NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis after failure of a previous TNF-α inhibitor

1 Guidance

This guidance should be read in conjunction with 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 130).

1.1 Adalimumab, etanercept and infliximab are not recommended for the treatment of rheumatoid arthritis after the failure of a previous tumour necrosis factor alpha (TNF-α) inhibitor, except in the context of research. Such research should be designed to evaluate the clinical effectiveness of adalimumab, etanercept and infliximab when used sequentially after the failure of a previous TNF-α inhibitor, in comparison with management strategies that do not include the use of TNF-α inhibitors.

1.2 People with rheumatoid arthritis currently receiving adalimumab, etanercept or infliximab after the failure of a previous TNF-α inhibitor should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

2 Clinical need and practice

2.1 Rheumatoid arthritis (RA) is a chronic and progressive disabling condition characterised by inflammation of the synovial tissue of the joints. It causes tenderness, stiffness and progressive destruction of joints, and other symptoms such as pain and fatigue. It affects

between 0.5% and 1% of the population, or approximately 400,000 people, in England and Wales. Of these, approximately 15% have severe disease. RA affects three times as many women as men and has a peak age of onset of 40–70 years.

2.2 In RA, the synovium becomes enlarged because of an increase in the number of synovial cells (hyperplasia), infiltration by white blood cells and formation of new blood vessels. There is an increase in fluid-containing inflammatory cells in the joint cavity (effusion) and, secondary to this, thinning of the bone around the joint (periarticular osteoporosis). Erosions of the bone occur where synovial tissue meets cartilage and bone, and these, together with the periarticular bone thinning, lead to irreversible damage to the structure and function of the joint.

2.3 Internationally agreed criteria (American College of Rheumatology [ACR] criteria of 1987) for the diagnosis of RA require four of the following features to be present: morning stiffness in joints exceeding an hour; physician-observed arthritis of three or more areas with soft-tissue swelling; arthritis involving hand joints; symmetrical arthritis; rheumatoid skin nodules; a positive blood test for rheumatoid factor; and radiographic changes typical of rheumatoid disease. However, clinicians may diagnose RA without reference to these criteria and patients may not meet formal disease classification criteria early on in their disease.

2.4 The course of RA is heterogeneous and variable. However, a number of factors have been identified as being associated with poor prognosis. These include the presence of rheumatoid factor or anti-cyclic citrullinated peptide (CCP) antibodies, high erythrocyte sedimentation rate or C-reactive protein (CRP) levels, early radiographic evidence of erosions, and the presence of swollen and tender joints. Within 2 years of diagnosis, patients usually

experience moderate disability and after 10 years 30% are severely disabled. Approximately a third of patients cease work because of the disease. Life expectancy in patients with RA is also reduced. For example, a 50-year-old woman with RA is expected to die 4 years earlier than a woman without RA.

2.5 There is no cure for RA; conventional treatment aims to control pain and inflammation, and to reduce joint damage, disability and loss of function, thereby improving quality of life. Treatment involves a combination of pharmacological and non-pharmacological interventions. Conventional drug therapy relies on various combinations of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs). DMARDs act to reduce symptoms and slow progression of structural damage; they are used as monotherapy or in combination, often with steroids. DMARD treatment is started soon after diagnosis, with the aim of trying to achieve remission. Methotrexate and sulfasalazine are DMARDs often used as initial therapy. Non-drug therapies include surgery, physiotherapy and occupational therapy.

2.6 Not all DMARDs are effective for all people and, where there is a response to treatment, the response may reduce over time. This means that people with RA usually require a series of treatments. NICE technology appraisal guidance 130 (TA130) recommends the use of one of the TNF-α inhibitors adalimumab, etanercept or infliximab after the failure of two conventional DMARDs, including methotrexate. If the first TNF-α inhibitor has to be stopped because of an adverse event in the first 6 months, NICE recommends that a second TNF-α inhibitor may be tried. NICE technology appraisal guidance 126 ('Rituximab for the treatment of rheumatoid arthritis') recommends the use of rituximab, a treatment that depletes B cells,

which is licensed for people for whom a TNF-α inhibitor has failed. Abatacept is a DMARD licensed for the treatment of RA after the failure of a TNF-α inhibitor. NICE technology appraisal guidance 141 ('Abatacept for the treatment of rheumatoid arthritis') does not recommend the use of abatacept for this indication.

2.7 Several measures have been developed to assess response to treatment in RA. For example, the ACR response criteria (ACR20, 50 and 70) require a specified percentage improvement (20, 50 or 70%, respectively) in tender joint count, swollen joint count, global assessments, pain, disability and circulating inflammatory markers (for example, erythrocyte sedimentation rate or CRP). The disease activity score (DAS) is an alternative scoring system developed in Europe. It is calculated using a formula that includes counts for tender and swollen joints (53 and 44 joints, respectively), an evaluation of general health by the patient (on a scale of 0 to 100) and a measure of circulating inflammatory markers. DAS28 is similar to DAS but uses only 28 joints for assessment. A DAS28 score of greater than 5.1 is considered to be indicative of high disease activity, of between 5.1 and 3.2 indicative of moderate disease activity and of less than 3.2 indicative of low disease activity. A patient scoring less than 2.6 is defined as being in remission. The European League Against Rheumatism (EULAR) response criteria are based on the DAS measure. A decrease in DAS28 score of 0.6 or less is considered to indicate a poor response, while decreases of greater than 1.2 points indicate a moderate or good response, dependent on whether an individual's DAS28 score at the end point is above or below 3.2, respectively. The Stanford Health Assessment Questionnaire (HAQ) scores ability to perform daily activities from 0 (least disability) to 3 (most severe disability).

3 The technologies

Adalimumab

3.1 Adalimumab (Humira, Abbott Laboratories) is a human-sequence antibody that binds specifically to TNF-α and neutralises its biological function by blocking its interaction with cell-surface TNF-α receptors. It also modulates biological responses that are induced or regulated by TNF-α, including changes in the levels of adhesion molecules responsible for leukocyte migration. Adalimumab is licensed for the treatment of moderate to severe active RA in adults when the response to DMARDs, including methotrexate, has been inadequate, and for the treatment of severe, active and progressive RA in adults not previously treated with methotrexate. The summary of product characteristics (SPC) states that adalimumab should be given in combination with methotrexate, except where methotrexate is not tolerated or is considered inappropriate.

3.2 According to the SPC, adverse events reported during adalimumab therapy include injection-site reactions and infections. Before initiation of therapy, all patients must be evaluated for both active and inactive (latent) tuberculosis infection. Adalimumab is contraindicated in people with moderate to severe heart failure, active tuberculosis or other active infections. For full details of side effects and contraindications, see the SPC.

3.3 Adalimumab is administered at a dose of 40 mg every other week via subcutaneous injection. In monotherapy, if patients experience a decrease in response the dose may be increased to 40 mg every week. The net price for a 40-mg prefilled syringe is £357.50 (excluding VAT; 'British National Formulary' [BNF] edition 55). The annual cost of adalimumab for 26 doses at a dose of 40 mg every

other week is £9295. Costs may vary in different settings because of negotiated procurement discounts.

Etanercept

3.4 Etanercept (Enbrel, Wyeth Pharmaceuticals) is a recombinant human TNF-α-receptor fusion protein. It interferes with the inflammatory cascade by binding to TNF-α, thereby blocking its interaction with cell-surface receptors. Etanercept is licensed for use in adults with active RA whose response to DMARDs, including methotrexate, has been inadequate. Etanercept is also licensed for the treatment of severe, active and progressive RA in adults not previously treated with methotrexate. The SPC states that, for people who have had an inadequate response to conventional DMARDs, etanercept should be given in combination with methotrexate, except where methotrexate is not tolerated or is considered inappropriate.

3.5 According to the SPC, adverse events reported during etanercept therapy include injection-site reactions, infections and allergic reactions. Etanercept is contraindicated in patients with sepsis or at risk of sepsis and in those with other active infections. For full details of side effects and contraindications, see the SPC.

3.6 Etanercept is administered by subcutaneous injection at a dose of 25 mg twice weekly. Alternatively, the SPC allows for a dose of 50 mg once weekly. Etanercept is available either in vials as powder for reconstitution or in prefilled syringes. The net price for both a 25-mg vial and a 25-mg prefilled syringe is £89.38 (excluding VAT; BNF edition 55). The annual cost of etanercept using either 52 once-weekly doses or 104 twice-weekly doses is £9295. Costs may vary in different settings because of negotiated procurement discounts.

Infliximab

3.7 Infliximab (Remicade, Schering-Plough) is a chimeric monoclonal antibody that binds with high affinity to TNF-α, thereby neutralising its activity. Infliximab is licensed for the treatment of active RA where the response to DMARDs, including methotrexate, has been inadequate, and for patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs. The SPC specifies that infliximab must be used in combination with methotrexate.

3.8 According to the SPC, adverse events reported during infliximab therapy include acute infusion-related reactions and infections. Infliximab is contraindicated in people with moderate or severe heart failure and active infections. Before treatment is initiated, people must be screened for both active and inactive tuberculosis. For full details of side effects and contraindications, see the SPC.

3.9 The starting dose for infliximab is 3 mg/kg administered by intravenous infusion over 2 hours at weeks 0, 2 and 6, and thereafter every 8 weeks. If a person has an inadequate response, or response is reduced, consideration may be given to increasing the dose step-wise by approximately 1.5 mg/kg, up to a maximum of 7.5 mg/kg every 8 weeks. Alternatively, administration of 3 mg/kg as often as every 4 weeks may be considered. If an adequate response is achieved, the person should be continued on the selected dose or dose frequency. The net price for a 100-mg vial is £419.62 (excluding VAT; BNF edition 55). The dosing of infliximab depends on the weight of the person to be infused. If a person weighs 70 kg, each dose of infliximab, at the licensed starting dose, requires three vials at a cost of £1259, assuming vial wastage. The three loading doses cost £3777, with an annual cost following the loading doses of between £7553 and £8812, depending on whether

six or seven doses are required, and assuming that only 3 mg/kg is required once every 8 weeks. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

4.1.1 Evidence for the clinical effectiveness of the use of a second TNF-α inhibitor, and of comparator treatments, was taken from a systematic review completed by NICE's Decision Support Unit (DSU). Twenty-nine studies were identified that investigated the efficacy of the use of a second TNF-α inhibitor after the first TNF-α inhibitor had failed. Data for one or more specified outcomes (ACR response, DAS28 score, EULAR response and HAQ score change) could be extracted from 19 of these studies, with a further four studies reporting these outcomes for the TNF-α inhibitors as a group rather than for the individual drugs. These 23 studies are reported in the following sections. Only one of the studies was a randomised controlled trial (RCT). In this study (n = 28), people with an inadequate response to etanercept were randomised to switch to infliximab or to continue with etanercept. The results of the studies could not be combined in meta-analysis. Therefore, only the range of responses observed in studies of a second TNF-α inhibitor is reported in the following clinical effectiveness sections.

Adalimumab

4.1.2 Ten studies investigated the effectiveness of adalimumab after the failure of either etanercept or infliximab, nine of which provided data for the review. Six studies compared the effect seen in first-time users of a TNF-α inhibitor with the effect seen in people who

had previously used a TNF-α inhibitor. One study compared the response of the same person to their first and second TNF-α inhibitor. The remaining two studies reported the response to a second TNF-α inhibitor but did not draw comparisons with response to the first. The follow-up in the studies ranged from 12 to 52 weeks. Five studies reported ACR response rates. The ACR20 response rates for adalimumab as a second TNF-α inhibitor ranged from 49% to 89%, ACR50 response rates ranged from 26% to 56% and ACR70 response rates ranged from 13% to 33%. Eight studies reported mean decrease in DAS28 score, which ranged from 0.9 to 2.7. EULAR response rates were reported in six studies. Non-response rates ranged from 22% to 62%, moderate response rates ranged from 25% to 62% and good response rates ranged from 7% to 25%. Three studies reported mean improvement in HAQ score, which ranged from 0.22 to 0.51.

4.1.3 The largest of the comparative studies was the Research in Active Rheumatoid Arthritis (ReACT) study, which investigated the response to adalimumab after the failure of a previous TNF-α inhibitor in 899 people, compared with the response in 5711 people who had not previously had a TNF-α inhibitor. This study suggested that the response to adalimumab was lower in people who had previously had a TNF-α inhibitor than in those who had not (mean change in HAQ score 0.55 for the first TNF-α inhibitor, compared with 0.48 for the second TNF-α inhibitor). It also suggested that the response rate to adalimumab was lowest among people whose condition did not respond to their first TNF-α inhibitor (mean change in HAQ score 0.44), rather than people who had had a reduction in the response to their first TNF-α inhibitor (mean change in HAQ score 0.51). These findings were supported by the other comparative studies. For example, another study reporting HAQ outcomes reported a mean change of 0.31 for the

first TNF-α inhibitor, 0.26 for a second TNF-α inhibitor among those who had a reduced response to the first, and 0.22 for a second TNF-α inhibitor among those whose condition had not responded to their first TNF-α inhibitor.

Etanercept

4.1.4 Fourteen studies investigated the effectiveness of etanercept used after the failure of either infliximab or adalimumab, 10 of which provided data for the review. One study compared the effect seen in first-time users of a TNF-α inhibitor with the effect seen in people who had previously used a TNF-α inhibitor. One study compared the response of the same person to their first and second TNF-α inhibitor. One study compared the effect seen in people who switched to etanercept with that seen in people who switched to infliximab, and one study compared the effect seen in people who switched TNF-α inhibitor with that seen in people who stayed on the same TNF-α inhibitor. A further five studies only reported response to a second TNF-α inhibitor without drawing comparisons with the response to the first TNF-α inhibitor, and one study included no numerical data for the comparator. Follow-up in the studies ranged from 12 to 26 weeks. Five studies reported ACR response rates. ACR20 response rates for etanercept as a second TNF-α inhibitor ranged from 38% to 90%, ACR50 response rates ranged from 23% to 66% and ACR70 response rates ranged from 5% to 33%. Six studies reported mean decrease in DAS28 score, which ranged from 1.2 to 2.4. EULAR response rate was reported in five studies. EULAR non-response rates ranged from 17% to 46%, moderate response rates ranged from 16% to 67% and good response rates ranged from 12% to 58%. Two studies reported mean improvement in HAQ score, one of 0.41 and the other of 0.45.

4.1.5 In the study that compared the second use with the first use of etanercept in different groups of people, the response rate to a second TNF-α inhibitor was lower (proportion of people having an ACR 20 response rate 63% for the first TNF-α inhibitor and 59% for the second). In the study that compared response rates for a second TNF-α inhibitor with the same person's response to their first TNF-α inhibitor, response rates were similar. A study that compared switching TNF-α inhibitors with staying on the same TNF-α inhibitor suggested higher response rates if a person changed TNF-α inhibitor (an ACR20 response rate for people staying on the same TNF-α inhibitor of 59% compared with approximately 70% people switching TNF-α inhibitor). Another study, which compared people who switched from etanercept to infliximab with those who switched from infliximab to etanercept, suggested that switching to etanercept was associated with higher response rates than switching to infliximab (mean change in HAQ score in the group switching to infliximab 0.13 compared with 0.43 in the group switching to etanercept).

Infliximab

4.1.6 Nine studies investigated the effectiveness of infliximab used after the failure of either etanercept or adalimumab, five of which provided data for the review. One RCT compared switching to infliximab with staying on etanercept. One study compared the effect seen in first-time users of a TNF-α inhibitor with the effect seen in people who had previously used a TNF-α inhibitor. One study compared the effect seen in people who switched to etanercept with that seen in people who switched to infliximab. One study only reported response to a second TNF-α inhibitor without drawing comparisons with the response to the first, and one study included no numerical data for the comparator. The follow-up in the studies ranged from 12 weeks to 26 weeks. Two studies reported

ACR20 response rates for a second TNF-α inhibitor of 62% and 67%, respectively, and one study reported an ACR50 response rate of 31%. No studies reported ACR70 response rates. Four studies reported mean decrease in DAS28 score, which ranged from 0.9 to 2.2. Two studies reported EULAR response rates, one of which had two groups. EULAR non-response rates ranged from 25% to 33%, moderate response rates ranged from 33% to 75% and good response rates ranged from 25% to 33%. One study reported a mean improvement in HAQ score of 0.13.

4.1.7 In a study that compared response rates for first and second TNF-α inhibitors in the same group of people, results were inconsistent across outcomes. A study that compared switching to a different TNF-α inhibitor with staying on the same TNF-α inhibitor suggested that switching was more effective (ACR 20 response rate for people staying on the same TNF-α inhibitor 29% compared with 62% for people switching to a different TNF-α inhibitor). A final study, which compared people who switched from etanercept to infliximab with those who switched from infliximab to etanercept, suggested that switching to infliximab was less effective than switching to etanercept (results reported in section 4.1.5).

TNF-α inhibitors as a group

4.1.8 Five studies investigated the effect of sequential use of TNF-α inhibitors but reported results for TNF-α inhibitors only as a group. Four of these studies provided data for the review, but two of these were not comparative. The studies that were not comparative both reported mean decrease in DAS28 score, which ranged from 0.8 to 1.42. One of the studies also reported a mean improvement in HAQ score of 0.34. The two comparative studies compared switching to a second TNF-α inhibitor with switching to rituximab. The follow-up period in the two comparative studies was 12 weeks. One study

included 20 people switching to a second TNF-α inhibitor and 10 people switching to rituximab, the other included 66 and 50 people, respectively. Both studies reported similar results: mean decrease in DAS28 score of 0.8 for the TNF-α inhibitor groups, and of 1.48 in one study and 1.28 in the other for the groups switching to rituximab.

4.1.9 Data for the effectiveness of TNF-α inhibitors as a group are also available from two observational registries. The first, unpublished data from the British Society for Rheumatology Biologics Register (BSRBR), includes 308 people who switched to a second TNF-α inhibitor. For people who had been followed-up for at least 6 months, the data suggested an improvement in mean HAQ score for a second TNF-α inhibitor of 0.15 (unadjusted) and 0.21 (adjusted for confounders). A subsequent publication from the same data source with follow-up of 331 people reports an improvement in mean HAQ score of 0.13 (unadjusted) and 0.18 (adjusted for confounders). In comparison, for people starting their first TNF-α inhibitor, the BSRBR shows a mean improvement in HAQ score of 0.30 (unadjusted) after 6 months for the whole cohort and 0.40 (unadjusted) after 6 months for those people remaining on treatment. In addition, a regression analysis of data from the BSRBR suggested that the likelihood of response for an 'average' person to a second TNF-α inhibitor (55%) was lower than for the first TNF-α inhibitor (85%). The second observational registry is the US National Databank for Rheumatic Diseases. This register has data for 284 people who switched TNF-α inhibitors. These data suggest an improvement in HAQ score of 0.04 after a year's follow-up. No comparative data for first use of a TNF-α inhibitor were available.

Conventional DMARDs

4.1.10 None of the studies identified in the systematic review enabled direct comparisons between switching to a second TNF-α inhibitor and returning to conventional DMARDs. A separate review of the literature identified no studies that had investigated the effect of conventional DMARDs in a group of people for whom TNF-α inhibitors had failed. Four studies were identified that investigated the effect of conventional DMARDs in people with established RA (on average longer than 3 years), but none of these studies included people for whom a TNF-α inhibitor had failed. The study that included people with the longest disease duration was an analysis of data from the control group in the BSRBR. This study suggests that for conventional DMARDs the probability of EULAR response reduces slightly as the disease duration and number of prior treatments increases.

4.1.11 Two further studies were identified that investigated the use of novel treatments, in people for whom TNF-α inhibitors had failed, in comparison with placebo when added to an ongoing DMARD regimen. Although not measuring the effect of an individual DMARD, these studies show the effect of adding placebo to baseline DMARD treatment (mean improvement in HAQ score of 0.11) and may provide an indication of the effect of DMARDs in people for whom TNF-α inhibitors have failed. Unpublished data were also identified from the US National Databank for Rheumatic Diseases. These data suggest no change in mean HAQ score after follow-up of 1 year for people who had switched to conventional DMARDs after having had a TNF-α inhibitor.

4.1.12 An additional study (the Behandel Strategieen (BeST) study) was identified that investigated different treatment sequences. In this study, people with early RA (n = 508; median time from diagnosis 2

weeks) were randomised to four different treatment sequences of conventional and biological DMARDs; all treatment sequences included one TNF-α inhibitor (infliximab) given at a different point in the care pathway. People switched treatments when their disease activity was equal to or greater than DAS44 2.4 (cut-off point for low disease activity). Results were presented for the efficacy of each treatment sequence. These show that after 2 years no statistically significant differences were observed between the four treatment arms (mean HAQ score change range 0.7 to 0.9). However, people on conventional DMARDs were moving through treatments more quickly than those who had started treatment with infliximab. Results presented in graphs suggest that at 2 years approximately 20% of people receiving conventional DMARD monotherapy were being maintained on either their second or third conventional DMARD in a state of low disease activity. This increased to approximately 30% of people in the group that received conventional DMARD combination therapy, and decreased to approximately 10% of people in the group that had been given infliximab as their first drug treatment, before moving on to conventional DMARDs.

4.1.13 Consultees identified a further study of treatment strategies by the British Rheumatoid Outcome Study Group (the BROSG study). This study randomised people with mild but established RA (n = 466) to either symptomatic or aggressive treatment. The study did not report the effectiveness of individual DMARDs, and people in the study did not start or switch treatments at specific time points. The study reported no statistically significant differences in efficacy between the aggressive and symptomatic treatment strategies, and after 3 years 64% of people in the symptomatic treatment group and 49% of those in the aggressive treatment group were defined as treatment successes. However, people in

both groups had experienced a deterioration in median HAQ score (median HAQ score at baseline 1.38, median HAQ score after 3 years 1.5).

4.1.14 An analysis following up a group of people enrolled in the BSRBR who had stopped their first TNF-α inhibitor and not subsequently switched to a second TNF-α inhibitor was published following the completion of the review by the DSU. This study reported that this group of people had no change in mean HAQ score over a year. The study additionally reported variation in response among the group, with 22% of people having an improvement in HAQ score greater than 0.22, but detailed information was not provided about the treatments received by this group of people. The publication reports that only 32% of people reported a change to their DMARD therapy (defined as either increased dose or a switch to a new therapy) over the 12 months after being classified as not having a response to the TNF-α inhibitor.

4.2 Cost effectiveness

4.2.1 Two manufacturers (Abbott Laboratories and Wyeth Pharmaceuticals) included analyses of sequential use of TNF-α inhibitors in their submissions for TA130. Both assumed no reduction in effectiveness when a TNF-α inhibitor was used after the failure of another. Analyses from the manufacturer of adalimumab suggested that providing adalimumab as a fifth-line therapy after infliximab had failed gave an estimate of incremental cost effectiveness of £19,800 per additional quality-adjusted life year (QALY) gained. Analyses from the manufacturer of etanercept provided estimates of incremental cost effectiveness of between £15,000 and almost £25,500 per additional QALY gained, depending on the exact sequence of TNF-α inhibitors used. In addition, sequential analyses were provided by the Arthritis

Musculoskeletal Alliance based on data from the BSRBR, although the economic model was not submitted to NICE. These analyses suggested that providing two TNF-α inhibitors sequentially in comparison with a single TNF-α inhibitor gave an estimate of incremental cost effectiveness of £27,000 per additional QALY gained. All these analyses were carried out using discount rates of 6% for costs and 1.5% for benefits.

4.2.2 Additional analyses of the cost effectiveness of the sequential use of TNF-α inhibitors were carried out using the economic model developed for TA130. The Birmingham Rheumatoid Arthritis Model (BRAM) is an individual sampling model, which assesses the cost effectiveness of adding a TNF-α inhibitor to a sequence of DMARDs when compared with the same sequence of DMARDs without a TNF-α inhibitor. In this model, the initial age and sex distributions, as well as the starting distribution of HAQ scores, were based on observational data from the Norfolk Arthritis Register, a primary-care-based cohort of patients with inflammatory polyarthritis. Change in HAQ score was modelled as a multiplier of the starting HAQ score; both were sampled from distributions rather than being constant. Utilities were estimated based on a mapping process whereby HAQ scores from the trial were mapped via an algorithm to EQ-5D scores in order to derive estimates of utility. The model included a proportion of people stopping treatment at 24 weeks due to toxicity and lack of efficacy. Joint replacement and associated costs were not included in the additional analyses, although these were included in sensitivity analyses of the first use of TNF-α inhibitors (TA130). In the absence of appropriate joint replacement data for this cohort, an assumption was made that people incurred an annual cost of £860 per unit of HAQ score (for example, a person with an HAQ score of 2 incurred £1720 per year).

4.2.3 Analyses were carried out comparing TNF-α inhibitors both with rituximab and with conventional DMARDs. For each of these, two sets of analyses were carried out, using effectiveness data for TNF-α inhibitors from two different sources. The first source was the BSRBR, which suggested a mean improvement in HAQ score after starting treatment of 0.21, following adjustment for confounding variables (see section 4.1.9). The second source was an adalimumab study (ReACT). This study was chosen based on the results of the systematic review carried out by the DSU that identified four studies that had measured HAQ score. Of these studies, only the ReACT study had sufficient detail to be included in the economic modelling. The ReACT study reported an improvement in HAQ score of between 0.33 and 0.51 depending on the previous treatment used and the reasons for its failure. The ReACT data also enabled separate analyses for the groups of primary and secondary failures. Each set of analyses was completed twice, using effectiveness data for conventional DMARDs after the use of the first TNF-α inhibitors from two different sources. The first source reflected that used in TA130 and was mainly derived from studies of people with early RA rather than people for whom a TNF-α inhibitor had failed. The second source was data from the placebo arm of a clinical trial that examined the effectiveness of abatacept for the treatment of RA in comparison with placebo combined with continuation of the conventional DMARDs being used, in a population for whom a TNF-α inhibitor had failed. This study reported a mean improvement in HAQ score of 0.11 in the placebo arm (see section 4.1.11).

4.2.4 Disease progression was modelled as a constant increase in HAQ score indicating worsening functional ability. On starting treatment, people on a TNF-α inhibitor were assumed to have no disease progression until treatment was stopped. People on palliative

therapy were assumed to have underlying disease progression twice that of the general population (HAQ score increase of 0.06 per year), while those on conventional DMARDs had an HAQ score increase of 0.045 per year. These assumptions are more favourable towards TNF-α inhibitors than those that were previously modelled as the base case in TA130, where it was assumed that people on TNF-α inhibitors have underlying disease progression commensurate with the general population (HAQ score increase of 0.03 per year). The discount rate was 3.5% for both costs and benefits.

4.2.5 For the comparison of TNF-α inhibitors with conventional DMARDs, the cost-effectiveness analyses using TNF-α inhibitor data from the BSRBR and the data for conventional DMARDs, as had been used in TA130, gave a range of estimates of incremental cost effectiveness of £136,000 to £164,000 per additional QALY gained. Substituting the TNF-α inhibitor data with that from the ReACT study reduced the estimate of incremental cost effectiveness to £56,000 to £94,500 per additional QALY gained. Using data from the placebo arm of the abatacept trial for conventional DMARDs and the BSRBR data for the TNF-α inhibitor reduced the estimate of incremental cost effectiveness to £44,500 to £47,500 per additional QALY gained. In a scenario that used both the abatacept placebo data for the conventional DMARDs and data from the ReACT study for the TNF-α inhibitor, the estimate of incremental cost effectiveness was £31,000 to £38,700 per additional QALY gained. A threshold analysis demonstrated that for TNF-α inhibitors to be cost effective at a threshold of £30,000, the effectiveness had to be greater than that observed in the ReACT study.

4.2.6 Cost-effectiveness analyses were carried out comparing the use of a second TNF-α inhibitor with the use of rituximab. These analyses

were carried out using the same combinations of effectiveness data for TNF-α inhibitor and conventional DMARD as were described in the previous analyses, but also included rituximab in the treatment sequence. The mean improvement in HAQ score on starting treatment with rituximab was 0.4 based on the results of the Randomised Evaluation of Long-term Efficacy of Rituximab (REFLEX) trial. In these analyses, it was assumed that people on rituximab had underlying disease progression modelled as an increase in HAQ score of 0.03 per annum, but that people on TNF-α inhibitors had no underlying disease progression while on treatment.

4.2.7 When switching to a second TNF-α inhibitor was compared with switching to rituximab, the same cost-effectiveness analyses as in TA130 were used, based on TNF-α inhibitor data from the BSRBR and data for conventional DMARDs. These produced a range of estimates of incremental cost effectiveness of £255,000 to £919,000 per additional QALY gained. Substituting the BSRBR TNF-α inhibitor data with that from the ReACT study reduced the estimate of incremental cost effectiveness to £56,900 to £138,000 per additional QALY gained. Using alternative data for conventional DMARDs from the placebo arm of the abatacept clinical trial and the TNF-α inhibitor data from the BSRBR reduced the estimate of incremental cost effectiveness to £56,400 to £74,800 per additional QALY gained. In a scenario that used placebo data from the abatacept trial to reflect conventional DMARDs and data from the ReACT study for the TNF-α inhibitor, the estimate of incremental cost effectiveness was £32,200 to £50,500 per additional QALY gained.

4.2.8 New cost-effectiveness analyses were carried out examining the impact on cost effectiveness of assuming no vial wastage for

infliximab, that is, assuming that any infliximab left over in the vial after withdrawing the appropriate dose for one person can be used for someone else. Using the BSRBR data for TNF-α inhibitors and data for conventional DMARDs, as had been used in TA130, suggested an estimate of incremental cost effectiveness of approximately £100,000 per additional QALY gained if no infliximab is wasted. Using the TNF-α inhibitor data from the ReACT study reduced the estimate of incremental cost effectiveness to approximately £40,000 per additional QALY gained. Using alternative data for conventional DMARDs from the placebo arm of the abatacept clinical trial and the BSRBR data for the TNF-α inhibitor reduced the estimate of incremental cost effectiveness to approximately £32,000 per additional QALY gained. In a scenario that used placebo data from the abatacept trial to reflect conventional DMARDs and data from the ReACT study for the TNF-α inhibitor, the estimate of incremental cost effectiveness was approximately £22,000 per additional QALY gained.

4.2.9 Additional analyses were also carried out examining the cost effectiveness of infliximab in comparison with conventional DMARDs for those people who required either an increase in the dose of infliximab or an increase in the frequency of dosing either to maintain or to generate a response to treatment. The estimates of incremental cost effectiveness ranged from approximately £40,000 to £211,000 and £60,000 to £314,000 per additional QALY gained for 5 mg/kg and 7.5 mg/kg, respectively. The estimates of incremental cost effectiveness ranged from approximately £41,000 to £224,000 and £61,000 to £320,000 per additional QALY gained when the time between 3 mg/kg doses was reduced to 6 weeks and 4 weeks, respectively. The estimates varied depending on the source of data used for TNF-α inhibitors and conventional DMARDs.

4.3 Consideration of the evidence

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of adalimumab, etanercept and infliximab, having considered evidence on the nature of the condition and the value placed on the benefits of adalimumab, etanercept and infliximab by people with RA, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

4.3.2 The Committee heard from clinical specialists and patient experts about the clinical management of people with RA. The Committee heard that the management of RA was changing, with more clinicians using an approach of maximising disease control by starting DMARDs early and increasing the dose of DMARDs quickly if control of disease was not achieved. The Committee heard from clinical specialists that, as a consequence of this accelerated approach to DMARD usage, treatment with TNF-α inhibitors was initiated sooner after diagnosis than had previously been the case and therefore the characteristics of the people being treated with TNF-α inhibitors had changed over time. The Committee considered that these changes to the management of RA needed to be taken into account while it examined the evidence that was available in the appraisal.

Clinical effectiveness

4.3.3 The Committee considered the studies of the clinical effectiveness of TNF-α inhibitors when used sequentially. The Committee noted that the available evidence was mainly from observational studies with a short follow-up period that included relatively small numbers of people. The Committee noted that many of the studies were not comparative and those that were comparative usually compared the response to a first TNF-α inhibitor with the response to a

second TNF-α inhibitor rather than comparing switches to different treatments. The Committee considered that that validity of the results from the studies of the sequential use of TNF-α inhibitors could be affected by their study design and that the generalisability of the results could be affected by changing clinical practice and small patient numbers. The Committee concluded that there were significant limitations in the evidence base available for this appraisal.

4.3.4 The Committee examined registry data from the BSRBR, which showed that the proportion of people whose condition responded to a second TNF-α inhibitor (that is, the response rate), and the average size of the treatment effect, were both lower than for the first TNF-α inhibitor. The Committee heard from clinical specialists that this was plausible and that the response to a second TNF-α inhibitor might be expected to be lower than when a TNF-α inhibitor is used for the first time. The Committee was aware of data from the National Databank for Rheumatic Disease (NDRD) that showed no effect of a second TNF-α inhibitor, but which were not consistent with the results of other studies. The Committee concluded that, based on current evidence, a second TNF-α inhibitor was clinically effective but on average less effective than when TNF-α inhibitors were used for the first time. In reaching this conclusion, the Committee noted that BSRBR data suggested that the likelihood of gaining a EULAR response to a second TNF-α inhibitor was approximately 55% compared to 85% for the first TNF-α inhibitor. In addition, the Committee noted that the unadjusted estimate of mean improvement in HAQ score for the second use of a TNF-α inhibitor was approximately half that for the first use.

4.3.5 The Committee noted that some differences in effectiveness of sequential TNF-α inhibitors had been observed between people

who had never had a response to the first treatment with a TNF-α inhibitor and people who had had a response to treatment that had reduced over time. The Committee also noted observational data that suggested that some sequences of TNF-α inhibitors had been shown to be more effective than others with regard to the response to the second treatment. The Committee heard from clinical specialists that differences in response to different treatments may be due to the development of antibodies to specific TNF-α inhibitors. However, these may vary and may not be the only mechanism responsible, so differences in response are not predictable. The Committee concluded that there were currently insufficient data to support a conclusion of differential effectiveness for different sequences of TNF-α inhibitors. The Committee also concluded that there was insufficient evidence to distinguish between the clinical effectiveness of the second TNF-α inhibitor when used in people whose condition did not show any response to their first TNF-α inhibitor (that is, primary failure) and people who, after an initial response to their first TNF-α inhibitor, had experienced a reduction in response (that is, secondary failure).

4.3.6 The Committee considered the evidence of the clinical effectiveness of conventional DMARDs after the failure of TNF-α inhibitors, as this would be an important comparator for a second TNF-α inhibitor after failure of the first. The Committee noted that a review of the evidence had identified no studies of the effectiveness of conventional DMARDs after the failure of a TNF-α inhibitor. The Committee noted that some evidence had been identified for the effectiveness of conventional DMARDs in people with disease of long duration, but that the relevance of these data to the current appraisal was limited because of the differences in the population characteristics. However, the Committee concluded that the data

suggested a decrease in the response to conventional DMARDs with increasing duration of disease and number of prior treatments.

4.3.7 The Committee examined registry data from the BSRBR that showed no change in average HAQ score for people who had stopped treatment with TNF-α inhibitors. The Committee heard from clinical specialists that if people had received appropriate clinical management early in the disease that included rapid escalation of conventional DMARDs, particularly methotrexate, it was less likely that conventional DMARDs would subsequently be effective. The clinical specialists also considered that any treatment effect for conventional DMARDs in this situation would be very limited. The Committee noted that the data from the BSRBR showed variation in response and that a proportion of people had a response to DMARDs after the failure of a TNF-α inhibitor. The clinical specialists agreed that there would be variation in response and accepted that an assumption that nobody would have a response was unlikely. The Committee considered that the data from the BSRBR were consistent with the possibility that conventional DMARDs used after the failure of the first TNF-α inhibitor could have a positive effect by preventing further HAQ score deterioration. Overall, the Committee concluded that the effect of conventional DMARDs in people for whom a TNF-α inhibitor had failed was likely to be small, but that an assumption of no positive effect was not supported by the evidence reviewed.

4.3.8 The Committee was mindful of comments from consultees that highlighted the results of the BeST and BROSG studies, which had investigated the effect of using different treatment strategies. The Committee noted that these studies did not provide clinical effectiveness evidence for individual DMARDs and therefore considered that they could not be used in the economic modelling.

The Committee also noted that the populations in these studies did not represent a group of people with established RA for whom a TNF-α inhibitor had failed. The Committee considered that the results of the BeST study indicated that a small proportion of people have a response to conventional DMARDs. The Committee therefore concluded that these studies did not demonstrate that DMARDs had no effect after failure of the first TNF-α inhibitor.

Cost effectiveness

4.3.9 The Committee examined the cost-effectiveness analysis of sequential use of TNF-α inhibitors and considered those carried out using the BRAM, as well as analyses that were available from the BSRBR. The Committee was aware that HAQ score had been used as the basis for the modelling in the BRAM. The Committee heard from clinical specialists that HAQ score was affected by both reversible and irreversible components of the disease process, and that for people with long-standing disease the potential for improvements in HAQ score may be reduced because of irreversible damage. In addition, as inflammation could be improved by treatment even though HAQ score did not change appreciably, the clinical specialists considered that there could still be an important benefit from treatment in this situation that would not be captured by HAQ score. The Committee concluded that the important factor in the modelling was how HAQ score mapped to EQ-5D to produce utility values rather than the HAQ scale itself. The Committee noted that analyses from the BSRBR had categorised people on the basis of DAS28 response, before calculating HAQ score improvement for people with each category of response which was then mapped to EQ-5D to calculate utility. The Committee considered that both models therefore based their estimation of utility on HAQ score. The Committee was also aware that documents submitted with the report of the BSRBR model

demonstrated that HAQ score was a reasonable predictor of EQ-5D. The Committee noted that the BRAM and BSRBR analyses had used different discount rates, and considered that if the same discount rates had been used the BSRBR estimates would have been similar to the lower estimates from the BRAM. The Committee concluded that it was appropriate to use the BRAM as a basis for the consideration of the cost effectiveness of the sequential use of TNF-α inhibitors and that this was consistent with the approach taken in TA130.

4.3.10 The Committee noted that the cost-effectiveness analyses had been carried out assuming no progression of disease while on treatment with TNF-α inhibitors, but assuming some progression of disease while on conventional DMARDs and rituximab. The Committee was aware that for TNF-α inhibitors this assumed both no underlying deterioration of physical function and no reduction in response to treatment. The Committee was aware that people with RA could experience a reduction in response to treatment (secondary failure) and that people without RA experienced some decline in physical function as they aged. Therefore the Committee concluded that the assumption of no deterioration in HAQ score whilst on treatment reflected a favourable modelling scenario for the first or second use of TNF-α inhibitors.

4.3.11 The Committee noted that the offset costs of avoiding or delaying joint replacement, outpatient visits and inpatient stays had not been included in the analyses of sequential use. The Committee was aware that offset costs had been included in the appraisals of rituximab and abatacept (TA126 and TA141), but that the only data source identified had been from a cohort of people enrolled in the Norfolk Arthritis Register (NOAR) which may not be representative of the costs accrued by a population of people receiving a second

TNF-α inhibitor. The Committee noted that sensitivity analyses including offset costs had been explored in the first-use analyses of TNF-α inhibitors (TA130) and that these had not demonstrated a significant impact on the incremental cost-effectiveness ratios (ICERs). The Committee concluded that consideration of offset costs was important, but that this had been explored by the Assessment Group in their original analyses and had been shown not to be a key driver of cost effectiveness.

4.3.12 The Committee then considered the different sources of clinical effectiveness estimates for TNF-α inhibitors that had been used in the economic modelling. The Committee heard that it had not been possible to use data from randomised comparisons in the economic modelling, and that this could affect the robustness of the results. The Committee noted that using clinical effectiveness data from the BSRBR produced less favourable estimates of cost effectiveness than using clinical effectiveness data from an adalimumab study (the ReACT study). The Committee heard from clinical specialists that, because of changes in clinical management and differences in clinical practice in other countries, neither source of data necessarily reflected current UK practice or the full implementation of the current NICE guidance. The Committee noted that an analysis to identify the minimum effectiveness required for TNF-α inhibitors to be cost effective at a willingness to pay of £30,000 per QALY suggested that the imputed clinical effectiveness would need to be higher than that shown in the ReACT study. The Committee was mindful that if the willingness to pay was £20,000 per additional QALY gained, then TNF-α inhibitors would have to be about twice as effective as the current estimates suggested. The Committee noted that if values for the effectiveness of second use of TNF-α inhibitors were higher than in the ReACT study, this would suggest levels of efficacy comparable to or higher than those

seen in RCTs of first use of TNF-α inhibitors. However, data from the BSRBR and other studies of sequential use of TNF-α inhibitors showed that TNF-α inhibitors when used for a second time were less effective than first use, and that this was also supported by clinical opinion. Therefore, the Committee concluded that the data available did not currently support greater clinical effectiveness of TNF-α inhibitors than was observed in the ReACT study.

4.3.13 The Committee examined the evidence of clinical effectiveness used in the economic modelling for conventional DMARDs. Again, the Committee noted that it had not been possible to use data from randomised comparisons, and that this could affect the robustness of the results. The Committee noted that the analyses had been carried out using the values used in the original assessment report as well as an alternative value from the placebo arm of the abatacept clinical trial. The Committee considered, on the basis of the evidence for this appraisal and the testimony of the clinical specialists, that the values for the clinical effectiveness of conventional DMARDs taken from studies of early RA and used in the original assessment report could overestimate the clinical effectiveness of conventional DMARDs used after the failure of a first TNF-α inhibitor.

4.3.14 The Committee therefore carefully considered the alternative value used for the treatment effect of conventional DMARDs, that is, from the placebo arm of the abatacept trial. The Committee noted that this approach of using placebo data had been used to represent the effectiveness of conventional DMARDs in the appraisals of rituximab and abatacept. However, it was aware that this value did not directly measure the effect of a conventional DMARD, as placebo had been added to an ongoing DMARD regimen. The Committee recognised that the data from the abatacept clinical trial

could reflect an effect of placebo or benefits associated with enrolment in a study. However, in the absence of studies that specifically examined the effect of individual DMARDs after the failure of a previous TNF-α inhibitor, the Committee was not persuaded that the placebo data had substantially overestimated the effect of conventional DMARDs.

4.3.15 The Committee noted comments from consultees that alternative data from the BSRBR (discussed in section 4.3.7) should be used to reflect the efficacy of conventional DMARDs and that this should be combined in the economic analyses with data from the ReACT study (discussed in section 4.3.12). The Committee considered that study enrolment could have affected the data for the effectiveness of TNF-α inhibitors taken from the ReACT trial, which would not have been observed from the BSRBR. Therefore the Committee was not persuaded that it would be appropriate to combine estimates of clinical effectiveness for TNF-α inhibitors from ReACT with those for conventional DMARDs from the BSRBR.

4.3.16 The Committee noted that the additional analyses undertaken for sequential use had been completed using discount rates of 3.5% for costs and benefits. The Committee recognised that the recommendations for first use of TNF-α inhibitors had been based on discount rates of 6% and 1.5% for costs and benefits, respectively. The Committee noted that the use of differential discount rates in the new sequential analyses would reduce the estimates of incremental cost effectiveness. The Committee was aware that the discount rates applied in the recently completed appraisals of rituximab and abatacept for RA were 3.5% for costs and benefits. The Committee concluded that whilst the use of different discount rates would alter the estimates of incremental cost effectiveness, it did not alter their conclusions regarding the

lack of robustness in the current evidence base for the clinical effectiveness of second-use TNF-α inhibitors upon which the estimates of cost effectiveness were based.

4.3.17 In considering the estimates of cost effectiveness of infliximab, the Committee recognised this agent was dosed according to weight. Drug costs therefore differed according to the weight of the person and this could alter the estimate of cost effectiveness for people of different weights. The Committee was also mindful that the analyses of the cost effectiveness of infliximab assumed no sharing of vial contents between people and that if it was possible to minimise vial wastage then the cost effectiveness would be improved. The Committee considered that it could not be assumed that there would be no vial wastage and that the original estimates of cost effectiveness that assumed that infliximab vials were not shared were appropriate. The Committee appreciated that adjustments to the dosing of infliximab would affect the calculation of cost effectiveness, but did not consider that it would change their view of the basis for the underlying estimates of clinical effectiveness for second use of TNF-α inhibitors.

4.3.18 The Committee noted changes to the licensed indication for infliximab that allowed for an increased dose of infliximab or increased frequency of administration. The Committee noted that the SPC stated that this should be considered for those people whose condition was not responding to infliximab or for whom the response to infliximab was reduced. On the basis of this information, the Committee considered that the assumption in the economic analyses of no additional benefit for the extra cost of increasing the dose of infliximab was appropriate. The Committee concluded that the costs of increasing the dose or frequency of administration of infliximab in order to maintain the same effect

would increase the ICER to the extent that the Committee could not recommend dose escalation or increased frequency of administration of infliximab to maintain clinical efficacy as being a cost-effective use of NHS resources.

4.3.19 The Committee considered the current NICE guidance on the use of rituximab. It noted that rituximab could be used at the same point in the treatment pathway as a second TNF-α inhibitor and could therefore be considered an appropriate comparator for the second use of a TNF-α inhibitor. The Committee noted that the estimates of incremental cost effectiveness for a second TNF-α inhibitor compared with rituximab using the lower estimates of efficacy for conventional DMARDs ranged from £32,000 (with clinical effectiveness data from the ReACT study) to £75,000 (with clinical effectiveness data from the BSRBR) per additional QALY gained. The Committee noted that the analyses of rituximab had assumed no deterioration in response between infusions and that the costs assumed an average of 9 months between infusions. The Committee recognised that the interval between infusions may be shorter in clinical practice but noted NICE guidance (TA126), which stated that it should be no shorter than 6 months. The Committee noted that if there were increased costs of rituximab treatment and a deterioration in response to rituximab between infusions, then this could reduce the estimate of incremental cost effectiveness. However, the Committee was also aware that the analyses assumed a higher rate of underlying disease progression for rituximab than for TNF-α inhibitors. The Committee recognised that if the difference between these estimates of underlying disease progression used in the model decreased this would increase the estimate of incremental cost effectiveness when comparing second-use TNF-α inhibitors with rituximab. The Committee was aware of comments from consultees about uncertainties in the

safety of rituximab and its place in the management of RA, but considered that these aspects were most appropriately considered as part of an appraisal of rituximab. On balance, the Committee was not persuaded that the current clinical evidence available supported a decision that TNF-α inhibitors when used as an alternative to rituximab after the failure of a previous TNF-α inhibitor would be an appropriate use of NHS resources.

4.3.20 The Committee was aware that for some people rituximab treatment may not be suitable because of intolerance or contraindications to rituximab or methotrexate, or because the presence of seronegative disease meant that rituximab treatment was less likely to be effective. The Committee recognised that for these people the range of treatment options available would be limited. Therefore, the Committee reviewed again the estimates of clinical effectiveness and cost effectiveness for the comparison of use of a second TNF-α inhibitor with conventional DMARDs that:

- assumed no progression of disease while on treatment
- used data from the placebo arm of an abatacept clinical trial to reflect the treatment effect of conventional DMARDs and
- used data from the ReACT study for the effectiveness of a TNF-α inhibitor.

The Committee noted that in this scenario the estimates of incremental cost effectiveness were £31,000 to £39,000 per additional QALY gained, but in an alternative scenario with clinical effectiveness data from the BSRBR the estimates were approximately £45,000 per additional QALY gained. The Committee considered that these scenarios were based on a number of assumptions that favoured TNF-α inhibitors and that the evidence for any of them was limited in terms of methodological rigour and the extent to which it represented current NHS clinical

practice. On balance, the Committee was not persuaded that the current clinical evidence available supported a decision that TNF-α inhibitors when used after the failure of a previous TNF-α inhibitor for the treatment of people who were intolerant of or had contraindications to rituximab or methotrexate, or because of the presence of seronegative disease, would be an appropriate use of NHS resources.

4.3.21 The Committee considered the value of doing further research regarding the clinical effectiveness of TNF-α inhibitors when used after the failure of a previous TNF-α inhibitor. The Committee considered that there were limitations to the evidence available for the clinical effectiveness of both TNF-α inhibitors when used sequentially, and alternative treatments such as conventional DMARDs and other biological drugs such as rituximab. The Committee agreed on the importance of further research that examined comparative efficacy of relevant options and that also reflected current best practice in the clinical management of people with RA. The Committee concluded that it would be appropriate to recommend the use of TNF-α inhibitors after failure of a previous TNF-α inhibitor only in the context of research.

5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

5.2 'Healthcare standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires local health boards and NHS trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAXXX). [NICE to amend list as needed at time of publication]

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

6 Recommendations for further research

The Committee considered that the following further research should be completed.

6.1 Clinical trials to evaluate the clinical effectiveness of adalimumab, etanercept and infliximab when used sequentially after the failure of a TNF-α inhibitor in comparison with management strategies that

do not include the use of TNF-α inhibitors, including untried DMARDs or biological DMARDs such as rituximab.

6.2 Investigations of underlying disease progression while on conventional and biological DMARDs.

7 Related NICE guidance

Published

Abatacept for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 141 (2008). Available from: www.nice.org.uk/TA141

Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 130 (2007). Available from: www.nice.org.uk/TA130

Rituximab for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 126 (2007). Available from: www.nice.org.uk/TA126

Anakinra for rheumatoid arthritis. NICE technology appraisal guidance 72 (2003). Available from: www.nice.org.uk/TA072

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Rheumatoid arthritis in adults. NICE clinical guideline (publication expected February 2009).

8 Proposed date for review of guidance

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 The guidance on this technology will be considered for review in July 2010. This is to coincide with the review date for 'Rituximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 126) and 'Abatacept for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 141).

David Barnett
Chair, Appraisal Committee
July 2008

Appendix A: Appraisal Committee members, guideline representatives and NICE project team

A Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its 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. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice-chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

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.

Professor Keith Abrams

Professor of Medical Statistics, University of Leicester

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Darren Ashcroft

Reader in Medicines Usage and Safety, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Professor Stirling Bryan

Head, Department of Health Economics, University of Birmingham

Professor John Cairns

Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Charkravarty

Director, External Relations, Procter and Gamble Health Care, Europe

Professor Jack Dowie

Health Economist, London School of Hygiene and Tropical Medicine

Ms Lynn Field

Nurse Director, Pan Birmingham Cancer Network

Professor Christopher Fowler

Professor of Surgical Education, Barts and The London, Queen Mary's School of Medicine and Dentistry, University of London

Dr Fergus Gleeson

Consultant Radiologist, Churchill Hospital, Oxford

Ms Sally Gooch

Independent Nursing and Healthcare Consultant

Mr Sanjay Gupta

Former Service Manager in Stroke, Gastroenterology, Diabetes and Endocrinology, Basildon and Thurrock University Hospitals Foundation NHS Trust

Dr Mike Laker (2005–2008)

Medical Director, Newcastle Hospitals NHS Trust

Mr Terence Lewis

Lay member

Professor Gary McVeigh

Professor of Cardiovascular Medicine, Queens University, Belfast and Consultant Physician, Belfast Trust

Dr Ruairidh Milne

Senior Lecturer in Public Health, National Coordinating Centre for Health Technology, University of Southampton

Dr Neil Milner

General Medical Practitioner, Tramways Medical Centre, Sheffield

Dr Rubin Minhas

General Practitioner, Coronary Heart Disease Clinical Lead, Medway PCT

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Rosalind Ramsay

Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital, London

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Dr Lindsay Smith

General Practitioner, East Somerset Research Consortium

Mr Roderick Smith

Finance Director, West Kent PCT

Mr Cliff Snelling

Lay member

Professor Ken Stein (Vice Chair)

Professor of Public Health, Peninsula College of Medicine and Dentistry, University of Exeter

Professor Andrew Stevens

Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Dr Rod Taylor

Associate Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth

B Guideline representatives

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

- Jill Parnham, Manager, National Collaborating Centre for Chronic Conditions
- Dr Christopher Deighton, Consultant Rheumatologist, Derbyshire Royal Infirmary

C NICE project team

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

Zoe Garrett
Technical Lead

Janet Robertson
Technical Adviser

Natalie Bemrose
Project Manager

Appendix B: Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by West Midlands Health Technology Assessment (HTA) Collaboration, University of Birmingham.

- Chen Y-F, Jobanputra P, Barton P et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness, Health Technology Assessment 2006; 10(42).

Extra analysis reports were prepared by the Decision Support Unit, The University of Sheffield, School of Health and Related Research (ScHARR).

- Wailoo A, Tosh J, The effectiveness of non biologic DMARDS after anti TNF α inhibitor failure, January 2008.
- Wailoo A, The sequential use of TNF α inhibitors, January 2008.

An extra analysis report was prepared by West Midlands HTA Collaboration, University of Birmingham.

- Barton P, Further cost-effectiveness analysis of sequential TNF inhibitors for rheumatoid arthritis patients, January 2008.

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

I Manufacturer/sponsors:

- Abbot Laboratories
- Wyeth Pharmaceuticals

- Schering-Plough

II Professional/specialist and patient/carer groups:

- Arthritis and Musculoskeletal Alliance
- Arthritis Care
- BackCare
- British Association of Spine Surgeons
- British Health Professionals in Rheumatology
- British Institute of Musculoskeletal Medicine
- British Orthopaedic Association
- British Society for Rheumatology
- Department of Health
- Eastern Hull Primary Care Trust
- National Rheumatoid Arthritis Society
- Primary Care Rheumatology Society
- Royal College of Nursing
- Royal College of Physicians
- Royal Pharmaceutical Society of Great Britain

III Other consultees:

- Somerset Coast Primary Care Trust
- Welsh Assembly Government

IV Commentator organisations (without the right of appeal):

- Arthritis Research Campaign
- Board of Community Health Councils in Wales
- British National Formulary
- National Public Health Service for Wales
- NHS Quality Improvement Scotland

C The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor 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 adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis after failure of a previous TNF-α inhibitor by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Robin Butler, Consultant Rheumatologist, Robert Jones and Agnes Hunt Orthopaedic Hospital nominated by British Health Professionals in Rheumatology and British Society for Rheumatology – clinical specialist
- Dr Frank McKenna, Consultant Physician and Rheumatologist, Trafford General Hospital nominated by the British Society for Rheumatology – clinical specialist
- Mrs Ailsa Bosworth, Chair of the National Rheumatoid Arthritis Society nominated by the National Rheumatoid Arthritis Society – patient expert
- Ms Homaira Khan nominated by Arthritis Care – patient expert