific groups of people for whom the technology is particularly cost effective.	
What are the key drivers of cost effectiveness?	The difference in the ICERs between the individual TNF-alpha inhibitors was driven entirely by different acquisition and administration costs. ICERs were sensitive to assumptions about the magnitude of the difference in baseline BASDAI/BASFI scores between responders and non-responders.	4.38 4.41, 4.44, 4.64, 4.66
Most likely cost-effectiveness estimate (given as an ICER)	For ankylosing spondylitis the ICERs for adalimumab, certolizumab pegol, etanercept and golimumab compared with conventional care ranged from approximately £21,100 per QALY gained for golimumab to £23,100 per QALY gained for certolizumab pegol in the Assessment Group's base case (assuming rebound to baseline). ICERs were substantially reduced when the difference in baseline scores between responders and non-responders was reduced in scenario 2 of the sensitivity analysis (ranging from approximately £16,500 for golimumab	4.64

	to £18,300 for certolizumab pegol, per QALY gained). The Committee concluded that these ICERs were all within the range considered to be a cost-effective use of NHS resources.	
	The ICERs for infliximab for ankylosing spondylitis were approximately £40,600 and £36,800 per QALY gained compared with conventional care, using the original and biosimilar prices respectively, in the Assessment Group's base case. All the company submissions also resulted in high ICERs for infliximab, ranging from approximately £37,700 to £44,400 per QALY. In the Assessment Group's sensitivity analyses the ICER for infliximab was approximately £34,200 per QALY gained compared with conventional care. The Committee concluded that the ICERs for infliximab were not within the range considered to be a cost effective use of NHS resources.	4.65
	For non-radiographic axial spondyloarthritis the ICERs for adalimumab, certolizumab pegol and etanercept compared with conventional care ranged from approximately £29,300 per QALY gained for adalimumab to £30,800 per	4.66

	QALY gained for certolizumab pegol in the Assessment Group's base case (assuming rebound to baseline). ICERs were reduced when the difference in baseline scores between responders and non-responders was reduced in scenario 2 of the sensitivity analysis (ranging from approximately £22,600 for adalimumab to £23,900 for certolizumab pegol, per QALY gained). The Committee referred to the conclusion that the benefit of TNF-alpha inhibitors was potentially underestimated in the clinical trials. It also noted that the Assessment Group's assumption of a slower disease progression rate in non-radiographic axial spondyloarthritis compared with ankylosing spondylitis was not confirmed by the clinical experts, and that this would in part have driven the increase in ICERs compared with ankylosing spondylitis. Considering both of these issues, the Committee considered that the most plausible ICERs were likely to be below those presented by the Assessment Group and the Committee concluded that adalimumab, certolizumab pegol and etanercept were within the range that would be considered a cost effective	

	use of NHS resources. The Committee noted the limited clinical-effectiveness data available for sequential TNF-alpha inhibitor use and concluded that it had insufficient cost-effectiveness evidence to allow it to recommend sequential use of TNF-alpha inhibitors as a cost-effective use of NHS resources.	4.69
How has the new cost-effectiveness evidence that has emerged since the original appraisal (TA143 and TA233) influenced the current (preliminary) recommendations?	Since the publication of TA143, certolizumab pegol has gained a marketing authorisation in the UK for ankylosing spondylitis and for non-radiographic axial spondyloarthritis. Adalimumab and etanercept also have marketing authorisations for non-radiographic axial spondyloarthritis. All are recommended within their marketing authorisations as treatment options for ankylosing spondylitis or non-radiographic axial spondyloarthritis.	1.1, 1.3, 3.2, 3.3
Additional factors taken into account		
Patient access schemes (PPRS)	Golimumab is recommended only when the company provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, in accordance with the patient access scheme.	1.1

Equalities considerations and social value judgements	When using BASDAI and spinal pain VAS scores, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the questionnaires, and make any adjustments they consider appropriate.	1.7, 4.72

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has ankylosing spondylitis and the doctor responsible for their care thinks that adalimumab, certolizumab pegol, etanercept or golimumab is the right treatment (or a patient has non-radiographic axial spondyloarthritis and the doctor responsible for their care thinks that adalimumab,

certolizumab pegol or etanercept is the right treatment), it should be available for use, in line with NICE's recommendations.

5.4 The Department of Health and Merck, Sharp & Dohme have agreed that golimumab will be available to the NHS with a patient access scheme which makes it available with a discount. This will make the 100 mg dose of golimumab available to the NHS at the same cost as the 50 mg dose.

5.5 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

Published

- Golimumab for the treatment of ankylosing spondylitis. NICE technology appraisal guidance 233 (2011).
- Adalimumab, etanercept and infliximab for ankylosing spondylitis. NICE technology appraisal guidance 143 (2008).

Under development

- Spondyloarthritis: diagnosis and management of spondyloarthritis. NICE clinical guideline. Publication date to be confirmed.

NICE pathways

There is a NICE pathway on ankylosing spondylitis, which is available from http://pathways.nice.org.uk/pathways/musculoskeletal-conditions/arthritis#content=view-node%3Anodes-ankylosing-spondylitis

7 Proposed date for review of guidance

7.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adams
Chair, Appraisal Committee
May 2015

8 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)
Consultant Radiologist, Department of Diagnostic Radiology, St George's Hospital, London

Professor Iain Squire (Vice-Chair)
Consultant Physician, University Hospitals of Leicester

Dr Graham Ash
Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Dr Jeremy Braybrooke
Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Professor Aileen Clarke

Professor of Public Health & Health Services Research, University of Warwick

Dr Andrew England

Senior Lecturer, Directorate of Radiography, University of Salford

Dr Ian Lewin

Honorary Consultant Physician and Endocrinologist, North Devon District Hospital

Professor John McMurray

Professor of Medical Cardiology, University of Glasgow

Dr Alec Miners

Senior lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr Mohit Misra

General Practitioner, Queen Elizabeth Hospital, London

Ms Sarah Parry

Clinical Nurse Specialist - Paediatric Pain Management, Bristol Royal Hospital for Children

Ms Pamela Rees

Lay Member

Mr Stephen Sharp

Senior Statistician, University of Cambridge MRC Epidemiology Unit

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Peter Sims

General Practitioner, Devon

Mr David Thomson

Lay member

Dr John Watkins

Clinical Senior Lecturer, Cardiff University; Consultant in Public Health Medicine, National Public Health Service Wales

Professor Olivia Wu

Professor of Health Technology Assessment, University of Glasgow

Guideline representatives

The following individuals, representing the Guideline Development Group responsible for developing NICE's clinical guideline related to this topic, were invited to attend the first ACD meeting to observe and to contribute as advisers to the Committee.

Dr Jon Packham

Consultant Rheumatolgist

Dr Louise Warburton

GPwSI (General Practitioner with a Special Interest) in Rheumatology

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Sophie Laurenson

Technical Lead

Joanna Richardson

Technical Adviser

Bijal Joshi
Project Manager

9 Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York:

- Corbett M, Soares M, Jhuti G, et al. 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, December 2014

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I. Companies:

- AbbVie (adalimumab)
- Merck, Sharp & Dohme (golimumab, infliximab)
- Pfizer (etanercept)
- UCB Pharma (certolizumab pegol)

- Celltrion Healthcare / Napp Pharmaceuticals (infliximab biosimilar) – (requested to be involved during assessment report consultation)
- Hospira UK (infliximab biosimilar) – (requested to be involved during appraisal consultation document consultation)

II. Professional/expert and patient/carer groups:

- British Society for Rheumatology
- National Ankylosing Spondylitis Society
- Primary Care Rheumatology Society
- Royal College of Nursing
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

III. Other consultees:

- Department of Health
- NHS England
- Welsh government

IV. Commentator organisations (without the right of appeal):

- Department of Health and Social Services and Public Safety, Northern Ireland (DHSSPSNI)
- Healthcare Improvement Scotland
- National Institute for Health Research Technology Assessment Programme (NETSCC)
- NHS Centre for Reviews & Dissemination and Centre for Health Economics –York
- Spondyloarthritis Guideline Development Group

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on TNF-alpha inhibitors by attending the initial Committee discussion and/or

providing a written statement to the Committee. They are invited to comment on the ACD.

- Dr Karl Gaffney, Consultant Rheumatologist, nominated by organisation representing British Society for Rheumatology – clinical expert
- Dr Raj Sengupta, Consultant Rheumatologist, nominated by organisation representing British Society for Rheumatology – clinical expert
- Mrs Debbie Cook, Chief Executive of National Ankylosing Spondylitis Society, nominated by organisation representing National Ankylosing Spondylitis Society – patient expert
- Mr Roger Stevens, nominated by organisation representing National Ankylosing Spondylitis Society – patient expert

D. Representatives from the following companies attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- AbbVie (adalimumab)
- Celltrion Healthcare / Napp Pharmaceuticals (infliximab biosimilar)
- Merck, Sharp & Dohme (golimumab, infliximab)
- Pfizer (etanercept)
- UCB Pharma (certolizumab pegol)