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Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor

**Part review of NICE technology appraisal guidance 36
Review of NICE technology appraisal guidance 126 and 141**

NICE technology appraisal guidance 195

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Ordering information

You can download the following documents from
www.nice.org.uk/guidance/TA195
- The NICE guidance (this document).
- A quick reference guide – the recommendations.
- 'Understanding NICE guidance' – a summary for patients and carers.
- Details of all the evidence that was looked at and other background information.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:
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Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36, review of NICE technology appraisal guidance 126 and 141)

NOTE: This guidance replaces NICE technology appraisal guidance 126 and 141 issued in August 2007 and April 2008 respectively. It also replaces the remaining recommendations in NICE technology appraisal guidance 36 issued in March 2002.

The appraisal of adalimumab and the review of the appraisals of etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis have resulted in changes in the guidance. Rituximab in combination with methotrexate is still recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor. Additional treatment options are now recommended for these adults if rituximab therapy is contraindicated or withdrawn because of an adverse event, specifically:

- If rituximab is contraindicated or withdrawn, adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate, are now recommended as treatment options.

- If rituximab therapy cannot be given because methotrexate is contraindicated or withdrawn because of an adverse event, adalimumab and etanercept, each as monotherapy, are now recommended as treatment options

1 Guidance

1.1 Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or are

intolerant of, other disease-modifying anti-rheumatic drugs (DMARDs), including at least one tumour necrosis factor (TNF) inhibitor. Treatment with rituximab should be given no more frequently than every 6 months.

1.2   Treatment with rituximab in combination with methotrexate should be continued only if there is an adequate response following initiation of therapy and if an adequate response is maintained following retreatment with a dosing interval of at least 6 months. An adequate response is defined as an improvement in disease activity score (DAS28) of 1.2 points or more.

1.3   Adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate, are recommended as treatment options only for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to rituximab, or when rituximab is withdrawn because of an adverse event.

1.4   Adalimumab monotherapy and etanercept monotherapy are recommended as treatment options for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to methotrexate, or when methotrexate is withdrawn because of an adverse event.

1.5   Treatment with adalimumab, etanercept, infliximab and abatacept should be continued only if there is an adequate response (as defined in 1.2) 6 months after initiation of therapy. Treatment should be monitored, with assessment of DAS28, at least every 6 months and continued only if an adequate response is maintained.

1.6   When using DAS28, healthcare professionals should take into
       account any physical, sensory or learning disabilities,
       communication difficulties, or disease characteristics that could
       adversely affect patient assessment and make any adjustments
       they consider appropriate.

1.7   A team experienced in the diagnosis and treatment of rheumatoid
       arthritis and working under the supervision of a rheumatologist
       should initiate, supervise and assess response to treatment with
       rituximab, adalimumab, etanercept, infliximab or abatacept.

2   Clinical need and practice

2.1   Rheumatoid arthritis is a chronic and progressive disabling
       condition characterised by inflammation of the synovial tissue of
       the joints. It may cause tenderness and stiffness of joints and their
       progressive destruction, and symptoms including pain and fatigue.
       It is estimated that 580,000 people in England and Wales,
       approximately 1% of the population, have rheumatoid arthritis. Of
       these, approximately 15% have severe disease. Rheumatoid
       arthritis affects three times as many women as men and has a
       peak age of onset of 40–70 years.

2.2   In rheumatoid arthritis, the synovial membrane thickens because
       of an increased number of synovial cells, infiltration by white blood
       cells and formation of new blood vessels. Synovial fluid increases
       within the joint cavity, and bone mineral density adjacent to the
       joint reduces. Erosions of the bone may occur at the margin of the
       joint where synovial tissue meets cartilage and bone, and this can
       lead to irreversible damage to the structure and function of the
       joint.

2.3   Inflammatory disease involving areas other than the joints can
       also occur. Dryness of the eyes and mouth and the formation of
       rheumatoid nodules may affect up to one third of people with

rheumatoid arthritis. More severe inflammatory manifestations may lead to fibrosis in the lungs and inflammation affecting the lining of the heart, lungs and blood vessels. Ischaemic heart disease and cardiac failure are more common in people with rheumatoid arthritis than in those without this condition. Osteoporosis is also more common because of reduced mobility, inflammation and/or the side effects of drugs used to treat rheumatoid arthritis, particularly corticosteroids. Corticosteroid use can also contribute to an increased risk of infection and diabetes mellitus.

2.4   Internationally agreed criteria for the diagnosis of rheumatoid arthritis (American College of Rheumatology [ACR] 1987) require four of the following features:

- joint stiffness in the morning exceeding 1 hour
- physician-observed arthritis of three or more areas with soft tissue swelling
- arthritis involving hand joints
- symmetrical arthritis
- rheumatoid skin nodules
- a positive blood test for rheumatoid factor
- radiographic changes typical of rheumatoid disease.

2.5   A diagnosis requires that, with the exception of the last criterion, all criteria must be present for a minimum of 6 weeks. However, clinicians sometimes diagnose rheumatoid arthritis without reference to these criteria.

2.6   The course of rheumatoid arthritis varies, and the following factors indicate poor prognosis: the presence of antibodies to rheumatoid factor or cyclic citrullinated peptide (CCP); high erythrocyte sedimentation rate or concentrations of C-reactive protein; early radiographic evidence of erosions; and the presence of swollen and tender joints. Within 2 years of diagnosis, people with

rheumatoid arthritis may experience moderate disability, and after 10 years 30% are severely disabled. Approximately one third of people with rheumatoid arthritis stop work because of the disease. Rheumatoid arthritis is associated with a reduced life expectancy; for example, a 50-year-old woman with rheumatoid arthritis is expected to die 4 years earlier than a 50-year-old woman without rheumatoid arthritis.

2.7   The aim of treatment is to induce remission of disease, control pain and inflammation, and reduce or prevent joint damage, disability and loss of function, thereby improving quality of life. Treatment involves a combination of pharmacological and non-pharmacological interventions. Pharmacological treatment includes various combinations of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids and disease modifying anti-rheumatic drugs (DMARDs). DMARDs reduce symptoms and slow progression of structural damage. DMARDs may be classified as conventional (for example methotrexate or sulfasalazine) or biological. Biological DMARDs include, but are not limited to, the TNF inhibitors adalimumab, etanercept and infliximab, as well as rituximab and abatacept. Non-pharmacological interventions include orthopaedic surgery, physiotherapy and occupational therapy.

2.8   NICE clinical guideline 79 (2009) recommends the use of a combination of conventional DMARDs (including methotrexate and at least one other conventional DMARD plus short-term glucocorticoids) as first-line treatment, beginning ideally within 3 months of the onset of persistent symptoms. When combination therapy is not appropriate (for example, in people with methotrexate intolerance), the guideline recommends monotherapy with a conventional DMARD with quick escalation to a clinically effective dose.

2.9   The TNF inhibitors adalimumab, etanercept or infliximab, (NICE technology appraisal guidance 130 [2007]) and certolizumab pegol (NICE technology appraisal guidance 186 [2010]), each in combination with methotrexate, are recommended as options for the treatment of adults with active rheumatoid arthritis who have a disease activity score (DAS28) greater than 5.1 and whose rheumatoid arthritis has failed to respond to at least two conventional DMARDs, including methotrexate. If a patient does not tolerate methotrexate or if treatment with methotrexate is considered to be inappropriate, adalimumab, etanercept and certolizumab pegol may be given as monotherapy. Treatment should be withdrawn if response is not adequate within 6 months (as defined by an improvement in DAS28 score of more than 1.2 points) or if response is not maintained. Response to treatment should be monitored at least every 6 months. An alternative TNF inhibitor may be considered when treatment with a first TNF inhibitor is withdrawn because of an adverse event before the initial 6-month assessment.

2.10   Several tools have been developed to assess the response to treatment in rheumatoid arthritis. The American College of Rheumatology (ACR) response criteria (ACR20, 50 and 70) require a specified improvement in the percentage (20%, 50% or 70% respectively) of tender joints, swollen joints, global assessments, pain, disability and circulating inflammatory markers (for example, erythrocyte sedimentation rate). 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 greater than 5.1 indicates high disease activity, between 3.2 and 5.1 moderate disease activity, and less than 3.2 low disease

activity. A score of less than 2.6 indicates disease remission. An improvement in DAS28 score of 0.6 or less is considered a poor response, and improvements greater than 1.2 points indicate a good response. The European League Against Rheumatism (EULAR) response criteria are based on the DAS measure. The Stanford Health Assessment Questionnaire (HAQ) comprises one component of the ACR criteria and scores the ability to perform daily activities; it ranges from 0 (least disability) to 3 (most severe disability). The modified Sharp score measures joint damage as assessed radiographically, and is scored on joint-space narrowing and erosions.

3   The technologies

Adalimumab

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

3.2   Common adverse effects of adalimumab therapy include injection-site reactions and infections. Adalimumab is contraindicated in people with moderate to severe heart failure, those with active

tuberculosis or those with other severe or opportunistic infections. Before initiating therapy, physicians should evaluate people for both active and inactive (latent) tuberculosis infection. For full details of adverse effects, contraindications, special warnings and precautions for use, see the SPC.

3.3   Adalimumab is administered at a dose of 40 mg every other week via subcutaneous injection. In monotherapy, if people 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', edition 59 [BNF59]). 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, Pfizer) is a recombinant human TNF receptor fusion protein. It interferes with the inflammatory cascade by binding to TNF, thereby blocking its interaction with cell-surface receptors. Etanercept has a marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis when the response to DMARDs, including methotrexate, has been inadequate. Etanercept is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. The SPC states that etanercept should be given in combination with methotrexate, except when methotrexate is not tolerated or is considered inappropriate.

3.5   Common adverse effects of etanercept therapy include injection-site reactions, infections and allergic reactions. Etanercept is contraindicated in people with sepsis or risk of sepsis, and those with other active infections. Before initiating therapy, physicians should evaluate people for both active and inactive (latent)

tuberculosis infection. For the full details of adverse effects, contraindications, special warnings and precautions for use, 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. The net price for a 25-mg vial is £89.38 (excluding VAT; BNF59). The annual cost of etanercept using either 52 once-weekly doses of 50 mg or 104 twice-weekly doses of 25 mg 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, thereby neutralising its activity. Infliximab has a marketing authorisation in combination with methotrexate for the treatment of active rheumatoid arthritis when the response to DMARDs, including methotrexate, has been inadequate, and for people with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

3.8 Common adverse effects of infliximab therapy include acute infusion-related reactions, infections and delayed hypersensitivity reactions. Infliximab is contraindicated in people with moderate or severe heart failure, and those with tuberculosis or other severe or opportunistic infections. For full details of adverse effects, contraindications, special warnings and precautions for use, see the SPC.

3.9 Infliximab is administered at a dose of 3 mg/kg by intravenous infusion over 2 hours at an initial infusion (week 0) and then at weeks 2 and 6, and thereafter every 8 weeks. If there is an inadequate response or a loss of response after 12 weeks, physicians may consider increasing the dose of infliximab

stepwise 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. The net price for a 100-mg vial is £419.62 (excluding VAT; BNF59). The annual drug costs associated with infliximab vary according to body weight and the number of infusions required. Assuming an average weight of 70 kg and a dose of 3 mg/kg, each dose of infliximab requires three vials at a cost of £1259. 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. Costs may vary in different settings because of negotiated procurement discounts.

Rituximab

3.10   Rituximab (MabThera, Roche Products) is a genetically engineered chimeric monoclonal antibody that depletes the B-cell population by targeting cells bearing the CD20 surface marker. Rituximab has a marketing authorisation for use in combination with methotrexate for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other DMARDs including one or more TNF inhibitor therapies.

3.11   Common adverse effects of rituximab therapy include infusion reactions and infections. Rituximab is contraindicated in people with severe heart failure or severe, uncontrolled cardiac disease, and those with active, severe infections. For full details of undesirable effects, contraindications, special warnings and precautions for use see the SPC.

3.12   A course of rituximab consists of two 1000-mg intravenous infusions given 2 weeks apart. The SPC specifies that courses of rituximab should be given at intervals of no less than 16 weeks. The cost to the NHS of 10-ml and 50-ml vials of rituximab is

£174.63 and £873.15 respectively (excluding VAT; BNF59). The cost of a single course of rituximab is £3492 (two 1000-mg intravenous infusions). Costs may vary in different settings because of negotiated procurement discounts.

Abatacept

3.13   Abatacept (Orencia, Bristol-Myers Squibb) is a selective T-cell co-stimulation modulator that blocks a key co-stimulatory signal required for T-cell activation. Abatacept has a marketing authorisation for use in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adults who have had an insufficient response or intolerance to other DMARDs, including at least one TNF inhibitor.

3.14   Common adverse effects of abatacept therapy include infections, including sepsis and pneumonia. Abatacept is contraindicated in people with severe, uncontrolled infections, and opportunistic infections. Before initiating therapy, physicians should evaluate people for both active and inactive (latent) tuberculosis infection. For full details of undesirable effects, contraindications, special warnings and precautions for use, see the SPC.

3.15   Abatacept is administered as a 30-minute intravenous infusion. After an initial infusion (week 0), it is repeated at week 2, week 4 and every 4 weeks thereafter. People require a total of 14 infusions in the first year and 13 infusions in subsequent years. Abatacept is available in 250-mg vials at a cost of £242.17 per vial (excluding VAT; BNF59). The dose of abatacept depends on body weight: people weighing less than 60 kg, 60–100 kg and over 100 kg require 500 mg, 750 mg and 1000 mg respectively. The annual drug costs associated with abatacept vary according to body weight and the number of infusions required. For a person weighing between 60 and 100 kg, the annual drug cost will be £10,171.14 in the first year and £9444.63 in subsequent years.

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   The Assessment Group completed a systematic review of the efficacy of the technologies for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. Thirty-five studies met the criteria for inclusion. Five of these were randomised controlled trials (RCTs), one was a non-randomised controlled study, and 29 were included in the Assessment Report as uncontrolled studies (including two long-term RCT extensions). Three of the RCTs were subsequently excluded from the review by the Assessment Group because the studies included regimens outside of their marketing authorisation or the comparator was not considered relevant. A sixth RCT (the SUNRISE trial) was identified but not included in the systematic review because the trial was unpublished and data from the manufacturer were not provided in time for inclusion in the analyses. The two included RCTs compared rituximab with placebo (the REFLEX trial) and abatacept with placebo (the ATTAIN trial), with all people in these two RCTs also receiving ongoing methotrexate or other conventional DMARDs. This section summarises the outcomes for clinical effectiveness in terms of ACR 20, 50 and 70 response rate and improvement in DAS28 and/or HAQ score for the studies identified in the Assessment Group's systematic review.

Adalimumab

4.1.2   For adalimumab, the Assessment Group identified five
         uncontrolled studies with durations of follow-up ranging from 3 to
         12 months. Four studies had small sample sizes ranging from 24
         to 41. The fifth, a multicentre study, included 899 people. The
         Assessment Group did not pool the results because of
         substantial clinical and statistical heterogeneity between studies.
         Three studies reported ACR 20, 50 and 70 response rates
         ranging from 46% to 75%, 27% to 50% and 13% to 33%
         respectively. Four studies reported mean improvements in
         DAS28 score ranging from 1.30 to 1.90 when compared with
         pre-treatment values. Three studies reported mean
         improvements in HAQ ranging from 0.21 to 0.48 when compared
         with pre-treatment values. None of the studies assessed joint
         damage or quality of life.

Etanercept

4.1.3   For etanercept, the Assessment Group identified seven
         uncontrolled studies with durations of follow-up ranging from
         3 months to over 9 months. Sample sizes ranged from 25 to
         201. The results were not pooled because of substantial clinical
         and statistical heterogeneity between studies. Four studies
         reported ACR 20, 50 and 70 response rates ranging from 38% to
         72%, 18% to 21% and 8% to 20% respectively. Four studies
         reported mean improvements in DAS28 score ranging from 0.47
         to 1.80 when compared with pre-treatment values. Three studies
         reported mean improvements in HAQ score ranging from zero to
         0.45 when compared with pre-treatment values. None of the
         studies assessed joint damage or quality of life.

Infliximab

4.1.4   For infliximab, the Assessment Group identified three
         uncontrolled studies, each with a small sample size ranging from
         20 to 24. The Assessment Group could not determine the

duration of follow-up in the studies. None of the studies reported
ACR response criteria or quantitative results of changes in
DAS28 and HAQ scores, or assessed joint damage or quality of
life.

TNF inhibitors as a group

4.1.5   Eight studies were identified. None provided separate outcome
data for individual TNF inhibitors. One non-randomised
controlled study compared TNF inhibitors with rituximab (see
section 4.1.10) and seven studies had no control group. The
duration of follow-up in the studies ranged from 3 months to
4 years and sample sizes ranged from 70 to 818. One study
reported ACR 20, 50 and 70 response rates of 46%, 26% and
7% respectively. A different study reported a mean improvement
in HAQ score of 0.11 when compared with pre-treatment values.
Three studies reported mean improvements in DAS28 score
ranging from 0.88 to 1.00 when compared with pre-treatment
values. No studies assessed joint damage or quality of life.

Rituximab

4.1.6   The Assessment Group identified one RCT (REFLEX, n = 517),
as well as the trial's long-term extension. The REFLEX trial
compared rituximab with placebo (with ongoing methotrexate in
both groups) in people who had had an inadequate response to
one or more TNF inhibitors. The primary outcome in the
REFLEX trial was ACR 20 response rate at 6 months. The
REFLEX trial reported statistically significant differences
favouring the rituximab group for ACR 20, 50 and 70 response
rates. For the rituximab group the values were 51%, 27% and
12%, and for the placebo group these were 18%, 5% and 1%
respectively (for all comparisons $p < 0.0001$). A statistically
significant difference in mean improvement in DAS28 was
reported (1.9 in the rituximab group compared with 0.4 in the
placebo group, $p < 0.0001$). A statistically significant difference

was also reported for mean improvement in HAQ score (0.40 in the rituximab group compared with 0.10 in the placebo group, p < 0.0001). The long-term observational extension of the REFLEX trial included people who had received up to three courses of rituximab. This reported that people receiving further courses of rituximab responded in terms of ACR comparably to patients who received rituximab in the randomised phase of the RCT.

4.1.7 The SUNRISE trial (n = 559) compared the safety and efficacy of one course of rituximab with two courses of rituximab. This trial was not included in the Assessment Group's analysis, but the results were later submitted by consultees. The study reported that of the people who had been randomised to a second course of rituximab at week 24, 54% had an ACR 20 at 48 weeks, whereas of those who had been randomised to placebo, 45% had an ACR 20 at 48 weeks (p = 0.02). A statistically significant difference in mean improvement in DAS28 was also reported (1.9 in the rituximab retreatment group compared with 1.5 in the placebo retreatment group, p < 0.01).

4.1.8 In addition to the REFLEX trial, the Assessment Group identified one non-randomised controlled study comparing TNF inhibitors with rituximab (see section 4.1.10), five uncontrolled studies and a pooled analysis combining data from the REFLEX trial, its long-term extension and other studies. Durations of follow-up in the uncontrolled studies ranged from 6 months to 1 year and sample sizes ranged from 20 to 158. The Assessment Group could not determine how many people the pooled analysis included. One study reported ACR 20, 50 and 70 response rates of 65%, 33% and 12% respectively. Another study reported a mean improvement in DAS of 1.61 when compared with pre-treatment values. None of the uncontrolled studies assessed improvement in HAQ score, joint damage or quality of life. The

pooled analysis included people who had had up to five courses of rituximab treatment; this study showed clinical outcomes similar to those seen for rituximab in the REFLEX trial.

Abatacept

4.1.9   The Assessment Group identified one RCT (ATTAIN) and its long-term extension. The ATTAIN trial compared abatacept with placebo (with ongoing DMARDs in both groups) in people with an inadequate response to one or more TNF inhibitors. The co-primary outcomes in the ATTAIN trial were ACR 20 response rate and change in HAQ score at 6 months. The ATTAIN trial reported statistically significant differences in response rates for abatacept compared with placebo. The values were 50% compared with 20% ($p < 0.001$) for ACR 20, 20% compared with 4% ($p < 0.001$) for ACR 50, and 10% compared with 2% ($p < 0.01$) for ACR 70. The ATTAIN trial also reported a statistically significant improvement in mean DAS28 score favouring the abatacept group (1.98 compared with 0.71, $p < 0.001$). In addition, the ATTAIN trial reported a statistically significant difference in mean improvement in the HAQ score favouring the abatacept group (0.45 compared with 0.11, $p < 0.001$). The long-term extension of the ATTAIN trial followed people for up to 5 years. This analysis showed that among people continuing on abatacept, clinical outcomes in terms of ACR response rates were comparable to those seen for abatacept in the randomised phase of the RCT. Further data were provided from a large prospective uncontrolled study (ARRIVE, n = 1046); this study reported an improvement in DAS28 of 2.00 when compared with pre-treatment values.

Comparative effectiveness

4.1.10   The Assessment Group did not identify any randomised controlled trials directly comparing the five technologies, or trials comparing the technologies with other biological DMARDs or

conventional DMARDs not previously tried by study participants. One non-randomised controlled study (n = 318) compared switching from a TNF inhibitor to rituximab with switching to an alternative TNF inhibitor. When a switch occurred because the first TNF inhibitor was not effective, the mean change in DAS28 score was reported to be significantly higher in the rituximab group (mean change -1.34) compared with the group who received an alternative TNF inhibitor (mean change -0.93) (p = 0.03).

4.1.11 The Assessment Group conducted an adjusted indirect comparison of rituximab and abatacept using data from placebo-controlled trials that included similar populations. The analysis suggested no statistically significant differences in response rates between abatacept and rituximab for ACR 20 (relative risk 1.12, 95% confidence interval [CI] 0.68 to 1.84), ACR 50 (relative risk 1.00, 95% CI 0.33 to 2.98) and ACR 70 (relative risk 1.80, 95% CI 0.24 to 13.35).

Subgroup analyses

4.1.12 The Assessment Group identified evidence for adalimumab, etanercept and abatacept that compared response to treatment according to the reason for withdrawal of the first TNF inhibitor. The evidence compared primary non-responses (when the disease had never responded to treatment with a TNF inhibitor) with secondary non-responses (when there was a reduction in disease response to the first TNF inhibitor). The majority of analyses suggested no statistically significant differences in response according to reason for withdrawal of the first TNF inhibitor. However, two analyses of adalimumab showed statistically significant higher response rates for ACR 20 (pooled estimate risk difference -0.20, 95% CI -0.37 to -0.02) and ACR 50 (pooled estimate risk difference -0.12, 95% CI -0.20 to -0.04) when the first TNF inhibitor had been withdrawn because

of a secondary non-response. Data for abatacept from the ATTAIN long-term extension study also suggested that in a non-intention-to-treat analysis of people who had a change in HAQ greater than 0.3 at 6 months, the proportion whose disease responded was higher among people who had experienced a secondary non-response than among those who experienced a primary non-response (risk difference -0.15, 95% CI -0.28 to -0.02). However, registry data for the TNF inhibitors as a group suggested that, when measured as EULAR response rates at 3 months, and assuming missing observations represented non-responders, there were statistically significantly higher response rates among people who stopped their first TNF inhibitor because of primary non-response (risk difference 0.30, 95% CI 0.13 to 0.46). No specific data for infliximab and rituximab were identified.

4.1.13   Evidence for the influence of the presence of auto-antibodies (that is, rheumatoid factor and anti-CCP antibody status) on effectiveness was available only for rituximab, from the REFLEX trial. The trial reported no statistically significant differences in relative treatment effect by rheumatoid factor status. However, absolute response rates were lower in both the rituximab and the placebo groups for people who were rheumatoid factor-negative than those who were rheumatoid factor-positive. When participants were stratified according to both rheumatoid factor and anti-CCP antibody status, the data suggested a greater treatment response in people who were either rheumatoid factor-positive or anti-CCP antibody-positive than in those who were negative for both rheumatoid factor and anti-CCP. The Assessment Group noted that this retrospective analysis should be treated with caution.

4.2   Cost effectiveness

Published literature

4.2.1   The Assessment Group identified four published economic analyses – two of rituximab and two of abatacept – that met the criteria for inclusion in the systematic review. All four used a decision analytic model. Three of the studies carried out a cost–utility analysis and reported results in terms of costs per quality-adjusted life years (QALYs) gained. The remaining study (of abatacept) reported results in terms of costs per additional case of 'low disease activity state' gained (DAS28 less than 2.6) and costs per additional remission gained (DAS28 up to 3.2). The Assessment Group could not perform a direct comparison of the incremental cost-effectiveness ratios (ICERs) from these studies because of different specifications of the models, including treatment sequence, time horizon, perspective and country of origin.

Manufacturers' submissions

4.2.2   All five manufacturers provided economic analyses to support their submissions. One analysis (etanercept, Pfizer) was provided only as a narrative summary and not as a fully executable model. All submissions were based on cost–utility analyses run over a lifetime horizon and from the perspective of the healthcare provider. All but one submission (abatacept, Bristol-Myers Squibb) used conventional DMARDs as the base-case comparator.

Abbott Laboratories (adalimumab)

4.2.3   Abbott Laboratories developed a discrete-event simulation model and performed a cost–utility analysis of adalimumab, etanercept, infliximab, rituximab and abatacept (all of which were considered in combination with methotrexate), each in

comparison with conventional DMARDs. The model also compared adalimumab with conventional DMARDs only, and the sequence of adalimumab followed by rituximab compared with each of the remaining biological DMARDs. The model simulated people with profiles based on the baseline characteristics of people in the British Society for Rheumatology Biologics Register. The model included adverse events. It also included a continuation rule using ACR 50 response to determine whether a person continued therapy after an initial trial period.

4.2.4   Response to treatment was based on ACR response rates mapped to a change in HAQ score. The manufacturer derived the ACR response rates from a mixed treatment comparison of 34 studies and assumed that the responses were equal across all TNF inhibitors (that is, that the response to adalimumab was not different from other TNF inhibitors). To map ACR to HAQ, the change in HAQ score associated with each ACR response category was calculated from adalimumab clinical trial data in which both HAQ and ACR were measured. The model assumed that when people discontinued treatment with a TNF inhibitor, the initial effect of treatment was lost. The model assumed that disease progressed while on treatment and that it progressed at a constant annual rate to a greater degree on conventional than on biological DMARDS. This was modelled in terms of an annual increase in HAQ score of 0.030 for biological DMARDs, 0.045 for conventional DMARDs and 0.060 for rescue therapy. To convert HAQ scores to EuroQol (EQ-5D) scores, the manufacturer used a non-linear mapping mechanism estimated using EQ-5D data collected in trials of tocilizumab (another biological DMARD).

4.2.5   Costs included drug acquisition, administration, monitoring and hospitalisation (including joint replacement surgery). The cost of administering intravenous drugs was estimated to be £462 for

each infusion, based on the Healthcare Resource Group 2007/08 tariff. The manufacturer of adalimumab assumed that administering subcutaneous drugs would require 3 hours of nurse training incurring a one-off cost of £129. The manufacturer assumed retreatment with rituximab would occur every 9 months. This assumption was tested in a sensitivity analysis using a retreatment schedule of every 6 months.

4.2.6 The base-case analysis showed that for rituximab in comparison with conventional DMARDs, the incremental QALY gain was 1.375 at an incremental cost of £15,100, giving an ICER of £10,986 per QALY gained. When it was assumed that treatment with rituximab was repeated every 6 months instead of every 9 months, the ICER increased from £10,986 per QALY gained in the base case to £15,856 per QALY gained. The base-case analysis showed that for adalimumab or etanercept in comparison with conventional DMARDs, the QALY gain was 1.467 at an incremental cost of £23,423, giving an ICER of £15,962 per QALY gained. For infliximab and abatacept (each in comparison with conventional DMARDs), the QALY gains were 1.451 and 1.136 respectively. The incremental costs were £31,241 and £34,188 respectively, giving ICERs of £21,529 and £30,104 per QALY gained. From the data presented, the ICER for adalimumab or etanercept compared with rituximab, given every 9 months, could be calculated to be £83,230 per QALY gained. Infliximab was dominated by adalimumab and etanercept, and abatacept was dominated by rituximab. From the data presented, the ICER for adalimumab or etanercept in comparison with rituximab given every 6 months could be calculated to be £16,280 per QALY gained. Infliximab was dominated by adalimumab and etanercept, and abatacept was dominated by rituximab. Univariate sensitivity analyses (altering one variable at a time) suggested that the model was most sensitive to the HAQ score at the start of treatment, change in

HAQ score while on treatment (that is, underlying disease
progression), assumptions regarding the loss or maintenance of
initial treatment effect upon stopping treatment, the way in which
HAQ was mapped to EQ-5D and the dosing schedule of
rituximab.

Pfizer (etanercept)

4.2.7 Pfizer presented the results of a Markov model with a 6-month
cycle. The model compared three strategies: treatment with two
sequential TNF inhibitors, treatment with a TNF inhibitor followed
by a conventional DMARD and treatment with a TNF inhibitor
followed by rituximab. The manufacturer did not include
abatacept in the economic analyses. Baseline patient
characteristics reflected those of the patients in the TEMPO trial
(an RCT of etanercept in people whose rheumatoid arthritis had
had an inadequate response to conventional DMARDs). The
model included serious adverse events. The base-case model
included a continuation rule using HAQ score mapped from
DAS28 to determine whether a person continued therapy after
an initial trial period.

4.2.8 The manufacturer defined response to treatment in terms of
mean change in HAQ score in people treated with a second TNF
inhibitor after primary non-response, secondary loss of response
or intolerance of their first TNF inhibitor. The data were taken
from a trial of adalimumab; the values used were -0.44, -0.51
and -0.55 respectively. The manufacturer estimated the mean
changes in HAQ score for those treated with rituximab (-0.40)
from the REFLEX trial; all were unadjusted estimates of absolute
treatment effect observed in the trial. The effect of conventional
DMARDs following failure of a TNF inhibitor was assumed to be
zero, based on data from the British Society for Rheumatology
Biologics Register. The model included underlying disease
progression while on treatment, modelled in terms of worsening

HAQ score over time. The manufacturer assumed that while on treatment with biological DMARDs the HAQ score remained unchanged (that is, disease did not progress/worsen) but that while on conventional DMARDs the HAQ score changed at a rate of 0.075 per 6-month cycle from the first 6 months up to 3 years, and then 0.10 per 6-month cycle from year 3 onwards. The manufacturer used a linear mapping mechanism to convert HAQ scores to EQ-5D scores during each model cycle.

4.2.9   Costs included drug acquisition and administration, and costs associated with hospitalisation, outpatient visits, primary care visits, investigations and monitoring. The cost of administration was unclear. Rituximab was assumed to be provided once every 6 months.

4.2.10   The manufacturer presented the base-case results for a range of assumptions regarding changes in HAQ score for both TNF inhibitors and conventional DMARDs. Total differences in costs and QALYs were presented only for people who had switched from one TNF inhibitor to another because of an adverse event. The ICER for TNF inhibitors compared with conventional DMARDs was £15,294 per QALY gained when switching as a result of primary non-response and £14,501 per QALY gained when switching as a result of secondary loss of response. The ICER for TNF inhibitors compared with rituximab was £19,077 per QALY gained and £16,225 per QALY gained following switching for primary non-response and secondary loss of response respectively. The manufacturer presented no probabilistic sensitivity analysis results in the submission.

Schering-Plough (infliximab)

4.2.11   Schering-Plough developed a patient-level simulation model and performed a cost–utility analysis of infliximab compared with adalimumab, etanercept, rituximab, and abatacept, all of which were considered in combination with methotrexate. Comparisons

were also made with conventional DMARDs only, and of the TNF inhibitors followed by rituximab. The model simulated people based on the characteristics at baseline of participants in the GO-AFTER trial (a trial of the TNF inhibitor golimumab in people with an inadequate response to a previous TNF inhibitor). The model did not include adverse events. The base-case model included a continuation rule using EULAR response to determine whether a person continued therapy after an initial trial period.

4.2.12 The manufacturer determined response to treatment by a multi-step process. First, baseline EULAR response rates from the British Society for Rheumatology Biologics Register were converted to baseline ACR response rates using an algorithm derived from the GO-AFTER trial. Treatment-specific ACR response rates were generated from the results of a mixed treatment comparison of RCTs of biological DMARDs. These ACR response rates were then converted back to EULAR response rates using the GO-AFTER algorithm. The EULAR response categories were then mapped to EQ-5D using algorithms derived from British Society for Rheumatology Biologics Register data that indirectly calculated EQ-5D from HAQ. In addition to the initial response to treatment, the model included underlying disease progression while on treatment, modelled using change in HAQ score over time. The manufacturer assumed that people treated with biological DMARDs experienced no progression in their disease whereas the condition deteriorated at a rate of 0.042 per year in people treated with conventional DMARDs.

4.2.13 Costs included drug acquisition and administration, monitoring and hospitalisation. It was assumed that in 63% of cases sharing of vials resulted in no wastage of unused infliximab. The cost of administering infused drugs was assumed to be £162.12, based on the cost given in the assessment report for NICE technology

appraisal guidance 130 and adjusted for inflation. The manufacturer presented two analyses for rituximab: one assuming retreatment every 6 months and the other every 9 months.

4.2.14   The base-case analysis showed that for rituximab in comparison with conventional DMARDs, the incremental QALY gain was 0.65 at an incremental cost of £11,325, giving an ICER of £17,422 per QALY gained (assuming 9-month retreatment intervals). Assuming retreatment with rituximab every 6 months, the ICER for rituximab compared with conventional DMARDs was £27,161 per QALY gained. The QALY gains for adalimumab, etanercept and infliximab were 0.66, 0.62 and 0.65 respectively. The respective incremental costs were £23,129, £22,257 and £18,628, giving ICERs of £35,138, £35,898 and £28,661 per QALY gained compared with conventional DMARDs. The strategy comparing abatacept with conventional DMARDs resulted in an incremental QALY gain of 0.63 for an incremental cost of £28,205, producing an ICER of £44,795 per QALY gained. From the data presented, the ICER for adalimumab in comparison with rituximab given every 9 months could be calculated to be £1,186,230 per QALY gained. Etanercept and abatacept were dominated by rituximab, and infliximab was extendedly dominated by rituximab. When rituximab was assumed to be given every 6 months, the ICER for adalimumab compared with rituximab could be calculated to be £553,700 per QALY gained. Etanercept and abatacept were dominated by rituximab, and infliximab was extendedly dominated by rituximab.

Roche Products (rituximab)

4.2.15   Roche Products developed a patient-level simulation model and performed a cost–utility analysis of rituximab compared with adalimumab, etanercept, infliximab and abatacept, all of which

were followed by a sequence of conventional DMARDs. The manufacturer also compared rituximab with conventional DMARDs alone. The model simulated people whose profiles were based on baseline characteristics of participants in the REFLEX trial. The manufacturer did not include adverse events.

4.2.16 Response to treatment was defined in terms of ACR response rates mapped to a change in HAQ score. ACR response rates were derived from two sources: a mixed treatment comparison of RCTs of TNF inhibitors in people whose rheumatoid arthritis had had an inadequate response to conventional DMARDs, and an indirect comparison of the abatacept ATTAIN trial and the rituximab REFLEX trial. The manufacturer then adjusted (reduced by 30%) the results of the mixed treatment comparison to reflect a lower response to treatment observed in people who had had an inadequate response to a first TNF inhibitor. The manufacturer converted ACR to HAQ using an algorithm from data in the REFLEX trial. When people discontinued treatment, the manufacturer assumed that the initial effect of treatment was lost. The model included both initial response to treatment and underlying disease progression while on treatment, each modelled as changes in HAQ score. It was assumed that while a person was on a biological DMARD there was no change in HAQ score. People on conventional DMARDs experienced an increase (worsening) in HAQ score of 0.0225 per 6-month cycle and people receiving palliative care experienced an increase in HAQ score of 0.03 per 6-month cycle. The manufacturer mapped HAQ scores to EQ-5D scores using a non-linear mapping mechanism derived from data from the tocilizumab trials.

4.2.17 The costs included drug acquisition and administration, monitoring and hospitalisation. The cost of administration was assumed to be £162 per infusion and this included all

premedication and monitoring costs. Subcutaneous drugs incurred monitoring and premedication costs of £1268 per year and administration costs (£136 for etanercept and £68 for adalimumab) to allow for the 10% of people who will receive injections from a district nurse. Retreatment with rituximab was assumed to occur every 8.7 months. This assumption was tested in sensitivity analysis.

4.2.18   The base-case analysis showed that for rituximab compared with conventional DMARDs, the incremental QALY gain was 1.071 with an incremental cost of £5,685, giving an ICER of £5,311 per QALY gained. Assuming retreatment with rituximab every 6 months, the ICER for rituximab compared with conventional DMARDs increased from £5,311 to £10,876 per QALY gained. The strategies comparing rituximab with etanercept, infliximab or abatacept showed rituximab to be both more effective and less costly. The strategy comparing rituximab with adalimumab showed rituximab to be less effective and less costly, with a QALY loss of 0.044 and an incremental reduction in cost of £13,551, resulting in an ICER for adalimumab compared with rituximab of £310,771 per QALY gained.

Bristol-Myers Squibb (abatacept)

4.2.19   Bristol-Myers Squibb developed a patient-level simulation model and performed a cost–utility analysis of abatacept compared with rituximab, both followed by infliximab. They also modelled abatacept compared with a basket of TNF inhibitors (reflecting the proportion of each drug's market share), both followed by another basket of TNF inhibitors. The model simulated people whose profiles were based on the baseline characteristics of participants in the ATTAIN trial. The model included adverse events for the first 6 months of treatment.

4.2.20   The manufacturer defined response to treatment in terms of mean change in HAQ score. Estimates for rituximab (0.38) and

abatacept (0.42) were based on a mixed treatment comparison of the ATTAIN and REFLEX trials. Estimates for TNF inhibitors (0.21) were taken from an analysis of data from the British Society for Rheumatology Biologics Register completed by NICE's Decision Support Unit for NICE technology appraisal guidance 130. The manufacturer assumed that people who discontinued treatment lost the initial effect of treatment. Underlying progression of disease while on treatment was modelled using HAQ score. For people treated with abatacept, disease was assumed to improve over time, with an annual improvement (HAQ score decrease) of 0.0729 in analyses compared with rituximab, and of 0.013 in analyses compared with TNF inhibitors. For the other biological treatments, the manufacturer assumed that disease worsened at an annual HAQ score increase of 0.012. A linear mapping mechanism was used to convert HAQ scores to Health Utilities Index Mark 3 scores during each model cycle.

4.2.21   Costs included drug acquisition and administration, monitoring, hospitalisation (including that for joint replacement surgery), outpatient visits and costs associated with adverse events. Different administration costs were used for the different drugs requiring intravenous infusion. For abatacept the cost per infusion was £141.83 based on the assessment report for NICE technology appraisal guidance 130 and adjusted for inflation to 2007/2008; for rituximab and infliximab the cost was £284.73 based on NHS reference costs. For subcutaneous treatments a one-off cost of £25.66 was incurred for training. Retreatment with rituximab occurred once every 6 months.

4.2.22   The base-case analysis showed that in comparison with the basket of TNF inhibitors, the QALY gain for abatacept was 0.47 at an incremental cost of £10,888, giving an ICER of £23,019 per QALY gained. The strategy comparing abatacept with

rituximab resulted in an incremental QALY gain of 0.45 for an incremental cost of £9238, producing an ICER of £20,438 per QALY gained. Sensitivity analyses showed that when it was assumed that there were no differences in the underlying progression of disease between the biological DMARDs (that is, a worsening of HAQ score of 0.012 per year was assumed for each biological treatment), the ICER for abatacept was £40,534 per QALY gained compared with rituximab, and £27,871 per QALY gained compared with TNF inhibitors.

The Birmingham Rheumatoid Arthritis Model

4.2.23   The Assessment Group carried out an independent economic analysis using the Birmingham Rheumatoid Arthritis Model. The model simulated people with rheumatoid arthritis based on the baseline characteristics of people in the British Society for Rheumatology Biologics Register. The model sampled people individually and compared each of the technologies (followed by a sequence of conventional DMARDs) with one another or with conventional DMARDs alone. It allowed for two stages of stopping treatment early. The first stage represented the possibility of stopping treatment after 6 weeks (assumed to be because of toxicity) and the second stage represented stopping treatment at between 6 and 24 weeks (assumed to be because of either toxicity or lack of efficacy). The model did not allow for stopping rituximab early because it was necessary to model the full costs of each cycle of treatment.

4.2.24   The Assessment Group modelled response to treatment using HAQ, with changes in HAQ scores calculated using a multiplier that represents a proportional change from a given baseline HAQ score. The respective HAQ multipliers for rituximab and abatacept were derived from the REFLEX and ATTAIN trials. The HAQ multipliers for adalimumab and etanercept were derived from uncontrolled studies. In the absence of data, the

HAQ multiplier for infliximab was assumed to be the same as for etanercept. The Assessment Group assumed that when people discontinue treatment, they lose the initial effect of treatment. In addition to the initial response to treatment, the model assumed that underlying disease progresses during treatment. This was modelled by increases in HAQ score. In the base-case analysis, it was assumed that HAQ score remains constant for a person treated with a biological DMARD, but increases (worsens) for people treated with conventional DMARDs or palliative care. The annual HAQ score increase was 0.045 for conventional DMARDs and 0.06 for palliative care. The Assessment Group used a non-linear equation to convert HAQ scores to EQ-5D scores.

4.2.25   Costs included drug acquisition and administration plus monitoring. The administration cost for drugs requiring infusion was assumed to be £141.83. Costs for hospitalisation and joint replacement were estimated using a cost per unit HAQ score. Retreatment with rituximab was assumed to occur every 8.7 months.

4.2.26   The base-case analysis showed that for rituximab compared with conventional DMARDs, the incremental QALY gain was 0.96 with an incremental cost of £20,400, giving an ICER of £21,100 per QALY gained. The QALY gains for adalimumab, etanercept and infliximab were 0.75, 0.67 and 0.67 respectively. The respective incremental costs were £25,800, £26,100 and £24,000, giving ICERs (rounded to the nearest £100) of £34,300, £38,900 and £36,100 per QALY gained. The strategy comparing abatacept with conventional DMARDs resulted in an incremental QALY gain of 1.15 for an incremental cost of £44,000, producing an ICER of £38,400 per QALY gained. Compared with the TNF inhibitors, rituximab was shown to be both less costly and more effective. The ICER for abatacept in

comparison with rituximab was £130,600 per QALY gained. The strategies comparing abatacept with adalimumab, etanercept and infliximab resulted in ICERs of £46,400 per QALY gained, £37,800 per QALY gained and £41,700 per QALY gained respectively.

4.2.27 Scenario analyses were undertaken to explore the impact of varying single assumptions within the model. These included: the time on treatment with the various therapies; the rituximab treatment interval; the efficacy of conventional DMARDs after the failure of a TNF inhibitor; the change in HAQ score while on biological DMARDs; the proportion of people stopping treatment early; the inclusion of costs of adverse events and palliation; and assumptions related to the equation used to map HAQ score to EQ-5D scores. These analyses indicated that the results are subject to considerable uncertainty.

4.2.28 Assuming that there was underlying progression of disease modelled as an increase in HAQ score of 0.03 per year while on biological DMARDs increased the ICERs for the comparison with conventional DMARDs. The ICERs were £61,300 per QALY gained for adalimumab, £76,300 per QALY gained for etanercept, £68,900 per QALY gained for infliximab, £46,000 per QALY gained for rituximab and £63,300 per QALY gained for abatacept.

4.2.29 Assuming conventional DMARDs were no more effective than placebo reduced the base-case ICERs for the comparison with conventional DMARDs to £28,100 per QALY gained for adalimumab, £31,100 per QALY gained for etanercept, £28,800 per QALY gained for infliximab, £16,300 per QALY gained for rituximab and £32,100 per QALY gained for abatacept. An incremental analysis demonstrated that rituximab was shown to be both less costly and more effective than each of the TNF

inhibitors. The ICER for abatacept in comparison with rituximab was £158,000 per QALY gained.

4.2.30 Using the same proportion of people stopping early as was used in the Roche model (based on failure to achieve an ACR 20 response) reduced the base-case ICERs for the comparison with conventional DMARDs to £22,200 per QALY gained for adalimumab, £23,400 per QALY gained for etanercept, £26,200 per QALY gained for infliximab, £19,500 per QALY gained for rituximab, and £24,100 per QALY gained for abatacept. A detailed analysis of the costs and QALYs provided as an addendum by the Assessment Group showed that abatacept (with costs of £70,500 and 2.82 QALYs) was dominated by rituximab (with costs of £62,300 and 2.91 QALYs). Adalimumab, etanercept and infliximab were associated with lower costs than rituximab (£61,700, £60,300, and £62,300, respectively). However, they were also associated with fewer QALYs (2.56, 2.47 and 2.49, respectively). In an incremental analysis, rituximab had the lowest ICER, with the other treatments being either dominated or extendedly dominated.

4.2.31 Results suggested that the model was sensitive to changes in the equation converting HAQ to health-related quality of life; and the assumed time between treatments for comparisons involving rituximab. Assuming retreatment with rituximab every 6 months instead of every 8.7 months, the ICER for rituximab in comparison with conventional DMARDs increased from £21,100 to £32,600 per QALY gained.

4.2.32 Results suggested that the model was not sensitive to changes in the cost parameters, including those associated with hospitalisation and joint replacement, palliative care, and adverse events. The base-case analysis assumed a cost of joint replacement and hospitalisation of £1120 per HAQ score unit. The exclusion of these costs increased the ICER in comparison

with conventional DMARDs by approximately £2500 per QALY gained. The inclusion of additional drug costs of palliation (that is, a £420 start-up cost and a subsequent annual cost of approximately £1000) reduced the ICERs in comparison with conventional DMARDs by approximately £1000 per QALY gained.

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, infliximab, rituximab and abatacept after the failure of a TNF inhibitor. The Committee considered evidence on the nature of rheumatoid arthritis and the value placed on the benefits of adalimumab, etanercept, infliximab, rituximab and abatacept by people with the condition, those who represent them and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.3.2   The Committee considered the current clinical management of people with rheumatoid arthritis. The Committee heard from clinical specialists that the pathway of care following the failure of treatment with a TNF inhibitor depends on the individual person's responses to therapies, the clinical experience of the physician and the person's preference. The Committee heard from patient experts that rheumatoid arthritis can have a severe impact on quality of life, and that fatigue, pain and depression are common among people with the disease. Patient experts reported that rheumatoid arthritis frequently affects people's ability to work, noting the considerable burden placed on the carers of people with the disease. The Committee heard that rheumatoid arthritis may not respond to a given treatment, or there may be a decline in response over time that requires a change in treatment. Clinical specialists and patient experts

emphasised the importance of having the option of multiple treatments for people whose disease has not responded adequately to initial treatment with a TNF inhibitor.

4.3.3   The Committee heard from clinical specialists that rheumatoid arthritis is heterogeneous and that different people may respond differently to a given treatment. In addition, it is difficult to predict whether an individual's disease will respond to a given treatment. Experts stated that people for whom a TNF inhibitor had never produced a response may be less suitable for a second TNF inhibitor than people whose rheumatoid arthritis had previously responded, and that people with seronegative antibody status may be less suitable for treatment with rituximab, than people with seropositive antibody status, although uncertainty surrounds this. The Committee therefore understood that response to treatments varies, and that it is not currently possible to target specific treatments to individuals because the response to any particular treatment cannot be predicted.

4.3.4   The Committee heard that the management of rheumatoid arthritis was changing in line with NICE guidelines for rheumatoid arthritis, and that more clinicians start DMARDs early and increase the dose of DMARDs quickly as required. The Committee heard from clinical specialists that, as a consequence of this accelerated approach to the use of DMARDs, physicians initiate treatment with TNF inhibitors sooner after diagnosis than they had done previously and therefore the characteristics of the people being treated with TNF inhibitors have changed over time. The Committee also heard from the clinical specialists that initiating treatment with TNF inhibitors earlier in the treatment pathway may increase people's potential to benefit from such treatment because of the reduced accumulation of irreversible joint damage. The Committee understood that these changes in the management

of rheumatoid arthritis limited the generalisability of data from the British Society for Rheumatology Biologics Register, as it represents a cohort of people whose characteristics (including disease duration and number of previously received treatments) may not reflect those of the people currently seen in clinical practice for whom the first biological DMARD has failed.

4.3.5   The Committee considered the decision problem in the scope, noting comments from consultees that three technologies (certolizumab pegol, golimumab and tocilizumab) defined as comparators in the scope had not been included in the Assessment Report because marketing authorisations had not been obtained at the point at which the protocol was finalised. The Committee noted that golimumab and tocilizumab were subject to separate ongoing appraisals and were not yet in routine clinical use. It recognised that NICE technology appraisal guidance 186 on certolizumab pegol for the treatment of rheumatoid arthritis did not include guidance on its use after the failure of a TNF inhibitor. The Committee heard that in the absence of NICE guidance, the use of certolizumab pegol in this patient group would be subject to local decision making. The Committee concluded that excluding certolizumab pegol, golimumab and tocilizumab from the Assessment Report was appropriate. The Committee noted, however, the availability of RCT data for golimumab (an alternative TNF inhibitor) after the failure of a TNF inhibitor, and agreed that consideration of this data would be relevant to the decision problem in the appraisal (section 4.3.7).

4.3.6   The Committee considered whether the TNF inhibitors could be considered as a group with respect to clinical effectiveness. The Committee was aware that each of the TNF inhibitors has a different mechanism of action. The Committee heard from clinical specialists that variations in the underlying mechanism of

disease across people coupled with different mechanisms of action of the individual drugs can result in a variety of responses to treatment with TNF inhibitors. The Committee heard from patient experts that the technologies should be considered separately. The Committee heard from clinical specialists that data from the British Society for Rheumatology Biologics Register show no statistically significant difference in effect between TNF inhibitors, but that these data reflect the effectiveness of the first use of TNF inhibitors and not the effectiveness after the failure of a previous TNF inhibitor. Based on advice from the clinical specialists and patient experts that disease can respond differently to different TNF inhibitors, the Committee concluded that it may not be appropriate to assume that the TNF inhibitors form a homogeneous group with regard to clinical effectiveness. However, in the absence of evidence either way, it was not currently possible to distinguish with certainty between the TNF inhibitors in terms of their clinical effectiveness.

4.3.7 The Committee discussed the clinical effectiveness of a second TNF inhibitor after the failure of a first. It noted that the review of the evidence by the Assessment Group had identified no RCTs and that the majority of other studies were uncontrolled observational or registry datasets, some of which had examined the TNF inhibitors as a group. The Committee heard from clinical specialists that for conventional DMARDs, the proportion of people whose condition responded to each successive treatment was reduced as the number of treatments increased, and that the same was considered to hold true for biological DMARDs. The clinical specialists noted that failure of a first TNF inhibitor was associated with an increased risk of failure of a second TNF inhibitor, but that the proportion of people with a good response was comparable. The clinical specialists therefore considered that a second TNF inhibitor was clinically effective. The

Committee noted the comment made in consultation that the GO-AFTER trial data for a different TNF inhibitor (golimumab) could be used to inform the relative treatment effect of the TNF inhibitors in comparison with placebo. It discussed data from this trial that showed a statistically significant benefit from treatment with the TNF inhibitor golimumab after the failure of a different TNF inhibitor when compared with placebo. However, while noting the availability of these data, the Committee were mindful of comments from the clinical specialists and patient experts that the TNF inhibitors should be considered separately (see section 4.3.6). Furthermore, the Committee agreed that it would not be appropriate to apply the results from a treatment not included in the appraisal to the drugs in the appraisal, but concluded that the results for golimumab could be seen as confirming a beneficial effect of TNF inhibitor treatment following failure of a first TNF inhibitor.

4.3.8   The Committee specifically considered the data from the British Society for Rheumatology Biologics Register. It heard from clinical specialists that the register reported an improvement in HAQ score of 0.11 among people receiving a second TNF inhibitor. The Committee also heard that this change did not differ from the average change in HAQ score (0.10) among people whose first TNF inhibitor had failed but who had continued to take it. The Committee heard from the clinical specialists that this change was smaller than the minimum value that is considered a clinically important difference within the context of a clinical trial (0.22) and within the context of an observational study (0.14). The Committee noted the limitations of the British Society for Rheumatology Biologics Register data. Considering these data in conjunction with the evidence discussed in section 4.3.7, the Committee concluded that although the studies suggest that a second TNF inhibitor is effective after the failure of a first, the absence of any rigorously

controlled data meant that it could not quantify with certainty the relative effects of adalimumab, etanercept or infliximab in comparison with either conventional DMARDs or alternative biological DMARDs.

4.3.9 The Committee considered the evidence from the randomised controlled trials of rituximab (REFLEX trial) and of abatacept (ATTAIN trial). The Committee noted the results of the Assessment Group's indirect comparison of rituximab and abatacept based on these trials, which did not show statistically significant differences between the two treatments, and that the conclusions were similar to those from the indirect comparisons carried out by Roche and Bristol Myers Squibb. The Committee concluded that both treatments had been shown to be clinically effective in comparison with placebo, but that one treatment had not been shown to be more effective than the other. The Committee concluded that the data for TNF inhibitors were insufficient to quantify with certainty the relative effect of rituximab and abatacept in comparison with adalimumab, etanercept or infliximab when used after the failure of the first TNF inhibitor.

4.3.10 The Committee considered specifically the evidence of clinical effectiveness for the subgroup of people defined by reason for withdrawal of the first TNF inhibitor. It heard from clinical specialists that they considered that people whose disease had not responded to the first TNF inhibitor (primary non-response) would be less likely to experience a response to a second TNF inhibitor in comparison with those whose disease had initially responded but who had later experienced diminishing benefit (secondary non-response). However, the Committee considered that the studies identified by the Assessment Group did not show a consistent difference in response (including less response, similar response and better response) between

secondary non-response and primary non-response. The Committee concluded that although some evidence and clinical testimony suggested a difference in response by reason for withdrawal, there was currently insufficient evidence for the Committee to use this as a basis for making recommendations for this specific subgroup.

4.3.11   The Committee also considered subgroups based on the presence of auto-antibodies (rheumatoid factor and anti-CCP antibody status) and the impact of the presence of auto-antibodies on the clinical and cost effectiveness of rituximab. The Committee heard from the clinical specialists that the presence of auto-antibodies is not a consistent measure in that the same person may have a positive test for auto-antibodies in one instance and a negative test in another. The Committee was aware that a post-hoc analysis of the REFLEX study showed no statistically significant differences in relative effectiveness between subgroups defined by auto-antibody status. The Committee recognised that the REFLEX study and several other studies highlighted by consultees showed a lower absolute response rate in people who test seronegative compared with those who test seropositive. The Committee heard from clinical specialists that draft guidelines from the British Society for Rheumatology advise that people who test seropositive for either rheumatoid factor or anti-CCP may be more likely to respond than people who test seronegative for the two antibodies, and that this should be taken into account when considering rituximab. However, the clinical specialists considered that people who test seronegative may still respond to rituximab treatment. The Committee was not aware of data showing with certainty that adalimumab, etanercept, infliximab or abatacept would be more clinically effective than rituximab in this situation and that people who test seronegative are not excluded from the current marketing authorisation for rituximab. On balance, the

Committee was not persuaded that there was currently sufficient evidence to conclude that rituximab treatment was inappropriate for people who test seronegative. Therefore, the Committee agreed not to make differential recommendations for a subgroup based on auto-antibody status.

4.3.12 The Committee noted that no studies had been identified that compared the biological DMARDs with a newly initiated conventional DMARD after the failure of a first TNF inhibitor. The Committee heard from clinical specialists that they considered that any treatment effect for conventional DMARDs in this situation would be very limited. The Committee was aware of evidence from the Behandel Strategieen (BeST) study, which investigated the effectiveness of different treatment sequences of biological and conventional DMARDs in people with early rheumatoid arthritis. The Committee heard from the Assessment Group that evidence from the BeST study was not appropriate in this instance, as it did not address the clinical effectiveness of individual DMARDs and the study population did not represent people with established rheumatoid arthritis. The Committee noted comments received in consultation stating that it would be appropriate to assume no effect of conventional DMARDs after failure of a TNF inhibitor, because data from the British Society for Rheumatology Biologics Register reported that people who stopped treatment with a TNF inhibitor showed no average change in HAQ score 12 months later. However, the Committee was mindful that these data were for people stopping treatment with a TNF inhibitor only and did not specifically measure the effect of treatment for people starting conventional DMARDs at that point. Overall, the Committee concluded that, on the basis of clinical opinion, the effect of conventional DMARDs in people for whom a TNF inhibitor had failed was likely to be small, but it did not accept that there would be no effect at all associated with therapy. In addition, the Committee agreed that the uncertainty

about the effectiveness of DMARDs contributed to the difficulty in quantifying with certainty the relative effect of biological treatments compared with DMARDs.

4.3.13 In summary, the Committee noted that, apart from the randomised controlled trials of rituximab and abatacept, the available evidence on the effectiveness of treatment with the considered technologies after the failure of a TNF inhibitor was mainly derived from observational studies with short follow-up periods that included relatively small numbers of participants. The Committee noted that many of the studies lacked a comparison group, so it was not clear what would have happened had participants not received therapy. The Committee considered that shortcomings in the design of studies of the sequential use of TNF inhibitors could affect the validity of the results. It also considered that characteristics of the study participants, changes in clinical practice, and, in some instances, small participant numbers could affect the generalisability of the results. The Committee considered that there are significant limitations in the evidence base available for this appraisal and that the relative clinical effectiveness of TNF inhibitors after the failure of a first TNF inhibitor remains uncertain. The Committee acknowledged that some of the manufacturers had carried out mixed treatment or indirect comparisons. It noted the concerns of the Assessment Group that these comparisons did not increase the robustness of the results because of the inclusion of populations outside the scope, and because of the possible shortcomings related to dealing with heterogeneity between the included studies. The Committee was aware that the analyses did not consistently demonstrate a similar pattern of effect between the technologies. On balance, the Committee was not persuaded that for this appraisal the nature of the evidence available would allow mixed treatment or indirect comparisons to adequately address the

underlying uncertainty in the effectiveness of these technologies. The Committee further noted that more research is needed, specifically using the DAS28 outcome measure (which forms the basis for the rules for continuing treatment in current NICE guidance on treatments for rheumatoid arthritis). The Committee heard from clinical specialists and manufacturers about ongoing research on the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. The Committee heard that a current clinical trial of infliximab (RESTART) is being undertaken in patients with active rheumatoid arthritis in whom treatment with etanercept or adalimumab has failed. It noted that a preliminary analysis from this trial had been provided by the manufacturer of infliximab as commercial in confidence.

Cost effectiveness

4.3.14 The Committee examined the cost-effectiveness analysis of sequential use of TNF inhibitors performed by the Assessment Group and the manufacturers of the technologies. The Committee noted that all analyses modelled a sequence of treatments, which it considered appropriate for rheumatoid arthritis. The Committee noted, however, that there were differences in the sequences modelled. The Committee was aware that one of the models (from Pfizer) had not been provided as an executable file, and had not included abatacept. This limited the Committee's ability to use the model to inform decision making. The Committee recognised that one of the models (from Bristol-Myers Squibb) had not included a comparison with conventional DMARDs, which limited the comparability of the model with those of the other manufacturers and of the Assessment Group.

4.3.15 The Committee was presented with information about the costs used in the economic models. The Committee recognised that the costs of hospitalisation and joint replacement had been

included in all of the manufacturers' models, and that these
costs were derived from a range of data sources including the
British Society for Rheumatology Biologics Register and the
Norfolk Arthritis Register. The Committee was aware that the
Birmingham Rheumatoid Arthritis Model included an assumed
cost for joint replacement and hospitalisation. The Committee
noted comments received during consultation that the costs of
palliative care had been underestimated in the Birmingham
Rheumatoid Arthritis Model. The Committee recognised that the
Assessment Group had carried out a series of analyses
examining the sensitivity of the ICERs to changes in the cost
parameters, including the removal of joint replacement and
hospitalisation costs, the addition of extra costs of palliation and
inclusion of the costs of adverse events. These analyses
showed that the ICERs were not very sensitive to changes in
these costs, and that the ICERs were most sensitive to changes
in the assumptions about the natural history of the disease, the
efficacy of the treatments and the proportion of people stopping
treatment early.

4.3.16   The Committee discussed the different sources of estimates of
clinical effectiveness for the biological DMARDs that had been
used in the economic modelling. The Committee noted that all
models had used the REFLEX and ATTAIN trials to inform the
estimates of rituximab and abatacept, but that sources varied for
the estimates for TNF inhibitors and conventional DMARDs. It
noted that some had included RCT data from populations
outside the scope of the appraisal, uncontrolled observational
studies or registry data. The Committee was aware that no
head-to-head evidence existed that compared all the biological
DMARDs, and as a result some models derived relative
treatment effect from indirect comparisons. The Committee
noted that these had included evidence from studies in which
participants had not previously been treated with a TNF inhibitor.

The Assessment Group reported that it considered the use of data from populations beyond the scope of the appraisal to complete an indirect comparison inappropriate because of the heterogeneity of the studies from which the data were taken. The Committee heard from the Assessment Group that it had modelled the rates of effectiveness for biological and conventional DMARDs as absolute rather than relative changes, even if from placebo-controlled randomised trials, because it considered that evidence did not allow for the completion of a mixed treatment or indirect comparison. The Committee noted that the use of non-randomised comparisons could affect the robustness of the results, but it accepted that the evidence base available for the sequential use of adalimumab, etanercept and infliximab did not currently allow for a robust analysis of the relative treatment effects.

4.3.17   The Committee considered the value of HAQ score as a measure of functional assessment. The Committee heard from clinical specialists that HAQ score was affected by both reversible and irreversible components of the disease process, and that longstanding disease lessens the potential for improvements in HAQ score because of irreversible damage. For this reason the Committee considered that HAQ score may not be an appropriate measure of clinical benefit in established disease. The clinical specialists and patient experts considered that treatment might benefit individuals in ways not captured by HAQ score (such as a reduction in inflammation). The Committee recognised that the HAQ may be subject to 'ceiling effects' (in certain circumstances, the score cannot worsen), and that it does not incorporate symptoms such as pain, fatigue and sleep disturbance. The Committee concluded that patients may derive benefits from the treatment that are not reflected in HAQ score because of irreversible joint damage.

4.3.18 The Committee discussed the range of methods used to model efficacy of the treatments, including responses in ACR categories mapped to changes in HAQ score, ACR response categories mapped to EULAR response and mean HAQ score change without the use of ACR response categories. The Committee was aware of the limitations of the HAQ score, including its insensitivity to small changes within the higher range of scores and its inability to capture meaningful improvements in pain and fatigue (see section 4.3.17). Following explanation from the Assessment Group, the Committee understood that HAQ multipliers represent a proportional change from a given baseline HAQ score. This means that for a baseline HAQ score of 2.00, the use of a HAQ multiplier of 0.25 translates into an HAQ improvement of 0.50, which results in a post-treatment HAQ score of 1.50. The Committee considered that the use of a multiplier to model changes in HAQ meant that absolute changes in the upper range of the HAQ scores were larger than those in the lower range, and that, using a HAQ multiplier, people with more severe disease would have larger absolute HAQ improvements than if the changes in HAQ score observed from the clinical studies were used directly. The Committee discussed comments received in consultation that the HAQ multiplier lacked face validity because the distribution of simulated changes in treatment-related HAQ score did not reflect the ranges observed in clinical trials. Bearing in mind these considerations, the Committee was not persuaded that the use of a HAQ multiplier was an unreasonable way to model changes in HAQ score. However, it agreed that alternative approaches should not be discounted and that it was appropriate to consider the cost-effectiveness analyses of the manufacturers who used alternative methods to calculate clinical effectiveness inputs.

4.3.19 The Committee discussed how the models had incorporated underlying progression of disease during treatment. The Committee noted that all but two analyses had been carried out assuming that disease did not progress in people receiving TNF inhibitors, rituximab and abatacept, but that disease did progress in people taking conventional DMARDs. The Committee was aware that for the biological DMARDs, the use of no progression assumed both no underlying deterioration of physical function and no reduction in response to treatment. The Committee noted that one of the analyses (from Bristol-Myers Squibb) had assumed that abatacept delayed progression more than the other biological DMARDs. It recognised that the values used came from two different sources: clinical trial data on abatacept and an analysis of natural history data not specific to biological DMARDs. The Committee was not persuaded that the evidence was sufficient to support an assumption that the different biological treatments differentially altered progression of disease. In conclusion, the Committee was persuaded that it was appropriate to assume that biological DMARDs delayed disease more than conventional DMARDs. However, the Committee was aware that people with rheumatoid arthritis normally experience a reduction in the response to treatment before stopping it (secondary loss of response). The Committee agreed to base its discussions on the ICERs that assumed no progression of disease for patients during treatment with the biological DMARDs, but was not persuaded that this assumption fully reflects the disease process. This is because people could experience some worsening of HAQ while on treatment, particularly in the period of time prior to stopping treatment because of secondary loss of response, in which case the ICERs assuming no progression of disease may overestimate the benefits of treatment.

4.3.20   The Committee noted that none of the economic models included health-related quality of life measured using a generic preference-based measure, but had mapped a disease-specific measure (HAQ or DAS) to a generic measure (EQ-5D). The Committee understood that in the case where DAS was mapped to EQ-5D, the algorithm used had been developed from EQ-5D data itself derived indirectly from HAQ data. The Committee noted that the mapping of HAQ to EQ-5D allowed for the symptoms of rheumatoid arthritis to cover a broad range of values on the quality-of-life scale, from excellent health to states worse than death. The Committee noted that mapping utilities was outside the reference case, but recognised it had been used in previous NICE technology appraisals of treatments for rheumatoid arthritis in the absence of directly-elicited EQ-5D data. The Committee heard from the Assessment Group that the Birmingham Rheumatoid Arthritis Model incorporated HAQ because it did not consider that DAS captured all aspects of disability that one would expect to correlate with health-related quality of life. The Committee heard from clinical specialists that evidence from the British Society for Rheumatology Biologics Register suggested that for more severe HAQ scores, mapping may underestimate the change in EQ-5D. However, the Committee was mindful that none of the models incorporated directly elicited EQ-5D data and all relied on mapping to inform estimates. The Committee noted that some of the manufacturers had mapped HAQ to EQ-5D using a linear function, while others had used a non-linear function. It heard from the Assessment Group that the use of a non-linear function places a greater value on changes at the lower end of the HAQ scale than at the upper end, but that this did not significantly change the estimated ICERs. The Committee concluded that mapping to EQ-5D had shortcomings, but in the absence of an alternative was an acceptable way to derive estimates of utility, and that the use of a non-linear function was not unreasonable.

4.3.21   The Committee discussed the time intervals between treatments with rituximab. The Committee was aware of the results of the REFLEX trial, in which the average time interval between treatments was 307 days, and the SPC for rituximab, which indicates treatment intervals of no less than 16 weeks. It heard from clinical specialists that they would offer to retreat a patient with rituximab before disease flared, that there was wide variation in time to retreatment with rituximab and that it would be reasonable to assume that treatment with rituximab would occur, on average, less frequently than every 6 months, with some people requiring an infusion less often than once a year. The Committee noted that the Birmingham Rheumatoid Arthritis Model modelled time to repeat treatment as 8.7 months in the base case, basing this estimate on Roche's submission. It noted that similar time to re-treatment had been assumed in a number of the other manufacturers' submissions. The Committee understood that recently published data from the SUNRISE trial indicate that two courses of rituximab given 6-monthly result in a statistically significantly higher ACR 20 response rate at 1 year than one course given per year. It noted the comments received in consultation from some of the manufacturers who, because of the newly available data from the SUNRISE trial, considered that their base-case analyses may overestimate the duration of time between rituximab retreatments. The Committee noted that in the Assessment Group's scenario analysis, the ICER for rituximab compared with conventional DMARDs was from £21,100 per QALY gained when time to retreatment was 8.7 months, and that this increased to £32,600 per QALY gained when time to retreatment was 6 months. The Committee concluded that an 8.7-month retreatment interval is likely to overestimate the time between consecutive courses of rituximab. However, on the basis of the clinical specialists' advice, the Committee considered that it was unlikely to be as frequent as every 6 months for every person receiving rituximab.

4.3.22   The Committee considered the use of stopping and continuation rules in the economic models. The Committee noted that current NICE guidance on the first use of TNF inhibitors (NICE technology appraisal guidance 130) recommends that TNF inhibitors should be not be continued unless there is an adequate response at 6 months following initiation of therapy. An adequate response is defined as an improvement in DAS28 of 1.2 points or more. The Committee heard from the clinical specialists that data from the British Society for Rheumatology Biologics Register indicate that a number of people will continue treatment with a TNF inhibitor in the absence of such a response, indicating that clinicians currently do not adhere strictly to continuation rules. However, it also heard from the clinical specialists that although implementing continuation rules could be difficult, clinicians were increasingly following guidance on continuation rules. The Committee was aware that four of the manufacturers had submitted models that included continuation rules, each based on a different response criterion (that is HAQ score, EULAR response, ACR 20 and ACR 50). The Committee understood that the Birmingham Rheumatoid Arthritis Model was not designed in a way that could incorporate continuation rules based on response. The Committee noted, however, the scenario analyses that included the proportions of people stopping treatment early that were used in the manufacturers' response-based models. These analyses lowered the ICERs for the TNF inhibitors and abatacept compared with conventional DMARDs by approximately £10,000 per QALY gained, to between £23,800 per QALY gained for adalimumab and £27,400 per QALY gained for infliximab. The Assessment Group explained that ICERs for rituximab did not change because the cost of rituximab treatment occurred at the start of each course of treatment. The Committee understood that consultees considered the modelling of continuation rules appropriate, as it reflects existing NICE guidance for the treatment of rheumatoid

arthritis. The Committee concluded that continuation rules should be considered in the estimation of cost effectiveness.

4.3.23 The Committee discussed the different ways in which the manufacturers and the Assessment Group had modelled the efficacy of conventional DMARDs. The Committee noted that the Birmingham Rheumatoid Arthritis Model assumed that the conventional DMARDs used after the failure of a TNF inhibitor were 50% as effective as when used in early rheumatoid arthritis. The Committee heard from the clinical specialists and from comments received in consultation that the assumption that conventional DMARDs used after the failure of a TNF inhibitor were 50% as effective as when used in early rheumatoid arthritis overestimated their effectiveness at this point in the treatment pathway. The Committee noted that the Assessment Group had completed a scenario analysis that assumed an efficacy of conventional DMARDs equal to that of placebo (reflecting the assumption used in the submission from Roche). This resulted in ICERs of approximately £16,000 per QALY gained for rituximab compared with conventional DMARDs, and between £28,000 and £32,000 per QALY gained for the other technologies compared with conventional DMARDs. The Assessment Group explained that the differences between the ICERs using different assumptions about DMARD efficacy were not larger because the Birmingham Rheumatoid Arthritis Model assumes that TNF inhibitors are added to a sequence rather than used as an alternative treatment. Therefore, the effects of the conventional DMARDs were observed in both the intervention and comparator sequences. The Committee discussed comments received on the effectiveness of conventional DMARDs. The Committee concluded that an analysis that assumed the effect of conventional DMARDs to be no more than that of placebo was not plausible, but accepted that the base-case assumption of a reduction of 50% was an underestimate of the reduction in effect

of conventional DMARDs, and therefore overestimated the ICERs in the Assessment Group's base-case analysis.

4.3.24 The Committee considered the estimates of cost effectiveness for the use of rituximab after the failure of a TNF inhibitor. It recognised that in all but one of the economic models, rituximab had been associated with the lowest ICERs of the biological DMARDs compared with conventional DMARDs. Rituximab was also associated with the lowest ICERs of the biological DMARDs in the Assessment Group's scenario analysis that assumed a poorer response to conventional DMARDs than was assumed in the base case. In addition, the Committee considered it was appropriate to incorporate continuation rules, and noted the ICERs from a sensitivity analysis carried out by the Assessment Group that included the assumptions regarding continuation rule from the model submitted by Roche. This analysis also showed that rituximab had the most favourable ICER among the technologies, with the other drugs being either dominated or extendedly dominated. Taking these results into account, as well as the estimates from the manufacturers' economic models, the Committee considered that the most plausible ICER for rituximab compared with DMARDs would be in the lower end of the range of £20,000 to £30,000 per QALY gained. The Committee concluded that rituximab could be considered a cost-effective use of NHS resources. The Committee recognised that rituximab treatment was not provided at regular intervals, but instead that people were retreated when treatment was required, which could mean some loss of response between infusions. However, the Committee noted the testimony from clinical specialists that they would aim to treat before disease flared. The Committee concluded that treatment could only be considered cost effective if an adequate response could be maintained following retreatment with a dosing interval of at least 6 months.

4.3.25   The Committee discussed the cost effectiveness of the TNF inhibitors. The Committee understood that that in the absence of robust data on the clinical effectiveness of the TNF inhibitors, the ICERs were uncertain. The Committee noted that the analyses by Pfizer comparing the TNF inhibitors with rituximab produced ICERs of £19,077 per QALY gained (with primary non-response to the first TNF inhibitor) and £16,225 per QALY gained (with secondary loss of response). However, as Pfizer did not include an economic model in their submission, these results could not be validated. The Committee noted that most of the other models, including the Assessment Group's model, showed that in comparison with rituximab, either the ICERs for the TNF inhibitors were very high (above £80,000 per QALY gained) or the TNF inhibitors were dominated by rituximab (that is, rituximab was both more effective and less costly). In the Abbott model the ICER for TNF inhibitors compared with rituximab was £16,000 when rituximab was given every 6 months. However, the Committee did not accept that the re-treatment interval with rituximab would on average be 6 months. The Committee was mindful of the differences in the analyses of clinical effectiveness used in the different economic models, and considered the comments from consultees on the Birmingham Rheumatoid Arthritis Model. The Committee considered the manufacturer's models and agreed that taking into account all data together did not alter the conclusion drawn from the Birmingham Rheumatoid Arthritis Model. The Committee was not persuaded that the current evidence available and the cost-effectiveness analyses presented could support a decision to recommend adalimumab, etanercept or infliximab as an alternative to rituximab after the failure of a previous TNF inhibitor as an appropriate use of NHS resources.

4.3.26   The Committee discussed the cost effectiveness of abatacept. The Committee considered that most of the economic models

showed that in comparison with rituximab, the ICERs for abatacept were either very high (above £100,000 per QALY gained in the Assessment Group base case) or abatacept was dominated by rituximab (that is, rituximab was both more effective and less costly). The analysis by Bristol-Myers Squibb that produced an ICER of £20,438 per QALY gained assumed an improvement in HAQ of 0.013 per year during treatment with abatacept. When the same rate of HAQ score increase was assumed for abatacept as for the other biological DMARDs in the base case (a worsening of 0.012 per year), the ICER increased to £40,534 per QALY gained. The Committee therefore concluded that abatacept when used as an alternative to rituximab after the failure of a previous TNF inhibitor would not be a cost-effective use of NHS resources.

4.3.27   The Committee was aware that for some people rituximab treatment may not be suitable because of a contraindication to rituximab or methotrexate, or that rituximab or methotrexate may need to be withdrawn because of an adverse event. The Committee was mindful that it had not been presented with any clinical evidence regarding the use of adalimumab, etanercept, infliximab or abatacept for patients for whom rituximab was contraindicated or not tolerated, and that any estimates of their effectiveness in this population were subject to additional uncertainty. However, it acknowledged that for people unable to take rituximab or methotrexate because of adverse events or contraindications, the appropriate comparator was conventional DMARDs. It considered the ICERs in the Birmingham Rheumatoid Arthritis Model that compared the TNF inhibitors with conventional DMARDs, noting that with the addition of continuation rules, the ICERs were between £23,800 and £27,400 per QALY gained, and would be lower if a lower effect of conventional DMARDs was assumed. The Committee considered these ICERs in light of the respective ICERs from the

manufacturers' models, which lay between £14,500 and £35,900 per QALY gained. The Committee concluded that, on balance, these ICERs were sufficiently low to compensate for the uncertainty about the effectiveness of these treatments to be accepted. The Committee considered the Assessment Group's ICER for abatacept (including the continuation rule) of £26,200 per QALY gained compared with conventional DMARDs and agreed that this would be lower if the model assumed a lower effect of conventional DMARDs. The Committee considered these ICERs and the respective ICERs for abatacept from the manufacturer's model. It noted that these lay between £21,500 and £44,700 per QALY gained. The Committee was persuaded that these data taken together could support a decision to recommend adalimumab, etanercept, infliximab or abatacept as treatment options to be used after the failure of a first TNF inhibitor for the treatment of people who cannot receive rituximab therapy because have a contraindication to rituximab or who have had an adverse event on treatment with rituximab, as an appropriate use of NHS resources. The Committee recognised that for people who cannot receive rituximab therapy because they have a contraindication to methotrexate or where methotrexate is withdrawn because of an adverse event, this choice would be limited to adalimumab and etanercept, because infliximab and abatacept have marketing authorisations for use in combination with methotrexate.

4.3.28 The Committee was aware that for some people rituximab treatment may fail to provide an adequate response. The Committee was mindful that it had not been presented with any clinical or cost-effectiveness evidence regarding the use of adalimumab, etanercept, infliximab or abatacept for this group of people. The Committee considered that all estimates of relative clinical effectiveness were subject to uncertainty, and that in this group of patients the estimates were subject to further

uncertainty because factors such as disease duration and prior treatment exposure may affect response to treatment (see section 4.3.7). Therefore, while accepting that the evidence submitted could be considered reflective of the group who had not received rituximab because of contraindications, or had not had an adequate trial because rituximab treatment was withdrawn because of an adverse event, the Committee was not persuaded that this evidence could be applied to the group of people for whom rituximab had failed to provide an adequate response. The Committee was therefore unable to make recommendations about the use of adalimumab, etanercept, infliximab or abatacept in people for whom rituximab has failed to provide an adequate response.

4.3.29   The Committee considered whether its recommendations were associated with any potential issues related to equality. The Committee was made aware that the use of the DAS28 would not be an appropriate tool for people with specific disabilities of the lower limbs and that the DAS44 would be a better tool to use for people with greater lower limb disease burden. The Committee agreed that it was important to allow clinicians to adjust the assessment of disease severity depending on the characteristics of the disease, and that the recommendations should reflect this. The Committee explored whether there were people, other than those who for whom rituximab or methotrexate was contraindicated or who had an adverse event on treatment with rituximab or methotrexate, who were unable to have rituximab because of a specific additional disability or comorbidity. The Committee noted that no such group of people had been identified during scoping or in consultation. The Committee was aware that people with mobility problems or visual impairment may find travel to hospital onerous or inconvenient. However, the Committee concluded that it was not clear that travel to receive infusions one or two times per year

was necessarily more onerous or inconvenient than the alternative of much more frequent injections. In any event, the Committee did not consider that the need to travel would make it impossible or unreasonably difficult for these people to obtain treatment with rituximab, and noted that they would need to travel to other hospital or healthcare appointments in relation to their condition. The Committee concluded that rituximab would still be the most appropriate treatment option, taking into account its cost-effectiveness data and the infrequent dosing interval, but that all reasonable steps should be taken to provide practical support and assistance to ensure access to treatment for this group of people.

4.3.30 The Committee noted a consultee's concerns about equity of access with other countries, but concluded that this concern did not pertain to any group protected by the equalities legislation, and that it would not be appropriate to address this as part of a technology appraisal. The Committee also noted a consultee's comment stating that the guidance may have a disproportional impact on patients who test seronegative, but agreed that its recommendations, not differentiating between groups of people, did not affect any group protected by the equalities legislation and that the issue of auto-antibody status had been addressed in detail.

Summary of Appraisal Committee's key conclusions

TA195 (MTA)	Appraisal title: Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36, review of NICE technology appraisal guidance 126 and 141)	FAD section
Key conclusions		
• Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other disease-modifying anti-rheumatic drugs (DMARDs), including at least one tumour necrosis factor (TNF) inhibitor. *Reason for recommendation* Rituximab was considered to be a cost-effective option, based on data from most of the models available for this appraisal.	1.1
• Adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate) are recommended as treatment options only for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to rituximab, or when rituximab is withdrawn because of an adverse event. • Adalimumab monotherapy and etanercept monotherapy are recommended as treatment options for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because have a contraindication to methotrexate, or when methotrexate is withdrawn because of an adverse event. *Reasons for recommendations* − Based on the evidence available, the ICERs for adalimumab, etanercept, infliximab and abatacept compared with rituximab were either very high, or these drugs were dominated by rituximab (that is, rituximab was both more effective and less costly). − For people who are unable to take rituximab or methotrexate, the appropriate comparator was conventional DMARDs. Based on the evidence available, adalimumab, etanercept, infliximab and abatacept compared with conventional DMARDs were	1.3 & 1.4

TA195 (MTA)	Appraisal title: Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36, review of NICE technology appraisal guidance 126 and 141)	FAD section
	considered cost-effective options based on data from most of the models available for this appraisal.	
Current practice		
Clinical need of patients	Rheumatoid arthritis has a severe impact on quality of life, with fatigue, pain and depression being common among people with the disease. In addition, rheumatoid arthritis frequently affects patients' abilities to work, and there is considerable burden placed on the carers of patients with the disease.	4.3.2
	Patients may not respond to a treatment, or may experience a decline in initial response over time, and therefore need to change treatments.	4.3.2
Availability of alternative treatments	The pathway of care following the failure of treatment with a TNF inhibitor depends on the individual person's responses to therapies, the clinical experience of the physician and the person's preference.	4.3.2
	It is not currently possible to target specific treatments to individual patients because the response to any particular treatment cannot be predicted.	4.3.3
The technology		
Proposed benefits of the technology from the manufacturer, clinician and patient perspective	Clinical specialists and patient experts emphasised the importance of having the option of multiple treatments for people whose disease has not responded adequately to initial treatment with a TNF inhibitor.	4.3.2
How innovative is the technology?	This is a review of established technologies.	N/A

TA195 (MTA)	Appraisal title: Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36, review of NICE technology appraisal guidance 126 and 141)	FAD section
Adverse events	This is a review of established technologies with known adverse events. Adverse events were not considered a key factor in distinguishing between the technologies.	N/A
Evidence for clinical effectiveness		
Quality of the evidence	The evidence review identified no randomised controlled trials (RCTs) on the effectiveness of the TNF inhibitors. The majority of studies were uncontrolled observational or registry datasets.	4.3.7
	Data from RCTs were available only for rituximab and abatacept.	4.3.7
	Subgroup analyses based on rheumatoid factor and anti-CCP antibody status were post hoc.	4.3.11
Availability and nature of evidence	Studies suggested that a second TNF inhibitor is effective after the failure of a first, but the absence of any rigorously controlled data meant that the relative effects of adalimumab, etanercept, or infliximab in comparison with either conventional DMARDs or alternative biological DMARDs could not be quantified with certainty.	4.3.8/9
	There was insufficient evidence suggesting a difference in response based on the reason for withdrawal of the first TNF inhibitor.	4.3.10
	There was insufficient evidence to make differential recommendations for subgroups based on the presence of auto-antibodies (rheumatoid factor and anti-CCP [cyclic citrullinated peptide] antibody).	4.3.11
	No studies were identified that compared biological DMARDs with newly-initiated conventional DMARDs after the failure of a first TNF inhibitor.	4.3.12
	The Committee concluded that, on the basis of	4.3.12

TA195 (MTA)	Appraisal title: Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36, review of NICE technology appraisal guidance 126 and 141)	FAD section
	clinical opinion, the effect of conventional DMARDs in people for whom a TNF inhibitor had failed was likely to be small, but it did not accept that there would be no effect at all associated with therapy. In addition, the Committee agreed that the uncertainty about the effectiveness of DMARDs contributed to the difficulty in quantifying with certainty the relative effect of biological treatments compared with DMARDs.	
Relevance to general clinical practice in the NHS	Changes in clinical management, including starting DMARDs earlier, increasing DMARD dosage more quickly and starting treatment with TNF inhibitors sooner than in the past limit the generalisability of some of the registry data presented.	4.3.4
	Patients may derive benefits from the treatment that would not be reflected in Stanford Health Assessment Questionnaire (HAQ) score because of the inclusion of irreversible joint damage in the score.	4.3.17
Uncertainties generated by the evidence	Based on advice from the clinical specialists and patient experts, it may not be appropriate to assume that TNF inhibitors form a homogeneous group with regard to clinical effectiveness. However, evidence was not available to enable any distinction to be made. (See also Availability and nature of evidence above.)	4.3.6
Evidence for cost effectiveness		
Availability and nature of evidence	One of the models was not provided as an executable file, limiting the ability to validate the modelling and ICERs. Another model did not include a comparison with conventional DMARDs, limiting the ability to compare it with other models.	4.3.14
	The model from the Assessment Group was	4.3.15

TA195 (MTA)	Appraisal title: Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36, review of NICE technology appraisal guidance 126 and 141)	FAD section
	not sensitive to assumptions about costs and was sensitive to assumptions about natural history, clinical effectiveness and number of people stopping treatment early.	4.3.16
	The sources of effectiveness evidence varied for the estimates of the TNF inhibitors and conventional DMARDs. Some included RCT data from populations outside the scope of the appraisal and/or uncontrolled observational studies or registry data.	4.3.16
	The Assessment Group modelled rates of effectiveness for biological DMARDs and conventional DMARDs as absolute (rather than relative) changes in disease measures, which could affect the robustness of the results.	4.3.18
	A range of methods were used to model efficacy of treatments, including mapping response criteria to HAQ change and use of HAQ change on its own. The Committee was not persuaded that the use of a HAQ multiplier was an unreasonable way to model changes in HAQ score. However, it agreed that alternative approaches should not be discounted and that it was appropriate to consider the cost-effectiveness analyses of the manufacturers who used alternative methods to calculate clinical effectiveness inputs.	4.3.19
	A variety of assumptions were made about progression of disease while on treatment with biological DMARDs including no progression, worsening disease and continuing improvement. All models except one assumed no progression for all biological DMARDs. The Committee did not consider that the evidence supported an assumption that the biological DMARDs differentially affected underlying disease progression.	
Uncertainties around and	The Committee considered estimates of cost effectiveness using an assumption of no	4.3.19

TA195 (MTA)	Appraisal title: Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36, review of NICE technology appraisal guidance 126 and 141)	FAD section
plausibility of assumptions and inputs in the economic model	progression of disease while on treatment with biological DMARDs, but was not persuaded that this fully reflects the disease process. Based on evidence from patient experts and clinical specialists, the Committee considered an assumed 50% reduction in the efficacy of conventional DMARDs to be an underestimate of the reduction in effect of conventional DMARDs, although the assumption that they are no more effective than placebo was also considered implausible.	4.3.23
	The Committee recognised that incorporating response-based continuation rules into the models lowered the ICERs for the TNF inhibitors and abatacept in comparison with conventional DMARDs. It concluded that the modelling of continuation rules should be considered when examining estimates of cost effectiveness.	4.3.22
	On the basis of the clinical specialists' advice, the Committee considered that treatment with rituximab would occur less frequently than every 6 months, but accepted that 8.7 months may be an overestimate.	4.3.21
Incorporation of health-related quality of life benefits and utility values	All models presented EuroQol (EQ-5D) data derived from a disease-specific measure. Mapping to EQ-5D has shortcomings but, in the absence of an alternative approach, was considered an acceptable way to derive estimates of utility. Use of a non-linear mapping function was not unreasonable.	4.3.20
Most likely cost-effectiveness estimate (given as an ICER)	For rituximab, the most plausible estimated ICER would be in the lower range of £20,000 to £30,000 per QALY gained.	4.3.24
	In the absence of robust data on the clinical effectiveness of the TNF inhibitors, the estimates of cost effectiveness were uncertain. Most models showed that, when compared	4.3.25

TA195 (MTA)	Appraisal title: Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36, review of NICE technology appraisal guidance 126 and 141)	FAD section
	with rituximab, the ICERs for the TNF inhibitors were either very high (above £80,000 per QALY gained) or that rituximab dominated the TNF inhibitors (that is, rituximab was both more effective and less costly than the TNF inhibitors). In the Abbott model the ICER for TNF inhibitors compared with rituximab was £16,000 when rituximab was given every 6 months. However, the Committee did not accept that the re-treatment interval with rituximab would on average be 6 months.	
	The Committee considered that most of the economic models showed that in comparison with rituximab, the ICERs for abatacept were either very high (above £100,000 per QALY gained in the Assessment Group base case) or abatacept was dominated by rituximab. The only exception was the analysis from the manufacturer of abatacept, which assumed an HAQ improvement while on abatacept (an assumption that the Committee did not accept).	4.3.26
	For people who are unable to have rituximab treatment because of a contraindication to rituximab or methotrexate, or for whom rituximab or methotrexate may need to be withdrawn because of an adverse event, the ICERs were based on a comparison with conventional DMARDs. The Assessment Group reported ICERs for adalimumab, etanercept, infliximab and abatacept of between £23,800 and £27,400 per QALY gained, including the addition of continuation rules, which would be lower if the model assumed a lower effect of conventional DMARDs.	4.3.27
Additional factors taken into account		
Equalities considerations, social value judgements	The Committee was made aware that the use of the DAS28 would not be an appropriate tool for people with specific disabilities of the lower limbs and that the DAS44 would be a better	4.3.29

TA195 (MTA)	Appraisal title: Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36, review of NICE technology appraisal guidance 126 and 141)	FAD section
	tool to use for people with greater lower limb disease burden. The Committee agreed that it was important to allow clinicians to adjust the assessment of disease severity depending on the characteristics of the disease, and that the recommendations should reflect this.	
	The Committee was aware that people with mobility problems or visual impairment may find travel to hospital onerous or inconvenient. The Committee concluded that rituximab would still be the most appropriate treatment option, taking into account its cost-effectiveness data and the infrequent dosing interval, but that all reasonable steps should be taken to provide practical support and assistance to ensure access to treatment for this group of people.	4.3.29
	The Committee concluded that concerns about equity of access with other countries did not pertain to any group protected by the equalities legislation, and that it would not be appropriate to address this as part of a technology appraisal. The Committee also noted a consultee's comment stating that the guidance may have a disproportional impact on patients who test seronegative, but agreed that its recommendations, not differentiating between groups of people, did not affect any group protected by the equalities legislation.	4.3.30

5   Implementation

5.1   The Secretary of State has issued directions to the NHS on
         implementing NICE technology appraisal guidance. When a NICE
         technology appraisal recommends use of a drug or treatment, or
         other technology, the NHS must provide funding and resources
         for it within 3 months of the guidance being published. If the
         Department of Health issues a variation to the 3-month funding

direction, details will be available on the NICE website. The NHS is not required to fund treatments that are not recommended by NICE.

5.2   NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TA195).

- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Audit support for monitoring local practice.

6   Recommendations for further research

6.1   Further clinical trials should be undertaken to compare the clinical effectiveness of adalimumab, etanercept and infliximab used sequentially after the failure of a TNF inhibitor with the clinical effectiveness of management strategies that do not include TNF inhibitors, including strategies that use untried DMARDs or biological DMARDs such as rituximab. This is important because there is currently no evidence on the clinical effectiveness of the TNF inhibitors at this stage in the treatment pathway compared with alternative treatment options (see section 4.3.6).

6.2   Further research should be undertaken to estimate utilities using directly observed health-related quality of life values (such as EQ−5D scores) in people with rheumatoid arthritis. This is important because current methods of establishing utility values do not allow for links to be made between utilities and common clinical measures such as DAS.

7   Related NICE guidance

Published

- Tocilizumab for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 198 (2010). Available from

www.nice.org.uk/guidance/TA198

- Certolizumab pegol for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 186 (2010). Available from www.nice.org.uk/guidance/TA186

- Rheumatoid arthritis: the management of rheumatoid arthritis in adults. NICE clinical guideline 79 (2009). Available from www.nice.org.uk/guidance/CG79

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

Under development

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

- Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying antirheumatic drugs. NICE technology appraisal guidance (publication expected March 2011).

8 Review of guidance

8.1 The guidance on these technologies will be considered for review by the Guidance Executive in June 2013. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon

Chief Executive

August 2010

Appendix A: Appraisal Committee members and NICE project team

A   Appraisal Committee members

The Appraisal Committee is one of NICE's standing advisory committees. 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.

Dr Amanda Adler (Chair)
Consultant Physician, Addenbrooke's Hospital

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 Peter Barry
Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Dr Michael Boscoe
Consultant Cardiothoracic Anaesthetist, Royal Brompton and Harefield NHS Foundation Trust

Professor John Cairns

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

Dr Mark Chakravarty

External Relations Director – Pharmaceuticals and Personal Health, Oral Care Europe

Dr Fergus Gleeson

Consultant Radiologist, Churchill Hospital, Oxford

Ms Sally Gooch

Independent Nursing and Healthcare Consultant

Mrs Eleanor Grey

Lay member

Mr Sanjay Gupta

YPD Service Case Manager, Southwark Health and Social Care, Southwark Primary Care Trust

Dr Neil Iosson

General Practitioner

Mr Terence Lewis

Lay member

Dr Ruairidh Milne

Director of Strategy and Development and Director for Public Health Research NIHR Evaluation, Trials and Studies Coordinating Centre, University of Southampton

Mr Stephen Palmer

Senior Research Fellow, Centre for Health Economics, University of York

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Mr Navin Sewak

Primary Care Pharmacist, NHS Hammersmith and Fulham

Dr Lindsay Smith

General Practitioner, East Somerset Research Consortium

Mr Roderick Smith

Finance Director, West Kent Primary Care Trust

Mr Cliff Snelling

Lay member

Professor Ken Stein (Vice Chair)

Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), 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

Mr Tom Wilson

Director of Contracting and Performance, NHS Tameside and Glossop

B   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.

Whitney Miller
Technical Lead

Zoe Garrett
Technical Adviser

Jeremy Powell
Project Manager

Appendix B: Sources of evidence considered by the Committee

A   The assessment report for this appraisal was prepared by the West Midlands Health Technology Assessment Collaboration:

- Malottki K., Barton P., et. al. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor: a systematic review and economic evaluation (November 2009)

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 and II were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I   Manufacturers/sponsors:

- Abbott
- Bristol-Myers Squibb
- Roche
- Schering-Plough
- Pfizer

II   Professional/specialist and patient/carer groups:

- Arthritis and Musculoskeletal Alliance (ARMA)
- Arthritis Care
- British Health Professionals in Rheumatology
- British Society for Rheumatology
- National Rheumatoid Arthritis Society
- Primary Care Rheumatology Society
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- South Asian Health Foundation

III   Other consultees:

- Department of Health

- Welsh Assembly Government

IV Commentator organisations (without the right of appeal):

- Arthritis Research Campaign
- AstraZeneca UK
- Department of Health, Social Services and Public Safety for Northern Ireland
- GlaxoSmithKline
- Medac UK
- NHS Quality Improvement Scotland
- Novartis
- Roche Products
- Sanofi Aventis
- UCB Pharma

C The following individuals were selected from clinical specialist and patient expert 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, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor by attending the initial Committee discussion and/or providing written evidence to the Committee. They were invited to comment on the ACD.

- Dr Chris Deighton, Consultant Rheumatologist, Derbyshire Royal Infirmary, nominated by the British Society for Rheumatology – clinical specialist
- Dr Frank McKenna, Consultant Rheumatologist, Trafford General Hospital, nominated by the British Society for Rheumatology – clinical specialist
- Ailsa Bosworth, Chief Executive Officer, National Rheumatoid Arthritis Society, nominated by the National Rheumatoid Arthritis Society – patient expert
- Jean Burke, nominated by the National Rheumatoid Arthritis Society – patient expert

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

- Abbott

- Bristol-Myers Squibb
- Roche
- Schering-Plough
- Pfizer