NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed

This guidance was developed using the multiple technology appraisal (MTA) process.

1 Guidance

1.1 Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept, all in combination with methotrexate, are recommended as options for treating rheumatoid arthritis, only if:

- disease is severe, that is, a disease activity score (DAS28) greater than 5.1 and
- disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs) and
- the companies provide certolizumab pegol, golimumab, abatacept and tocilizumab with the discount agreed in their patient access schemes.

1.2 Adalimumab, etanercept, certolizumab pegol or tocilizumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance where the criteria in section 1.1 are met.

1.3 Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy.

1.4 After initial response within 6 months, withdraw treatment if a moderate EULAR response is not maintained.

1.5 Start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may need to be varied for some people because of differences in the mode of administration and treatment schedules.

1.6 People whose treatment with adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab or abatacept is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 Clinical need and practice

2.1 Rheumatoid arthritis is a systemic chronic inflammatory autoimmune disease that typically affects synovial joints (such as those in the hands and feet), causing swelling, stiffness, pain and progressive irreversible joint destruction. Disease can also occur outside the joints, affecting other organs, including the lungs, heart and eyes. Rheumatoid arthritis is associated with increased mortality and increasing disability, which has a severe effect on quality of life. It is associated with substantial costs; direct costs of

drug acquisition and hospitalisation and indirect costs of reduced productivity.

2.2 There are estimated to be around 400,000 people with rheumatoid arthritis in the UK. Of these, approximately 15% have severe disease. It is about 2–4 times more prevalent in women than in men. It can develop at any age, but the peak age of onset in the UK is about 40–70 years.

2.3 There is no cure for rheumatoid arthritis. In early disease, management aims to suppress disease activity and induce remission, prevent loss of function, control joint damage, control pain and enhance self-management. In established disease, management should address complications and associated comorbidity, as well as the effect of the condition on the person's quality of life.

2.4 Treatment for rheumatoid arthritis usually includes non-steroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors, which reduce pain, fever, and joint swelling and inflammation, and disease-modifying antirheumatic drugs (DMARDs). DMARDs slow the disease process and reduce joint damage. DMARDs can include drugs such as methotrexate, leflunomide and sulfasalazine (referred to as conventional DMARDs). Also available are a group of drugs including monoclonal antibodies and soluble receptors that modify the disease process by blocking key protein messenger molecules (such as cytokines) or cells (such as B-lymphocytes). Such drugs are referred to as biological DMARDs. For some people their disease may not respond to DMARDs and for others the response to DMARDs often reduces over time. Therefore people need a sequence of treatments. Glucocorticoids are also used to control inflammation.

2.5 For people with newly diagnosed rheumatoid arthritis, the NICE guideline on rheumatoid arthritis recommends a combination of conventional DMARDs (including methotrexate and at least 1 other conventional DMARD, plus short-term glucocorticoids) as first-line treatment, ideally beginning within 3 months of the onset of persistent symptoms. When combination therapies are not appropriate, conventional DMARD monotherapy is used.

2.6 Measures of response to treatment include the American College of Rheumatology (ACR) response criteria (ACR20, 50 and 70). These require a specified improvement in tender joint count, swollen joint count, global assessments, pain, disability and an acute-phase reactant (for example, erythrocyte sedimentation rate or C-reactive protein). The disease activity score (DAS28) is an alternative scoring system that has been developed in Europe. It is calculated using a formula that includes counts for tender and swollen joints, an evaluation of general health by the person (on a scale of 0–100), and erythrocyte sedimentation rate or C-reactive protein. A DAS28 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. The European League Against Rheumatism (EULAR) response criteria use the degree of change in DAS28 and the DAS28 reached to determine good, moderate or non-response. The Stanford Health Assessment Questionnaire (HAQ) is 1 component of the ACR criteria and scores physical disability and pain from 0 (least disability) to 3 (most severe disability).

3 The technologies

3.1 This technology appraisal includes 7 different biological medicines. In addition, for infliximab, there is an originator biological medicine and 2 biosimilar products available in the NHS. A biosimilar medicine is a medicine that is developed to be similar to an existing

biological medicine. The technologies have different mechanisms of action. Adalimumab, etanercept, infliximab, certolizumab pegol and golimumab all inhibit the activity of tumour necrosis factor (TNF)-alpha, a pro-inflammatory mediator that is partly responsible for damage to the joints in rheumatoid arthritis. They are referred to as TNF-alpha inhibitors. Tocilizumab inhibits the activity of interleukin-6 (IL-6), a pro-inflammatory cytokine that is also partly responsible for damage to the joints in rheumatoid arthritis. Abatacept is a selective modulator of the T-lymphocyte activation pathway. It binds to molecules on the surface of antigen-presenting cells, preventing full activation of the T-lymphocytes and interrupting the inflammatory process.

Table 1 Summary of the marketing authorisations for the technologies

Technology	MTX-experienced RA	MTX-naive RA	In combination with MTX	Mono-therapy	SC or IV
Adalimumab	+	+	+	+	SC
Etanercept	+	+	+	+	SC
Infliximab	+	+	+	–	IV
Infliximab biosimilars	+	+	+	–	IV
Certolizumab pegol	+	–	+	+	SC
Golimumab	+	+	+	–	SC
Abatacept	+	–	+	–	IV or SC
Tocilizumab	+	+*	+	+	IV or SC*

Abbreviations: RA, rheumatoid arthritis; MTX, methotrexate; SC, subcutaneous injection; IV, intravenous infusion; +, licensed for use; MTX-experienced, disease previously treated with methotrexate; MTX-naive, disease not previously treated with methotrexate.

*tocilizumab in methotrexate-naive rheumatoid arthritis and the subcutaneous formulation are not part of this appraisal.

Adalimumab

3.2 Adalimumab (Humira, AbbVie), in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to

severe, active rheumatoid arthritis in adults when the response to DMARDs, including methotrexate, has been inadequate and for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

3.3 Adalimumab is contraindicated in people with active tuberculosis or other severe infections, and people with moderate or severe heart failure. The summary of product characteristics notes the following adverse reactions as very common: respiratory tract infections, leukopenia, anaemia, increased lipids, headache, abdominal pain, nausea and vomiting, elevated liver enzymes, rash, musculoskeletal pain and injection site reaction. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.4 Adalimumab is administered subcutaneously as a 40-mg dose every other week. The net price of adalimumab is £352.14 per 40-mg prefilled pen or prefilled syringe, or £352.14 per 40-mg/0.8-ml vial (British national formulary [BNF], July 2015). Assuming 26 doses per year, the annual cost of adalimumab is £9155.64. For adalimumab monotherapy, the dose may be increased up to 40 mg per week for people who have a decrease in response. Costs may vary in different settings because of negotiated procurement discounts.

Etanercept

3.5 Etanercept (Enbrel, Pfizer), in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to DMARDs, including methotrexate (unless contraindicated), has been inadequate, and for the treatment of severe, active and

progressive rheumatoid arthritis in adults not previously treated with methotrexate. Etanercept can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

3.6 Etanercept is contraindicated in people with sepsis or who are at risk of sepsis, and people with active infections including chronic or localised infections. The summary of product characteristics notes the following adverse reactions as very common: infections and injection site reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.7 Etanercept is administered subcutaneously as a 25-mg dose twice weekly or alternatively as a 50-mg dose every week. The net price of etanercept is £89.38 per 25-mg prefilled syringe, or £178.75 per 50-mg prefilled pen or prefilled syringe (BNF, July 2015). Assuming 52 doses per year, the annual cost of etanercept is £9295. Costs may vary in different settings because of negotiated procurement discounts.

Infliximab

3.8 Infliximab (Remicade, Merck Sharp & Dohme), in combination with methotrexate, has a UK marketing authorisation for the reduction of signs and symptoms of rheumatoid arthritis as well as the improvement in physical function in adults with active disease when the response to DMARDs, including methotrexate, has been inadequate. It is also licensed for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs.

3.9 Infliximab is contraindicated in people with active tuberculosis or other severe infections, and people with moderate or severe heart failure. The summary of product characteristics notes the following adverse reactions as very common: viral infection, headache,

upper respiratory tract infection, sinusitis, abdominal pain, nausea, infusion-related reaction and pain. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.10 Infliximab is administered as an intravenous infusion at a dose of 3 mg/kg, with initial doses at 0, 2 and 6 weeks, and then every 8 weeks thereafter. For disease that has an inadequate response or loss of response after 12 weeks of treatment, consideration may be given to increasing the dose step-wise by approximately 1.5 mg/kg up to a maximum of 7.5 mg/kg every 8 weeks. Alternatively, administration of 3 mg/kg as often as every 4 weeks may be considered. The net price of infliximab is £419.62 per 100-mg vial (BNF, July 2015). Assuming a weight per person of 70 kg, vial wastage and 3 initial doses followed by treatment every 8 weeks, the cost in the first year is £10,070.88, and then £8812.02 per year. Costs may vary in different settings because of negotiated procurement discounts.

Infliximab biosimilars

3.11 Infliximab biosimilars (Remsima, Napp Pharmaceuticals and Inflectra, Hospira UK), in combination with methotrexate, have the same UK marketing authorisation as the infliximab originator product; that is, for the reduction of signs and symptoms of rheumatoid arthritis as well as the improvement in physical function in adults with active disease when the response to DMARDs, including methotrexate, has been inadequate. They are also licensed for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs. The contraindications, adverse reactions and administration schedule are the same as for infliximab (see sections 3.9–3.10), but both biosimilars are subject to increased safety monitoring.

3.12 The list price of infliximab biosimilars is £377.66 per 100-mg vial (information provided by the companies). Assuming a weight per person of 70 kg, vial wastage, and 3 initial doses in the first year followed by treatment every 8 weeks, the cost in the first year is £9063.84, and then £7930.86 per year. The infliximab biosimilars are available to the NHS at contract prices negotiated through the Commercial Medicines Unit. These prices are lower than the list price but are commercial in confidence.

Certolizumab pegol

3.13 Certolizumab pegol (Cimzia, UCB Pharma), in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to DMARDs, including methotrexate, has been inadequate. Certolizumab pegol can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

3.14 Certolizumab pegol is contraindicated in people with active tuberculosis or other severe infections, and in people with moderate or severe heart failure. The summary of product characteristics lists no adverse reactions as very common but notes that in clinical trials the most common adverse reactions were bacterial and viral infections. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.15 Certolizumab pegol is administered subcutaneously as initial 400-mg doses at 0, 2 and 4 weeks, followed by maintenance doses of 200 mg every 2 weeks. Alternatively, administration of 400 mg every 4 weeks can be considered, once clinical response is confirmed. The net price of certolizumab pegol is £357.50 per 200-mg prefilled syringe (BNF, July 2015). Assuming 3 initial doses

of 400 mg followed by maintenance doses every 2 weeks, the cost (without the patient access scheme) in the first year is £10,367.50, and then £9295 per year. Costs may vary in different settings because of negotiated procurement discounts.

3.16 The company has agreed a patient access scheme with the Department of Health. In the scheme, the first 12 weeks of therapy (currently 10 pre-loaded syringes of 200 mg each) with certolizumab pegol are free of charge.

3.17 The Department of Health considered that the certolizumab pegol, patient access scheme does not constitute an excessive administrative burden on the NHS.

Golimumab

3.18 Golimumab (Simponi, Merck Sharp & Dohme), in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to DMARD therapy including methotrexate has been inadequate, and for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

3.19 Golimumab is contraindicated in people with active tuberculosis or other severe infections and in people with moderate or severe heart failure. The summary of product characteristics notes that upper respiratory tract infections are very common adverse events. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.20 Golimumab is administered subcutaneously as a 50-mg dose every month on the same day each month. For people weighing more than 100 kg, a dose of 100 mg may be considered if the disease has an inadequate clinical response after 3–4 doses. The net price

of golimumab is £762.97 per 50-mg prefilled pen or prefilled syringe (BNF, July 2015). For people weighing less than 100 kg and assuming 12 doses per year, the annual cost of golimumab is £9155.64. Costs may vary in different settings because of negotiated procurement discounts.

3.21 The company has agreed a patient access scheme with the Department of Health, in which the 100-mg dose of golimumab will be available to the NHS at the same cost as the 50-mg dose.

3.22 The Department of Health considered that the golimumab patient access scheme does not constitute an excessive administrative burden on the NHS.

Abatacept

3.23 Abatacept (Orencia, Bristol–Myers Squibb) in combination with methotrexate has a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis in adults whose disease responded inadequately to previous therapy with 1 or more DMARDs including methotrexate or a TNF-alpha inhibitor.

3.24 Abatacept is contraindicated in people with severe and uncontrolled infections. The summary of product characteristics notes that upper respiratory tract infections are very common adverse events. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.25 Abatacept is given by intravenous infusion at a dose of 500 mg for a person weighing less than 60 kg, 750 mg for a person weighing between 60 kg and 100 kg, and 1000 mg for a person weighing more than 100 kg. It is given initially at 0, 2 and 4 weeks, then every 4 weeks thereafter. The net price of abatacept for intravenous infusion is £302.40 per 250 mg vial (BNF, July 2015). For people weighing between 60 and 100 kg, the cost of treatment

for the first year is £12,700.80 and then £11,793.60 per year (without the patient access scheme). Costs may vary in different settings because of negotiated procurement discounts.

3.26 Abatacept is given by subcutaneous injection at a dose of 125 mg once weekly regardless of weight. Subcutaneous abatacept can be started with or without a single initial intravenous dose (using the doses specified in section 3.25). The net price of abatacept for subcutaneous injection is £302.40 per 125-mg prefilled syringe (BNF, July 2015). Assuming a weight per person of 70 kg, 1 intravenous loading dose followed by subcutaneous treatment doses every week, the cost (without the patient access scheme) of the initial intravenous dose is £907.20, and then £15,724.80 per year. Costs may vary in different settings because of negotiated procurement discounts.

3.27 The company has agreed a patient access scheme with the Department of Health in which abatacept will be available with a discount. The level of discount is commercial in confidence.

3.28 The Department of Health considered that the abatacept patient access scheme does not constitute an excessive administrative burden on the NHS.

Tocilizumab

3.29 Tocilizumab (RoActemra, Roche), in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis in adults whose disease has responded inadequately, or adults who were intolerant, to previous therapy with 1 or more DMARDs or TNF-alpha inhibitors. In these people, tocilizumab can be given as monotherapy in cases of intolerance to methotrexate or if continued treatment with methotrexate is inappropriate. In July 2014 the marketing authorisation for tocilizumab was extended to include

treatment of severe active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. A marketing authorisation for a subcutaneous formulation was granted in February 2014. The subject of this appraisal is the intravenous formulation of tocilizumab for rheumatoid arthritis that has been treated with methotrexate before.

3.30 Tocilizumab is contraindicated in people with active, severe infections. The summary of product characteristics notes the following adverse reactions as very common: upper respiratory tract infections and hypercholesterolaemia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.31 Tocilizumab is administered as a dose of 8 mg/kg every 4 weeks. The net price of tocilizumab is £102.40 per 4-ml (80-mg) vial, £256.00 per 10-ml (200 mg) vial, or £512.00 per 20-ml (400-mg) vial (BNF, July 2015). Assuming a weight per person of 70 kg, vial wastage, and 13 doses each year, the annual cost (without the patient access scheme) of tocilizumab is £9318.40. Costs may vary in different settings because of negotiated procurement discounts.

3.32 The company has agreed a patient access scheme with the Department of Health in which tocilizumab will be available with a discount. The level of discount is commercial in confidence.

3.33 The Department of Health considered that the tocilizumab patient access scheme does not constitute an excessive administrative burden on the NHS.

4 Evidence and interpretation

Details of membership of the Appraisal Committee are given in section 9, and a list of the sources of evidence used in the preparation of this document is given in section 10.

Clinical effectiveness

4.1 Sixty randomised controlled trials were identified by the Assessment Group as meeting the criteria for inclusion in the systematic review:

- 6 trials were head-to-head comparisons that compared 1 biological disease-modifying antirheumatic drug (DMARD) with another biological DMARD
- 1 trial compared tumour necrosis factor (TNF)-alpha inhibitors (as a group) with combination conventional DMARDs (TACIT trial)
- 53 trials compared a biological DMARD with placebo or conventional DMARDs.

4.2 The Assessment Group reported that many of the trials included in the systematic review were of good quality, and had a reasonably low risk of bias. The Assessment Group noted that there may be issues with generalisability to the UK, because some of the trials done in Japan used low-dose methotrexate treatment before randomisation, which could affect the rate of methotrexate response among the trial populations. The Assessment Group also noted that the strict trial inclusion criteria applied resulted in study populations who may not fully reflect the range of patients seen in clinical practice in England, and that randomised controlled trials may not capture rare adverse events. For the Assessment Group the primary outcomes of interest were American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) response data.

Head-to-head biological DMARD trials

4.3 There were 6 head-to-head trials of biological DMARDs, 5 of which included people who had previously had methotrexate. Four of the trials provided ACR response data. Three of the trials reported that

ACR response rates were similar for both of the biological DMARDs included in the trial: adalimumab and subcutaneous abatacept (AMPLE), etanercept and infliximab (De Filippis) and intravenous abatacept and infliximab (ATTEST). However, in the ADACTA study, ACR response rates were statistically significantly higher with tocilizumab monotherapy than with adalimumab monotherapy. Three trials provided EULAR response data for the population who had had methotrexate before. Two of the trials reported that EULAR response rates were similar for both of the biological DMARDs included in the trial: adalimumab and etanercept (RED-SEA) and abatacept and infliximab (ATTEST). However, the ADACTA study reported that, at 6-month follow-up, the EULAR response rates were statistically significantly higher with tocilizumab monotherapy than with adalimumab monotherapy.

Network meta-analysis

4.4 The Assessment Group did a network meta-analysis including 38 trials in the systematic review that included ACR response or EULAR response measured at any time point between 22 and 30 weeks. An additional 12 trials that had been excluded from the systematic review because they included a small proportion of people who had biological DMARDs before or people who had low background methotrexate use were included in sensitivity analyses. Two trials of tofacitinib were also included in sensitivity analyses to create further links between treatments.

People not previously treated with methotrexate

4.5 For the population of people not previously treated with methotrexate, the Assessment Group did a network meta-analysis of ACR response that included 8 trials. The network compared the effects of adalimumab (with and without methotrexate), etanercept (with and without methotrexate), infliximab plus methotrexate, golimumab plus methotrexate, intensive conventional DMARDs

plus prednisolone, stepped-up combination conventional DMARDs (that is, when the intensity of treatment is increased over time to maximise disease control) and conventional DMARDs. Data were not available to complete an analysis using EULAR response.

4.6 The results showed that all interventions except for adalimumab monotherapy were associated with beneficial treatment effects compared with conventional DMARDs. The credible intervals for all the interventions, both biological and non-biological, tended to overlap with each other. There was a trend for higher estimated probability of achieving ACR20, 50 or 70 response for the biological DMARD combination therapy than for biological monotherapy. The probabilities of response are shown in table 2.

Table 2: Probability of ACR responses in the severe methotrexate-naive population (population 1)

	At least ACR20 (95% CrI)	At least ACR50 (95% CrI)	At least ACR70 (95% CrI)
Conventional DMARDs	0.56 (0.49–0.63)	0.32 (0.24–0.41)	0.17 (0.12–0.24)
Intensive therapy with a combination of conventional DMARDs	0.76 (0.59–0.90)	0.54 (0.34–0.75)	0.35 (0.18–0.587)
Step-up combination DMARDs	0.64 (0.45–0.83)	0.40 (0.22–0.63)	0.22 (0.10–0.43)
ADA+MTX	0.72 (0.60–0.82)	0.49 (0.35–0.63)	0.30 (0.18–0.44)
ADA	0.51 (0.32–0.69)	0.27 (0.13–0.46)	0.14 (0.05–0.28)
ETN+MTX	0.79 (0.61–0.90)	0.57 (0.36–0.75)	0.37 (0.20–0.58)
ETN	0.67 (0.47–0.83)	0.42 (0.24–0.63)	0.25 (0.11–0.44)
IFX+MTX	0.83 (0.70–0.94)	0.63 (0.45–0.82)	0.43 (0.27–0.66)
GOL+MTX	0.69 (0.48–0.84)	0.45 (0.25–0.65)	0.26 (0.12–0.46)
Abbreviations: ACR, American College of Rheumatology; CrI, credible intervals; DMARDs, disease-modifying anti-rheumatic drugs; ADA, adalimumab; MTX, methotrexate; ETN, etanercept; IFX, infliximab; GOL, golimumab			

People previously treated with methotrexate

4.7 For the population of people previously treated with methotrexate, the Assessment Group did network meta-analyses for EULAR and ACR responses. The Assessment Group did sensitivity analyses that included the additional trials excluded from the network meta-analysis.

4.8 In the main analysis, the Assessment Group included 15 trials reporting EULAR response and compared the effects of the following treatments with conventional DMARDs:

- intravenous abatacept plus methotrexate
- adalimumab (with and without methotrexate)
- intensive conventional DMARDs
- etanercept (with and without methotrexate)
- golimumab plus methotrexate
- infliximab plus methotrexate
- placebo
- tocilizumab (with and without methotrexate)
- the grouped biological DMARDs from the TACIT trial
- certolizumab pegol plus methotrexate.

4.9 All interventions were associated with beneficial treatment effects compared with conventional DMARDs. However, the differences were only statistically significant ($p<0.05$) for golimumab plus methotrexate and for tocilizumab (with and without methotrexate). The probabilities of response are shown in table 3.

Table 3: Probability of EULAR responses in the methotrexate-experienced populations (populations 2 and 3)

	At least moderate EULAR response (95% CrI)	At least good EULAR response (95% CrI)
Conventional DMARDs	0.45 (0.38–0.52)	0.09 (0.06–0.14)
Intensive therapy with a combination of conventional DMARDs	0.58 (0.18–0.91)	0.16 (0.02–0.57)
ABT IV+MTX	0.69 (0.36–0.91)	0.24 (0.06–0.57)
ADA+MTX	0.70 (0.33–0.93)	0.25 (0.05–0.63)
ADA	0.76 (0.33–0.98)	0.31 (0.05–0.78)
ETN+MTX	0.89 (0.43–1.0)	0.52 (0.08–0.93)
ETN	0.71 (0.12–0.99)	0.26 (0.01–0.87)
GOL+MTX	0.79 (0.55–0.93)	0.35 (0.13–0.62)
IFX+MTX	0.69 (0.44–0.87)	0.24 (0.08–0.49)
PBO	0.50 (0.07–0.94)	0.12 (0.05–0.65)
TCZ+MTX	0.91 (0.74–0.98)	0.57 (0.28–0.83)
TCZ	0.93 (0.77–0.99)	0.61 (0.32–0.88)
CTZ+MTX	0.78 (0.43–0.96)	0.34 (0.08–0.71)
Grouped biologicals	0.75 (0.21–0.98)	0.30 (0.02–0.82)

Abbreviations: EULAR, European League Against Rheumatism; CrI, credible intervals; DMARDs, disease-modifying anti-rheumatic drugs; ADA, adalimumab; MTX, methotrexate; ETN, etanercept; IFX, infliximab; GOL, golimumab; ABT, abatacept; IV, intravenous; PBO, placebo; TCZ, tocilizumab; CTZ, certolizumab pegol

4.10 The Assessment Group did a sensitivity analysis that used a wider network of evidence. This included the trials including people who had biological DMARDs before, and mapped the ACR data from the trials to the EULAR response data. This allowed the inclusion of all biological treatments, with the exception of certolizumab pegol monotherapy.

4.11 All interventions except for placebo were associated with beneficial treatment effects compared with conventional DMARDs. The differences were statistically significant ($p<0.05$) for all interventions, except for placebo and adalimumab monotherapy. The probabilities of response are shown in table 4.

Table 4: Probability of ACR responses for the methotrexate-experienced populations (population 2 and 3)

	At least ACR20 (95% CrI)	At least ACR50 (95% CrI)	At least ACR70 (95% CrI)
Conventional DMARDs	0.28 (0.24–0.32)	0.12 (0.10–0.14)	0.04 (0.03–0.05)
Intensive combination conventional DMARDs	0.46 (0.29–0.67)	0.25 (0.12–0.43)	0.11 (0.04–0.23)
ABT IV+MTX	0.56 (0.44–0.66)	0.32 (0.23–0.43)	0.15 (0.09–0.22)
ADA+MTX	0.57 (0.48–0.66)	0.33 (0.25–0.42)	0.16 (0.11–0.22)
ADA	0.43 (0.25–0.63)	0.22 (0.10–0.39)	0.09 (0.03–0.19)
ETN+MTX	0.69 (0.56–0.80)	0.46 (0.33–0.59)	0.25 (0.15–0.37)
ETN	0.62 (0.45–0.76)	0.38 (0.23–0.54)	0.19 (0.10–0.32)
GOL+MTX	0.62 (0.46–0.76)	0.38 (0.24–0.54)	0.19 (0.10–0.32)
IFX+MTX	0.57 (0.45–0.68)	0.34 (0.23–0.45)	0.16 (0.10–0.24)
PBO	0.14 (0.05–0.29)	0.05 (0.01–0.13)	0.01 (0.00–0.04)
TCZ+MTX	0.64	0.40	0.20

	(0.53–0.73)	(0.30–0.51)	(0.13–0.29)
TCZ	0.64 (0.52–0.76)	0.40 (0.29–0.51)	0.20 (0.13–0.29)
CTZ+MTX	0.72 (0.62–0.80)	0.49 (0.38–0.60)	0.27 (0.19–0.37)
ABT SC+MTX	0.58 (0.43–0.72)	0.34 (0.22–0.50)	0.16 (0.09–0.23)
Abbreviations: ACR, American College of Rheumatology; CrI, credible intervals; DMARDs, disease-modifying anti-rheumatic drugs; ADA, adalimumab; MTX, methotrexate; ETN, etanercept; IFX, infliximab; GOL, golimumab; ABT, abatacept; IV, intravenous; PBO, placebo; TCZ, tocilizumab; CTZ, certolizumab pegol; SC, subcutaneous			

Cost effectiveness

4.12 The Assessment Group included 30 studies in their systematic review of the literature. Twenty-three studies evaluated biological DMARDs in people who had previously had DMARDs, 6 studies evaluated biological DMARDs in people who had not previously had DMARDs, and 1 study evaluated people in both groups. Most studies were of etanercept, infliximab and adalimumab, with no studies found for certolizumab pegol or golimumab. The studies had a wide range of model methods, time horizons, price years, currencies and discount rates. The Assessment Group stated that a detailed analysis of the parameters used in each study was not feasible, and that drawing strong conclusions on the cost effectiveness of individual therapies was not possible. The results of the Assessment Group's systematic review indicated that, in people who had previously had DMARD therapy, many biological DMARDs had incremental cost-effectiveness ratios (ICERs) close to £30,000 per quality-adjusted life year (QALY) gained in both directions, and that the ICERs were often higher for those people not previously treated with DMARDs. No individual biological DMARD was seen to be consistently more cost effective than any other biological DMARD. The Assessment Group noted that 3 studies (Jobanputra 2002; Barton 2004; Chen 2006) had been

used in previous NICE technology appraisal guidance on adalimumab, etanercept and infliximab and adalimumab, etanercept, infliximab, rituximab and abatacept for rheumatoid arthritis.

Company's economic models

4.13 The 6 companies submitted models for each of the 7 drugs. The models for golimumab and infliximab were similar, because they are both manufactured by Merck Sharpe & Dohme, and are described together in this document.

AbbVie (adalimumab)

4.14 AbbVie submitted separate analyses for the severe active and the moderate active disease populations of people who had previously had methotrexate and the severe active population who had not previously had methotrexate, both as monotherapy and with methotrexate. Adalimumab was compared with other biological DMARDs and with conventional DMARDs.

4.15 The model was an individual patient simulation in ARENA software. It used a discrete simulation approach so there were no time cycles. The model used a lifetime time horizon, the perspective of the NHS and personal social services and a discount rate of 3.5% for costs and benefits. The available patient access schemes were not included in the model. Costs of serious infections were included. Disease-related costs were included and these were based on the Norfolk Arthritis Register (NOAR) database. The model assumed an increased risk of death for a person with rheumatoid arthritis of 1.33 per Health Assessment Questionnaire (HAQ) score unit increase.

4.16 Baseline characteristics of people with severe active disease previously treated with methotrexate were taken from the British Society for Rheumatology Biologics Register (BSRBR). For people

with moderate active disease previously treated with methotrexate, the ReAct study was used. For people with severe active disease not previously treated with methotrexate, the source was the PREMIER trial. People moved through a sequence of treatments depending on response to treatment, which included the use of rituximab and tocilizumab after the failure of a TNF-alpha inhibitor, as well as conventional DMARDs. The response criterion in the model was ACR50. All people were assumed to stay on treatment for 6 months, unless an adverse event occurred.

Bristol–Myers Squibb (abatacept)

4.17 Bristol–Myers Squibb submitted a combined analysis for severe active and moderate active rheumatoid arthritis, for a population who had previously had abatacept plus methotrexate. Abatacept was compared with other biological DMARDs and with conventional DMARDs.

4.18 The model was an individual patient model implemented in Simul8 and did not need time cycles. The structure of the model was similar to that used in the NICE technology appraisal guidance on adalimumab, etanercept, infliximab, rituximab and abatacept (the use of biological DMARDs after the failure of a TNF-alpha inhibitor), but added an additional biological DMARD to the start of the model. The model used a lifetime time horizon, the perspective of the NHS and personal social services and a discount rate of 3.5% for costs and benefits. All the available patient access schemes were included in the model. Costs and disutilities associated with adverse events were not included. Disease-related costs were included. These were assumed to be a cost per HAQ unit score of £1245 based on those used in the NICE technology appraisal guidance on adalimumab, etanercept, infliximab, rituximab and abatacept. The model assumed an increased risk of death of 1.33 per HAQ score unit for a person with rheumatoid arthritis.

4.19 Baseline characteristics of patients were based on those used in the NICE technology appraisal guidance on adalimumab, etanercept and infliximab from Chen et al. (2006). People moved through a sequence of treatments based on response, which included the use of rituximab and tocilizumab after the failure of a TNF-alpha inhibitor, as well as conventional DMARDs. The response criterion in the model was an improvement of 1.2 in disease activity score (DAS28). People were assumed to stay on treatment for 6 months, unless an adverse event occurred.

Merck Sharp & Dohme (golimumab and infliximab)

4.20 Merck Sharp & Dohme submitted an analysis for severe active rheumatoid arthritis, and a combined analysis for severe active and moderate active rheumatoid arthritis, both in combination with methotrexate, for a population previously treated with methotrexate. Both infliximab and golimumab were compared with other biological DMARDs and with conventional DMARDs.

4.21 Separate models were provided for each intervention, but for both Merck Sharp & Dohme constructed a cohort Markov model in Excel, with a time cycle of 6 months with a half-cycle correction. The time horizon of the models was 45 years with the perspective of the NHS and personal social services and a discount rate of 3.5% for costs and benefits. The patient access schemes for golimumab, tocilizumab and certolizumab pegol were included in the model. Costs and disutilities associated with adverse events were not included. Disease-related costs were included using data from Brennan et al. (2007) to estimate the number of hospitalisations. The model included an increased risk of death associated with rheumatoid arthritis using a standardised mortality ratio of 1.65 that was taken from Chenhata et al. (2001) and was not HAQ dependent.

4.22 Patient baseline characteristics were taken from the GO-FORWARD trial for golimumab and from the ATTRACT trial for infliximab. People moved through a sequence of treatments based on response, which included the use of rituximab after the failure of a TNF-alpha inhibitor, as well as conventional DMARDs. The sequence of treatments did not include tocilizumab. The response criterion in the model was ACR20 response and all patients were assumed to stay on treatment for 6 months.

Pfizer (etanercept)

4.23 Pfizer included analyses for severe active and moderate active rheumatoid arthritis previously treated with methotrexate and severe active rheumatoid arthritis not previously treated with methotrexate, in combination with methotrexate, and as monotherapy. Etanercept was compared with other biological DMARDs and with conventional DMARDs.

4.24 Pfizer submitted an individual patient-level model using a discrete event simulation approach built in Excel. The approach meant there were no time cycles. The model used a lifetime time horizon, the perspective of the NHS and personal social services and a discount rate of 3.5% for costs and benefits. The patient access schemes for golimumab and certolizumab pegol were included in the model. Costs and disutilities associated with adverse events were included in a scenario analysis. Disease-related costs were included using Kobelt et al. (2002) based on the Early Rheumatoid Arthritis Study, to estimate the direct annual costs of medical resources. The model included an increased risk of death for a person with rheumatoid arthritis using Brennan et al. (2007). It also assumed an age and sex-specific standardised mortality ratio, based on the UK population, and was not HAQ dependent.

4.25 For people with severe active disease who had previously used DMARDs, baseline patient characteristics were taken from the etanercept BSRBR cohort. For people with moderate active disease who had previously used DMARDs, patient characteristics were based on the PRESERVE trial. For people with severe active disease who had not previously had DMARDs, patient characteristics were taken from the COMET trial. People moved through a sequence of treatments depending on response, which included the use of rituximab and tocilizumab after the failure of a TNF-alpha inhibitor, as well as conventional DMARDs. The response criterion in the model was ACR20 (used in the base-case analysis) or ACR50. All patients were assumed to stay on treatment for 6 months.

Roche (tocilizumab)

4.26 Roche submitted an analysis of people who could not tolerate methotrexate or for whom it was contraindicated (the severe active and moderate active populations combined) who had previously had methotrexate. Tocilizumab was included as a first-line biological treatment and compared with a sequence of care including 3 lines of biological DMARDs (certolizumab pegol, etanercept and adalimumab).

4.27 Roche submitted an individual patient level model in Excel. The model used a 6-month cycle length with half-cycle correction. The model used a lifetime time horizon, the perspective of the NHS and personal social services and a discount rate of 3.5% for costs and benefits. The patient access schemes for tocilizumab and certolizumab pegol were included in the model. Costs and disutilities associated with adverse events were not included. Disease-related costs were included, with inpatient costs calculated using the NOAR dataset. The model assumed an increased risk of death of 1.33 per HAQ score unit for rheumatoid arthritis.

4.28 Baseline patient characteristics were taken from the ADACTA trial, but instead of using the 77 kg average weight per person in the ADACTA trial, a 70 kg average weight per person was used, as previously accepted in the NICE technology appraisal guidance on adalimumab, etanercept and infliximab, adalimumab, etanercept, infliximab, rituximab and abatacept and tocilizumab. Tocilizumab was included as a first-line biological treatment to create 4 lines of biological DMARDs (that is, a sequence of 4 biological DMARDs including tocilizumab was compared with a sequence of 3 biological DMARDs without tocilizumab). Conventional DMARDs were not included in the sequence. The response criterion in the model was ACR20 response at 6 months, but people whose disease did not respond to treatment were assumed to only incur costs of treatment for 3 months.

UCB (certolizumab pegol)

4.29 UCB submitted analyses for the severe active population (as monotherapy and in combination with methotrexate) and moderate active populations (in combination with methotrexate only) who had previously had methotrexate. Certolizumab pegol was compared with other biological DMARDs, but was not compared with conventional DMARDs in the analyses for severe active rheumatoid arthritis.

4.30 UCB submitted a model with a Markov (cohort health state transition) structure built in Excel. After the first 12 months, the cycle length was 6 months, and a half-cycle correction was used. The time horizon of the model was 45 years with the perspective of the NHS and personal social services and a discount rate of 3.5% for costs and benefits. The patient access schemes for golimumab and certolizumab pegol were included in the model. Costs and disutilities associated with adverse events were not included. Disease-related costs were included using Kobelt et al. (2002)

based on the Early Rheumatoid Arthritis Study. The model assumed an increased risk of death of 1.33 per HAQ score unit for a person with rheumatoid arthritis.

4.31 Baseline characteristics for people with severe active disease previously treated with methotrexate were based on pooled mean estimates from the RAPID 1, RAPID 2 and FAST4WARD trials including both placebo and certolizumab pegol arms. For people with moderate active disease previously treated with methotrexate, UCB used pooled mean estimates from the CERTAIN trial, including both placebo and certolizumab pegol arms. The model included a sequence of treatments that included the use of rituximab but not tocilizumab after the failure of a TNF-alpha inhibitor, as well as conventional DMARDs. The response criterion in the model could be either ACR20 response or EULAR response and the time before measurement of response could be changed between 3 and 6 months.

Modelling the effects of treatment

4.32 The companies used comparable methods to model the effects of treatment. On starting treatment, disease either responds or does not respond to treatment. If the disease responds, this is recorded in terms of ACR20, 50 or 70 response or EULAR moderate or good response. The ACR or EULAR response is then related to a change in HAQ score or health-related quality of life (if health-related quality of life data are available). A better response is related to a larger change in HAQ or health-related quality of life. The scoring of the HAQ means that an improvement in function is related to a decrease in HAQ, and worsening of disease is related to an increase in HAQ. If HAQ instead of health-related quality of life is used, the HAQ change is then mapped to health-related quality of life data to produce a utility. This effect of treatment is assumed to be lost when treatment is stopped (described as the

'rebound effect'). Treatment was also modelled as slowing disease progression, calculated as an annual change in HAQ while on treatments. The annual change in HAQ score is assumed to be greater for a person having conventional DMARDs than for a person having biological DMARDs.

4.33 The companies had different approaches to modelling the initial response to treatment. AbbVie, Merck Sharp & Dohme, Pfizer, Roche and UCB included network meta-analyses for ACR20, 50 and 70 response rates. Bristol–Myers Squibb and UCB included network meta-analyses for change in DAS28 or EULAR response. Bristol–Myers Squibb and Pfizer included network meta-analyses for change in HAQ. Not all analyses were completed for each population modelled. Most of the companies related the ACR or EULAR response derived from the network meta-analyses to a change in HAQ that was then mapped to EQ-5D utility. However, UCB used directly collected EQ-5D data from their clinical trials. Of the mapping equations, those used in the NICE technology appraisal guidance on adalimumab, etanercept and infliximab (Hurst et al. [1997] or Chen et al. [2006]) and adalimumab, etanercept, infliximab, rituximab and abatacept (Malottki et al. 2011) were used as the base case by AbbVie, Bristol–Myers Squibb, Merck Sharp & Dohme and Pfizer.

4.34 To model the change in HAQ score as disease progressed, the companies used values from previous NICE appraisals that assumed a linear rate of progression. No progression was assumed to occur for people having treatment with biological DMARDs. For people having treatment with conventional DMARDs, there was a 0.045 increase (worsening) in HAQ score per year, and for people on treatment with palliative care there was a 0.060 increase (worsening) in HAQ score per year. These changes in

HAQ were also related to a change in utility using equations as in the companies' submissions for HAQ or EQ-5D mapping.

4.35 UCB included a different approach and reported that after initial response HAQ would decrease (that is, disease would improve) by 0.0963 every 6 months while on first-line treatment (an improvement in utility of 0.0202 every 6 months). After treatment with the first biological DMARD failed, people on conventional DMARDs or palliative care had an annual increase in HAQ of 0.03 (a worsening of utility of 0.0063), whereas people having further biological DMARDs had a worsening of utility of 0.003. The long-term change in HAQ score was related to health-related quality of life using a mapping function.

Cost-effectiveness results from the companies' submissions

Biological DMARDs plus methotrexate for severe active rheumatoid arthritis previously treated with methotrexate

4.36 Results for biological DMARDs plus methotrexate in people with severe active rheumatoid arthritis previously treated with methotrexate were provided by AbbVie, Merck Sharp & Dohme, Pfizer and UCB. UCB did not compare them with conventional DMARDs. Each of the other companies concluded that their intervention was cost effective compared with conventional DMARDs. AbbVie presented ICERs for the biological DMARDs compared with conventional DMARDs ranging from £16,571 to £24,172 per QALY gained. Merck Sharp & Dohme presented ICERs for golimumab and infliximab compared with conventional DMARDs of £21,013 and £24,968 per QALY gained, respectively. Pairwise ICERs calculated from the Pfizer submission for biological DMARDs compared with conventional DMARDs ranged from £20,518 to £56,624 per QALY gained.

4.37 Both AbbVie and Pfizer provided incremental analyses. Both suggested that etanercept was the most cost-effective biological DMARD with an ICER of £16,571 and £20,520 per QALY gained respectively. Other biological DMARDs were dominated (more expensive and less effective than the comparator) or extendedly dominated (more expensive and less effective than a combination of other drugs). The incremental analysis provided by UCB suggested that certolizumab pegol was the most cost-effective treatment at a maximum acceptable ICER of £4822 per QALY gained.

Biological DMARDs plus methotrexate for moderate active rheumatoid arthritis previously treated with methotrexate

4.38 Results for biological DMARDs plus methotrexate in people with moderate active rheumatoid arthritis previously treated with methotrexate were provided by AbbVie, Pfizer and UCB. All companies except UCB concluded that their intervention was cost effective. AbbVie presented ICERs for the biological DMARDs compared with conventional DMARDs ranging from £18,792 to £26,952 per QALY gained. Pfizer presented an ICER for etanercept compared with conventional DMARDs of £24,727 per QALY gained. Pfizer stated that there was a lack of randomised control trial data for the use of biological DMARDs in a population with truly moderately active disease. The 2 available trials (PRESERVE and CERTAIN) could not be combined in a network meta-analysis. UCB presented an ICER for certolizumab pegol compared with conventional DMARDs of £49,226 per QALY gained. AbbVie provided an incremental analysis that suggested that etanercept was the most cost-effective biological DMARD with an ICER of £18,721 per QALY gained. Other biological DMARDs were dominated or extendedly dominated.

Biological DMARDs plus methotrexate for moderate or severe active rheumatoid arthritis previously treated with methotrexate

4.39 Results for biological DMARDs plus methotrexate in people with moderate or severe active rheumatoid arthritis previously treated with methotrexate were provided by Bristol–Myers Squibb and Merck Sharp & Dohme. The ICERs provided by Bristol–Myers Squibb were provided as commercial in confidence and cannot be presented here. The ICERs presented by Merck Sharp & Dohme for biological DMARDs compared with conventional DMARDs ranged from £18,817 to £44,232 per QALY gained in the golimumab submission and from £21,011 to £55,234 per QALY gained in the infliximab submission.

4.40 Merck Sharp & Dohme presented incremental analyses for both golimumab and infliximab. The Assessment Group reported that both Merck Sharp & Dohme incremental analyses were incorrect. The analyses in both submissions with the Assessment Group corrections suggested that certolizumab pegol was the most cost-effective treatment with an ICER of £18,817 per QALY gained in the golimumab submission and £21,011 per QALY gained in the infliximab submission. Other biological DMARDs were either dominated or extendedly dominated.

Biological DMARDs plus methotrexate for severe active rheumatoid arthritis not previously treated with methotrexate

4.41 Results for biological DMARDs plus methotrexate in people with severe active rheumatoid arthritis not previously treated with methotrexate were provided by AbbVie and Pfizer.

4.42 AbbVie included a comparison with the licensed biological DMARDs, methotrexate monotherapy and methotrexate plus hydroxychloroquine. The ICERs presented for biological DMARDs compared with conventional DMARDs were £30,071 to £33,055 per

QALY gained. Their incremental analyses reported an ICER for methotrexate plus hydroxychloroquine compared with methotrexate of £18,381 per QALY gained and an ICER for adalimumab compared with methotrexate plus hydroxychloroquine of £69,971 per QALY gained. Other treatment options were dominated.

4.43 Pfizer only included a comparison of etanercept with conventional DMARDs, including adalimumab in a secondary analysis. Their incremental analysis suggested that the ICER for etanercept compared with combination conventional DMARDs was £34,373 per QALY gained, with conventional DMARD monotherapy dominated.

Biological DMARD monotherapy for a population with severe active rheumatoid arthritis previously treated with methotrexate

4.44 Results for biological monotherapy in people with severe active rheumatoid arthritis previously treated with methotrexate were provided by AbbVie, Pfizer and UCB. UCB included other biological DMARDs in its analysis but did not compare certolizumab pegol with conventional DMARDs. The ICERs presented by AbbVie for biological DMARDs compared with conventional DMARDs ranged from £29,338 to £50,972 per QALY gained. Pairwise ICERs calculated from the Pfizer submission ranged from £26,339 to £30,277 per QALY gained.

4.45 The incremental analysis provided by AbbVie suggested that etanercept was the most cost-effective biological DMARD with an ICER of £29,338 per QALY gained. Other biological DMARDs were dominated or extendedly dominated. The incremental analysis provided by Pfizer also suggested that etanercept was the most cost-effective biological DMARD with an ICER of £26,335 per QALY gained. In this analysis, rather than tocilizumab being dominated or extendedly dominated it was associated with an ICER

of £34,227 per QALY gained compared with etanercept. The incremental analysis by UCB suggested that, at an ICER range of £0 to £9587 per QALY gained, adalimumab was the most cost-effective treatment, and at an ICER range of £9587 to £962,778 per QALY gained, certolizumab pegol was the most cost-effective treatment.

Biological DMARD monotherapy for moderate active rheumatoid arthritis previously treated with methotrexate

4.46 Results for this population were provided by AbbVie. The ICERs presented by AbbVie for biological DMARDs compared with conventional DMARDs ranged from £32,276 to £55,844 per QALY gained.

4.47 The incremental analysis provided by AbbVie suggested that etanercept was the most cost-effective biological DMARD with an ICER of £32,276 per QALY gained. Other biological DMARDs were dominated or extendedly dominated.

Biological DMARD monotherapy for moderate or severe active rheumatoid arthritis previously treated with methotrexate

4.48 Results for biological monotherapy in people with moderate or severe active rheumatoid arthritis were provided by Roche. Adding tocilizumab monotherapy to a sequence of 3 biological DMARDs was associated with an ICER of £14,520 per QALY gained.

Biological DMARD monotherapy for severe active rheumatoid arthritis not previously treated with methotrexate

4.49 Results for this population were provided by AbbVie and Pfizer. AbbVie compared adalimumab and etanercept monotherapy and sulfasalazine plus hydroxychloroquine followed by adalimumab. Their incremental analysis suggested that the use of sulfasalazine and hydroxychloroquine before adalimumab was the most cost-effective strategy with an ICER of £18,540 per QALY gained. Other

treatment strategies were dominated. Pfizer presented an ICER for etanercept compared with conventional DMARDs of £34,572 per QALY gained.

Assessment Group cost-effectiveness analysis

4.50 The Assessment Group developed an individual patient-based discrete event simulation model for their economic evaluation. The model incorporated a response criterion based on EULAR response at 6 months to reflect UK clinical practice. The Assessment Group modelled:

- people with severe active disease previously treated with methotrexate
- people with moderate active disease previously treated with methotrexate
- people with severe active disease not previously treated with methotrexate.

Technologies were assessed both in combination with methotrexate and as monotherapy in the 3 populations.

4.51 The model approach meant that there were no time cycles. The model had a lifetime time horizon similar to those in the companies' submissions. The Assessment Group used an NHS and personal social services perspective and a discount rate of 3.5% for both costs and benefits.

Strategies modelled

4.52 The scope for the appraisal includes only the first-line use of biological DMARDs. Therefore the Assessment Group assumed that after the first biological treatment has failed, NICE guidance was followed. This means that after the first biological DMARD, rituximab plus methotrexate followed by tocilizumab plus methotrexate was used for people who can tolerate methotrexate.

Because of lack of evidence on the clinical effectiveness of conventional DMARDs after biological DMARDs, the Assessment Group decided to limit the sequence of treatments modelled to 1 further conventional DMARD (typically methotrexate, but a different conventional DMARD if methotrexate was unsuitable) after biological DMARDs and before moving to a selection of conventional DMARDs that may be given in established disease (referred to as 'non-biological therapy'). Non-biological therapy was assumed to have no initial EULAR response, unlike methotrexate, which was assumed to have a EULAR response based on the network meta-analysis. The Assessment Group commented that the strategies were similar to those modelled by the companies, except for the generic conventional DMARD sequence rather than named conventional DMARDs.

Baseline population characteristics

4.53 The Assessment Group used the BSRBR to provide baseline characteristics for people who had previously had methotrexate, which allowed for correlation to be maintained between age, sex, disease duration, DAS28, prior DMARD use, HAQ score and weight. For people who had not previously had methotrexate, the Assessment Group used the COMET trial as used in the Pfizer submission.

Cost of the interventions

4.54 The Assessment Group took into account all the patient access schemes (certolizumab pegol, golimumab, abatacept, and tocilizumab), and did not use a fixed weight for weight-based interventions. In the absence of robust data, the Assessment Group used an infusion cost of £154 and a time of 1 hour, taken from the NICE technology appraisal guidance on tocilizumab. The Assessment Group used the average administration cost per subcutaneous injection of £3.05.

Comparative treatment efficacy

4.55 The initial response to treatment was modelled using the EULAR response data from the Assessment Group network meta-analysis. Because a smaller number of trials included EULAR response data compared with ACR response data and not all interventions could be included in the EULAR network, a separate analysis was also done in which ACR data were mapped to EULAR response using individual patient level data from the Veterans Affairs Rheumatoid Arthritis (VARA) database. The Assessment Group also did scenario analyses in which it extended the network of evidence to include the 12 trials that had been excluded from the systematic review and network meta-analysis.

HAQ change in relation to response levels

4.56 The Assessment Group estimated a change in HAQ after EULAR response using data from the BSRBR cohort. The Assessment Group assumed that the relationship between EULAR response and HAQ improvement was independent of the biological DMARD used or whether biological or conventional DMARDs were used. Comparing the predicted and observed data in the BSRBR, for a person with the mean characteristics of the sample, the model used by the Assessment Group predicted a change of 0.29 in HAQ for a moderate EULAR response compared with 0.33 in the BSRBR data and a change of 0.54 in HAQ for a good EULAR response, compared with a change of 0.55 in the BSRBR data. When this was applied in the economic model, a person with the mean characteristics of the overall sample had a change in HAQ of 0.317 for a moderate EULAR response and 0.672 for a good EULAR response.

HAQ trajectory after initial response

4.57 For biological DMARDs, the Assessment Group explored 3-year data from the BSRBR to estimate the change in HAQ over time

after the initial response. The HAQ change on a biological DMARD was a function of the person's baseline characteristics and 6-month EULAR response. The Assessment Group used data from 2417 people who had a good response, 5492 who had a moderate response, and 2277 who had no response. HAQ decreased in the first 6 months (with a greater response for better EULAR responses), then levelled off by the end of the 3-year observation. The Assessment Group's analysis showed that the change in HAQ after the initial response was close to no progression and therefore it made a simplifying assumption of no progression of disease while on biological DMARDs.

4.58 For conventional DMARDs, the Assessment Group used an analysis by Norton et al. (2012) as a basis for estimating HAQ progression. Norton et al. used data from the Early Rheumatoid Arthritis Study (ERAS) inception cohort and identified 4 different types or 'classes' of trajectory for disease progression. The Norton data suggested 'J'-shaped HAQ progression curves for 3 groups of patients, with an initial improvement in HAQ on treatment and then worsening over time. The fourth group showed general worsening over time. In all 4 groups the rate of worsening decreased over time, rather than remaining constant over time.

4.59 The Assessment Group modified the Norton et al. (2012) model so that patient variables were used as covariates for explanatory variables. The Assessment Group incorporated age at disease onset, sex, deprivation level, disease duration, rheumatoid factor status at baseline, ACR criteria at baseline, DAS at baseline, failure of 2 DMARDs and DAS at 6 months. This allowed the Assessment Group to sample patients with characteristics of those likely to be treated with biological DMARDs. The sampling process meant that approximately 70% of patients were from the classes with the worst underlying disease progression in the first 10 years. Overall, the

Assessment Group sample had an HAQ progression of approximately 0.06 between years 2 and 7 with a slowing down in the rate of worsening after this point. After 15 years the Assessment Group assumed that the trajectory of the curve was flat.

4.60 The values from previous NICE appraisals and the company submissions assumed a linear rate of progression of 0.045 in HAQ score per year, rising to 0.06 per year when patients moved to palliative care. The Assessment Group considered that the 'J'-shaped curve was a more appropriate reflection of a chronic disease than the linear annual progression. It tested the impact of using the values from previous NICE appraisals in sensitivity analyses.

Time to discontinuation on treatment

4.61 The Assessment Group used the BSRBR database to estimate the time on treatment for the first biological DMARD for people with disease that had a good or moderate EULAR response. Age, sex, disease duration at baseline, DAS score, number of previous DMARDs and HAQ score at baseline were included as covariates. Given the scarcity of the data available, separate terms for covariates for individual biological therapies were not used.

4.62 The Assessment Group stated that, because of scarcity of data, it assumed that the duration on treatment was unaffected by whether or not conventional DMARDs had previously been used and that the time on treatment for each EULAR response category for biological DMARDs would apply to conventional DMARDs. The Assessment Group assumed that people would not switch to a subsequent treatment within 6 months of starting treatment, so that any adverse event would be detected before treatment change.

Post-treatment rebound

4.63 The Assessment Group assumed that after stopping treatment the initial improvement in HAQ would be lost. The resulting HAQ was assumed to remain for the subsequent 6 months when the next treatment was trialled. The Assessment Group commented that this was in line with the assumptions made by the companies.

Assumed NHS costs per HAQ band

4.64 The Assessment Group used the hospital costs reported by AbbVie in their base-case analyses. These were among the lowest presented and were relatively constant until the person had a severe HAQ score (2.125 or more). The data were taken from the NOAR database for inpatient days and joint replacements, multiplied by NHS reference costs.

Utility related to HAQ

4.65 The Assessment Group considered that the estimate of EQ-5D was more accurate when it was based on pain and HAQ rather than HAQ alone. To include pain, the Assessment Group simulated the expected pain score associated with HAQ for each person within the model. The Assessment Group commented that this incorporated the assumption that all treatments affect pain proportionate to their effect on HAQ, but noted that this assumption is implicit in all models that exclude pain. The Assessment Group used data from ERAS to calculate the mean pain score and variance estimated for each valid HAQ score. To calculate the EQ-5D from the HAQ score and simulated pain score, the Assessment Group used a method based on mixture models from Hernandez Alava et al. (2013) using data from 16,011 patients from the US National Data Bank for Rheumatic Diseases (NDB).

The assumed costs and disutilities associated with adverse events

4.66 The Assessment Group assumed that only serious infections would have a large effect on costs and utilities, and therefore limited the adverse events within the model to serious infections alone. A Cochrane review (Singh et al. 2011) indicated that serious infections were seen in 35 per 1000 patients (95% confidence interval [CI] 27 to 46) for biological DMARDs, and 26 per 1000 (95% CI not reported) for conventional DMARDs. The Assessment Group assumed the infection rate was independent of the biological DMARD used. The Assessment Group used the costs (£1479 per episode) and undiscounted QALY loss (a loss in utility of 0.156 for 28 days) associated with serious infections from the Pfizer submission. The Assessment Group assumed that using biological DMARDs would incur an additional £13.31 cost and QALY loss of 0.0001 per typical person treated.

Mortality associated with rheumatoid arthritis

4.67 The Assessment Group stated that the companies had used a variety of approaches in their submissions, but that the majority of company submissions had assumed that an increase in HAQ was associated with an increase in expected mortality. The Assessment Group assumed that only baseline HAQ score predicted mortality. If initial baseline HAQ was higher, a higher mortality hazard ratio was applied, with the hazard ratio being independent of time. The Assessment Group noted that there is limited evidence available to support the relationship between change in HAQ and change in expected mortality.

Cost-effectiveness results from the Assessment Group model

4.68 The Assessment Group analysed 24 combinations of factors – the 3 populations (the severe active and moderate active disease populations who had been previously treated with methotrexate, and the severe active population who had not been previously

treated with methotrexate), whether the treatment was provided as monotherapy or with methotrexate, whether EULAR or ACR mapped to EULAR response data were used in the model, and whether the HAQ trajectory for conventional DMARDs was taken from ERAS or from previous NICE technology appraisal guidance. EULAR response in people who had not previously had methotrexate was not analysed because no data were available. The Assessment Group also did sensitivity analyses assessing the effect of including different randomised controlled trials in the network meta-analysis, using different mapping functions of HAQ to utility, using the discount rates in the NICE technology appraisal guidance on adalimumab, etanercept and infliximab, increasing the effect of adverse events and using a different assumed relationship between HAQ and pain.

4.69 The Assessment Group presented the median ICERs for biological DMARDs for the 3 different populations. For the population who had not had methotrexate before, no results were presented for a model based on EULAR response because of lack of data. The results provided use ACR data mapped to EULAR response. The incremental costs and QALYs are not presented in this document because some of the patient access schemes are commercial in confidence. However, the Assessment Group noted that there were only small differences in costs and QALYs between the different biological DMARDs. On this basis it noted that the fully incremental cost-effectiveness analyses may be misleading.

4.70 The Assessment Group compared the results of their model with those of the companies and also with the ICERs presented in the NICE technology appraisal guidance on adalimumab, etanercept and infliximab. Using the assumption of linear HAQ progression as used in the companies' models and in previous NICE appraisals, the ICERs were between £35,000 and £40,000 per QALY gained.

Using the discount rates applied in the NICE technology appraisal guidance on adalimumab, etanercept and infliximab (that is, the discount rates of 6% for costs and 1.5% for benefits) the ICERs reduced further to approximately £25,000 per QALY gained. The Assessment Group considered that these results demonstrated that their model, using similar inputs, produced comparable ICERs to those of the economic models and that had been used in previous appraisals.

Biological DMARDs plus methotrexate for severe active rheumatoid arthritis previously treated with methotrexate

4.71 For severe active rheumatoid arthritis previously treated with methotrexate, biological DMARDs plus methotrexate were associated with a median ICER (that is, the median of the ICERs for each individual biological DMARD) of £41,600 per QALY gained using the base-case assumptions (that is, response based on EULAR data collected in clinical studies and the non-linear estimate of HAQ progression from ERAS). The deterministic ICERs for the individual biological DMARDs plus methotrexate compared with methotrexate alone were between £39,100 and £42,200 per QALY gained. Using the wider network of evidence slightly changed the median ICER to £41,000 per QALY gained. The estimate of the median ICER was reduced to £37,900 per QALY gained if the linear HAQ progression assumption from previous appraisals was used. Using the alternative utility mapping function from Malottki et al. (2011) as used in the NICE technology appraisal guidance on adalimumab, etanercept, infliximab, rituximab and abatacept gave a median ICER of £34,700 per QALY gained using the non-linear estimate of HAQ progression. The probabilistic median ICER was similar to the median base-case deterministic ICER; £41,300 per QALY gained.

Biological DMARDs plus methotrexate for moderate active rheumatoid arthritis previously treated with methotrexate

4.72 For moderate active rheumatoid arthritis previously treated with methotrexate, biological DMARDs plus methotrexate were associated with a median ICER of £51,100 per QALY gained using the base-case assumptions. The deterministic ICERs for the individual biological DMARDs plus methotrexate compared with methotrexate alone were between £47,500 and £51,600 per QALY gained. Using the wider network of evidence, the median ICER changed to £52,100 per QALY gained. The median ICER was reduced to £37,500 per QALY gained if the linear HAQ progression assumption from previous NICE technology appraisals was used. Using the alternative utility mapping function from Malottki et al. (2011), as used in previous NICE technology appraisal guidance, gave a median ICER of £36,300 per QALY gained. The probabilistic median ICER was similar to the median base-case deterministic ICER; £52,000 per QALY gained.

Biological DMARDs plus methotrexate for severe active rheumatoid arthritis not previously treated with methotrexate

4.73 For severe active rheumatoid arthritis not previously treated with methotrexate, given the small differences between the biological DMARDs, the Assessment Group assumed that the ICER for etanercept plus methotrexate would represent the ICERs for the other biological DMARDs. The ICER comparing etanercept plus methotrexate with methotrexate followed by other non-biological therapies was £68,300 per QALY gained using the base-case assumptions. Using the wider network of evidence, the ICER changed to £68,200 per QALY gained. The estimate of the ICER was reduced to £58,300 per QALY gained if the linear HAQ progression assumption from previous appraisals was used. Using the alternative utility mapping function from Malottki et al. (2011) as

used in previous NICE technology appraisal guidance, gave an ICER of £50,500 per QALY gained. For the probabilistic base-case analysis in this population, the ICER comparing etanercept plus methotrexate with methotrexate followed by other non-biological therapies was £66,100 per QALY gained.

Biological DMARD monotherapy for a population with severe active rheumatoid arthritis previously treated with methotrexate

4.74 For severe active rheumatoid arthritis previously treated with methotrexate, biological DMARD monotherapy was associated with a median ICER of £48,300 per QALY gained using the base-case assumptions. The deterministic ICERs for the individual biological DMARDs plus methotrexate compared with methotrexate alone were between £46,300 and £48,500 per QALY gained. Using the wider network of evidence, the median ICER changed to £49,500 per QALY gained. The median ICER was reduced to £39,600 per QALY gained, if the linear HAQ progression assumption from previous NICE technology appraisals was used. Using the alternative utility mapping function from Malottki et al. (2011) as used in previous NICE technology appraisal guidance, gave a median ICER of £40,200 per QALY gained. The probabilistic median ICER was similar to the median base-case deterministic ICER; £48,200 per QALY gained.

Biological DMARD monotherapy for moderate active rheumatoid arthritis previously treated with methotrexate

4.75 For moderate active rheumatoid arthritis previously treated with methotrexate, biological DMARD monotherapy was associated with a median ICER of £58,800 per QALY gained using the base-case assumptions. The deterministic ICERs for the individual biological DMARDs plus methotrexate compared with methotrexate alone were between £58,700 and £59,000 per QALY gained. Using the wider network of evidence, the median ICER changed to £62,400

per QALY gained. The median ICER was reduced to £41,400 per QALY gained, if the linear HAQ progression assumption from previous NICE technology appraisals was used. Using the alternative utility mapping function from Malottki et al. (2011) as used in previous NICE technology appraisal guidance, gave a median ICER of £40,200 per QALY gained. The probabilistic median ICER was similar to the median base-case deterministic ICER; £59,700 per QALY gained.

Biological DMARD monotherapy for severe active rheumatoid arthritis not previously treated with methotrexate

4.76 For severe active rheumatoid arthritis not previously treated with methotrexate, biological DMARD monotherapy was associated with an ICER of £77,500 per QALY gained using the base-case assumptions. Using the wider network of evidence, the ICER was £78,000 per QALY gained. The ICER was reduced to £63,200 per QALY gained if the linear HAQ progression assumption from previous NICE technology appraisals was used. Using the alternative utility mapping function from Malottki et al. (2011) as used in previous NICE technology appraisal guidance, gave an ICER of £57,800 per QALY gained. For the probabilistic base-case analysis in this population, the ICER was £76,200 per QALY gained.

Decision Support Unit work on HAQ progression

4.77 After the first Committee meeting the Decision Support Unit (DSU) was asked to do further work on HAQ progression. This was because of the differences between the company submissions and the assessment report in the underlying assumptions of modelling disease progression for patients treated with conventional DMARDs. The DSU was to provide additional information on the rate of HAQ progression over time for people with rheumatoid arthritis having non-biological therapies.

4.78 A literature review by the DSU identified studies that included rheumatoid arthritis patients with established disease who were having non-biological therapy, with more than 5 years of follow-up. The studies provided information on HAQ progression. Nine studies had more than 8 years of follow-up; 5 of these studies suggested that HAQ does not follow a linear progression rate because rapid worsening followed by a period of slower worsening was seen.

4.79 The DSU identified 5 datasets that followed up patients for 5 years or more and were suitable for further analysis. These datasets were:

- Early Rheumatoid Arthritis Study (ERAS)
- Early Rheumatoid Arthritis Network (ERAN)
- Better Anti-Rheumatic PharmacOTherapy (BARFOT)
- National Data Bank for Rheumatic Diseases (NDB)
- The Leiden Early Arthritis Clinic Cohort (Leiden)

The DSU analysed the patient level data in these datasets.

4.80 The DSU's preferred model for estimating the rate of underlying disease progression replicated the latent class growth model reported by Norton et al. (2012), which also formed the basis of the Assessment Group's calculations of HAQ progression in its base-case. It was based on the cubic specification of the ERAS dataset and comprised 4 latent classes. The model showed that the rate of the worsening of the disease was faster between years 2 and 8 (that is, the early part of the disease) and this rate slowed over time. To test the reliability of the results the DSU did alternative modelling, which was also based on the ERAS dataset and showed similar results to the DSU's preferred model discussed above. The length of follow up in the datasets meant that the dropout rates in each were high. To account for dropout, the DSU applied 4

different methods, all of which supported the original findings of the latent class model.

4.81 Subgroup analysis was also done by the DSU. This analysis only included the data for patients who would meet the current NICE criteria for starting treatment with biological DMARDs (that is, people in whom 2 DMARDs had failed and who had a DAS28 higher than 5.1). This analysis used a much smaller sample size; therefore the uncertainty around the results is greater. Although the 'J'-shaped curve was not seen in these analyses, the results suggested a lower overall rate of HAQ progression than the rate used in previous NICE appraisals: 0.045 per year.

4.82 The Assessment Group did not update its base-case analysis as a result of the DSU report. However, it did exploratory analyses that assumed that a subgroup of patients with the greatest HAQ progression can be identified. It used the analyses from the DSU report, adjusted for dropout up to year 15, and then assumed that the trajectory for progression was flat for all patients after year 15. The analyses were run for the analysis using EULAR response data reported directly from the trials. The results showed that the median ICER for the subgroup was lower than for the base-case population; when biological DMARDs plus methotrexate were considered, the ICER was £25,300 per QALY gained for the severe active population and £28,500 per QALY gained for the moderate active population.

4.83 The Assessment Group also did analyses using the patient characteristics from the British Society for Rheumatology Biologics Register (BSRBR), for people with rheumatoid arthritis diagnosed after 2010 or later. This assumed a larger reduction in HAQ score (0.500) on starting treatment for patients with moderate EULAR response and of 1.000 for patients with good EULAR response. This scenario resulted in a median ICER of £52,000 per QALY

gained for the severe active population who had had methotrexate before, and an ICER of £58,900 per QALY gained for the moderate active population who had had methotrexate before.

Further analyses by the Assessment Group

The Assessment Group did further analyses after consultation on the updated assessment report and appraisal consultation document and an update to the scope of the appraisal to include biosimilars of infliximab.

4.84 The Assessment Group did exploratory analyses that assumed that patients with the fastest HAQ progression can be identified. It used the HAQ progression analyses from the DSU report, adjusted for dropout up to year 15, and then assumed that the trajectory for progression was flat for all patients after year 15. The analyses using the fastest rates of HAQ progression were run for the scenario in the Assessment Group model that used EULAR response data reported directly from the trials. The median ICERs using the fastest HAQ progression were lower than for the base-case populations; when biological DMARDs plus methotrexate were considered, the ICER was £25,300 per QALY gained for the severe active population and £28,500 per QALY gained for the moderate active population. For the population who cannot take methotrexate the ICER was £29,000 per QALY gained for the severe active population, and £32,800 per QALY gained for the moderate active population.

4.85 The Assessment Group also did analyses using the patient characteristics from the British Society for Rheumatology Biologics Register (BSRBR), for people with rheumatoid arthritis diagnosed after 2010 or later. This analysis also assumed a larger reduction in HAQ score (0.500) on starting treatment for patients with moderate EULAR response and of 1.000 for patients with good EULAR

response. This scenario increased the ICERs for the base-case populations, and resulted in a median ICER of £52,000 per QALY gained for the severe active population who had had methotrexate before, and an ICER of £58,900 per QALY gained for the moderate active population who had had methotrexate before.

4.86 The Assessment Group tested the effect of its original assumption of HAQ progression being flat after 15 years. The Assessment Group ran an exploratory analysis in which it assumed that worsening of HAQ progression after year 15 would continue in some patient groups with the progression seen between years 12 and 15 maintained until year 40. Analyses were run for the severe active and moderate active populations who had had methotrexate before and also for the analysis of patients with the fastest HAQ progression. This scenario reduced the ICERs for the base-case populations by a small amount. The median ICERs for this scenario were £40,800 per QALY gained for the severe active population and an ICER of £49,100 per QALY gained for the moderate active population. For the patients with the fastest HAQ progression, the median ICERs were £23,900 and £25,700 per QALY gained, respectively.

4.87 The Assessment Group also explored the effect of sequencing on the ICERs. In one analysis they removed tocilizumab and rituximab from the treatment sequence to test the effect of using only 1 biological DMARD before switching to non-biological therapy. This increased the median ICER to £46,100 per QALY gained for the severe active population who had had methotrexate before. In another analysis the Assessment Group explored the effect of including rituximab in the treatment sequence for people having monotherapy. This reduced the median ICERs. The ICERs were £41,600 per QALY gained for the severe active population, and £49,800 per QALY gained for the moderate active population.

4.88 The Assessment Group also explored the effect of using the NHS contract prices of the infliximab biosimilars. Using the highest NHS contract price, the ICER for infliximab was reduced to £30,445 per QALY gained for the severe active subgroup, and to £37,658 per QALY gained in the moderate active subgroup. For the group of patients with the fastest HAQ progression the ICERs were £18,130 per QALY gained for the severe active subgroup and £20,462 per QALY gained for the moderate active subgroup.

Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept. The Committee considered evidence on the nature of rheumatoid arthritis and the value placed on the benefits of these technologies by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.89 The Committee discussed the impact of rheumatoid arthritis on people with the condition, and how this was affected by the current use of DMARDs. The Committee was aware that rheumatoid arthritis can affect parts of the body other than the joints and that it has a significant effect on social life, employment and mental health. It heard from the patient expert that biological DMARDs can enable patients to continue working. It also heard that when treatment has to be temporarily stopped before surgery, deterioration in mobility could mean that a wheelchair is needed, with a significant effect on daily activities. The Committee concluded that rheumatoid arthritis can have a significant effect on the lives of patients and their families.

4.90 The Committee discussed clinical practice in early rheumatoid arthritis. It heard from clinical experts about the importance of early diagnosis and treatment to prevent irreversible joint damage. The Committee heard that the NICE guideline on rheumatoid arthritis recommends combination DMARD therapy, which in clinical practice would be intensive therapy with a combination of conventional DMARDs or stepped-up conventional DMARD therapy, normally including methotrexate, hydroxychloroquine, sulfasalazine and a glucocorticoid. The Committee heard from the clinical experts that after starting treatment, clinical management aims to adjust conventional DMARD therapy to achieve tight disease control, that is, low disease activity or remission. The clinical experts stated that intensive conventional DMARD therapy is effective in preventing permanent joint damage and that most people would have methotrexate before biological DMARD therapy was considered. The Committee understood that for treating early rheumatoid arthritis conventional DMARDs were an effective treatment and that the main clinical interest in using biological DMARDs was after conventional DMARDs had failed.

4.91 The Committee discussed the management of established rheumatoid arthritis. The Committee heard from clinical experts that patients whose disease does not respond to intensive combination therapy with conventional DMARDs are likely to have disease that progresses more quickly with worse outcomes. The clinical experts estimated that this was the case for approximately 15% of patients with rheumatoid arthritis, and that it is these people who currently have biological DMARDs. The Committee understood that most people have biological DMARDs in combination with methotrexate, but heard from clinical experts that there is a small minority of people who cannot take methotrexate (because it is contraindicated or because of intolerance) for whom biological DMARDs are used as monotherapy. The Committee heard from both the clinical

experts and the patient expert that it was not possible to predict which biological DMARDs the disease will respond to before starting treatment. Therefore having a variety of biological DMARDs available was important. The Committee heard that, if there are no contraindications, clinicians may prefer to use a TNF-alpha inhibitor because of its established use. However in other people, such as those with systemic disease, tocilizumab may be preferred, and in people with prior malignancy or with uveitis, particular biological DMARDs may be chosen in preference to others. The Committee understood the importance that clinicians placed on having a selection of biological DMARDs available.

4.92 The Committee discussed unmet need in clinical practice. The Committee heard from clinical experts that the NICE guidance being reviewed in this appraisal restricts the use of biological DMARDs to people with a disease activity score (DAS28) greater than 5.1. However, there is a group of people with lower levels of disease activity whose disease is not controlled on conventional DMARDs, and who need glucocorticoids to maintain disease control. For these people the availability of biological DMARDs would be welcomed, because currently the only way they can be offered biological DMARDs is if their glucocorticoids are withdrawn and their disease worsens to become severe active disease. The clinical experts noted that when disease responds badly to conventional DMARD therapy, there is less chance that it will respond well to other treatments. This is the case regardless of DAS. The Committee understood that there was clinical interest in the use of biological DMARDs in people with moderate active disease (that is, with a DAS28 of less than 5.1) whose disease was not controlled on conventional DMARDs.

4.93 The Committee discussed the different measures of response used in clinical practice and in the clinical trials. The Committee

understood from clinical experts that although ACR20 was used in the clinical trials, it did not represent a significant clinical improvement; although people would have relief from some symptoms, they would still have disability. ACR70, however represented a significant improvement in symptoms (similar to that seen in remission, and was closer to the current aim of clinical management. The Committee also discussed how disease status is determined in UK clinical practice. It heard from clinical experts that the most commonly used measures of disease response are DAS and EULAR response, rather than ACR response. This is because DAS is a continuous measurement, unlike ACR response which is categorical. The Committee heard from the clinical experts that the cut-off points for DAS being low, moderate or severe disease activity are arbitrary and that there are not necessarily significant clinical distinctions on either side of the boundaries of the cut-off points. The Committee, while noting the limitations of the DAS and EULAR response measures, concluded that these are the most commonly used measures of disease response in the NHS in England.

4.94 The Committee noted comments from consultation that DAS does not define patients with rapid disease progression, and that rather than using only DAS to identify people suitable for treatment with biological DMARDs, treatment can be targeted at people likely to have rapid disease progression. These people can be identified based on persistent synovitis and failure of the disease to respond to combination therapy with conventional DMARDs, plus:

- persistent elevation of inflammatory markers (such as C-reactive protein [CRP]) and
- presence of erosions on X-ray and
- positive for anti-citrullinated protein antibodies (ACPA).

The Committee discussed whether it is possible to use these criteria to identify a group of patients with rapid disease progression. The clinical experts explained that each of these measures had been validated individually, and that they are all used in clinical practice in the NHS. Clinical experts considered that disease which has not responded to combination therapy, in people who have these criteria, would progress faster than in people who do not have these criteria. The Committee also heard from one of the company representatives that there is evidence to show that these criteria, taken together, can predict rapid progression in people with rheumatoid arthritis. The Committee supported the concept of identifying people likely to have rapid disease progression in order to target treatment with biological DMARDs. However, it noted that some of the criteria proposed are already used in rheumatoid arthritis diagnosis (for example, ACPA positivity) and that clinical experts suggested that, taken together, the measures would identify approximately one third to one half of patients with moderate active disease. The Committee was not persuaded of the sensitivity of the measures for identifying people with the fastest disease progression. The Committee also noted that, although individually validated, the measures were not necessarily independent of each other, and different thresholds for presence or absence can be applied. It also noted that the effect of these different thresholds on speed of progression, when combined with thresholds applied for the other measures, was unclear. It also noted that no economic modelling had been provided for this group, and that it had not been provided with any clinical evidence to support the assumption that disease with these characteristics would respond well to biological DMARDs. The Committee concluded that further research is needed on the use of these criteria in combination with each other to identify patients with rapid disease progression, and the clinical effectiveness of treatment in

the presence of these criteria. However, currently these criteria cannot be used in decision-making.

Clinical effectiveness

4.95 The Committee considered the clinical evidence presented by the Assessment Group and noted that the network meta-analysis had been updated after consultation on the assessment report and economic model. The Committee heard from the companies that they had concerns with some trials that were included in the Assessment Group's analyses, in particular Swefot, in which a small proportion of people had switched to etanercept. The Committee also noted concerns from the companies that some trial data were not included in the Assessment Group's base-case analyses, notably RAPID 1, RAPID 2, JRAPID, FAST4WARD and HIKARI. The Committee heard from the Assessment Group that they considered the proportion of people in Swefot who switched to etanercept be sufficiently small (5 in approximately 100) to be unlikely to affect the overall results. The Committee also heard that the Assessment Group had excluded trials that included people who had previously had biological treatments; this approach was supported by some stakeholders, but it meant that the RAPID trials for certolizumab pegol were excluded. The Assessment Group clarified that these had been included in both clinical and cost-effectiveness sensitivity analyses, so that the effect on the ICERs of the inclusion and exclusion criteria of the systematic review could be seen. The Committee understood that the Assessment Group's systematic review had excluded some certolizumab pegol monotherapy data, but that this had been provided by the company. The Assessment Group noted that the ICERs were not sensitive to the estimates of initial treatment response. The Committee accepted the Assessment Group's explanation. It concluded that it was appropriate to consider the main analysis

presented by the Assessment Group and also their sensitivity analyses using the wider set of clinical trials.

4.96 The Committee discussed the results of the network meta-analyses done by the Assessment Group. It noted that for the analysis of rheumatoid arthritis not previously treated with methotrexate, intensive combination DMARDs appeared to have a similar probability of response as the biological DMARDs. However, for rheumatoid arthritis previously treated with methotrexate, analyses showed a bigger difference in the probability of response between conventional DMARDs and biological DMARDs. The Committee discussed whether the clinical evidence suggested that 1 biological DMARD might be more effective than the others. It considered that for all of the biological DMARDs there were similar results for both ACR and EULAR response, and that the overlapping credible intervals were often wide, indicating uncertainty in the true estimate of effect. The Committee concluded that the evidence of greater clinical effectiveness for biological DMARDs compared with conventional DMARDs was more compelling in disease previously treated with methotrexate and that the evidence did not suggest differential effectiveness between the biological DMARDs. The clinical experts confirmed that this was their view too.

Cost effectiveness

4.97 The Committee considered the economic models submitted by the companies. The Committee noted that most of the companies' models had used ACR response criteria, which, although reflecting the measure often used in the clinical trials, did not reflect the measures used in UK clinical practice. It noted that none of the models submitted by the companies used EULAR response data for all of the populations and interventions specified in the scope, whereas the model developed by the Assessment Group did. The Committee concluded that the use of the EULAR response

measure was appropriate and that the Assessment Group's model most accurately reflected rheumatoid arthritis care in the UK. The Committee understood that using EULAR response had meant that a smaller number of trials could be taken into account, but noted that the effect of the full set of trials was considered, by mapping ACR response data to EULAR scores when necessary.

4.98 The Committee noted that the Assessment Group completed a series of analyses to make the assumptions used in their model more similar to those used in the companies' models and the models used in the previous NICE technology appraisals. The Committee understood from the Assessment Group that these analyses – using the rates of underlying disease progression and discount rates used in previous appraisals – produced ICERs that were not dissimilar to those seen in previous appraisals. The Committee was aware of comments from consultation that the Assessment Group model didn't associate increases in HAQ with increases in expected mortality, as had been modelled in previous appraisals. It heard from the Assessment Group that the evidence they identified reported that baseline HAQ was associated with mortality risk, and change in HAQ did not improve predictive accuracy. The Committee concluded that the Assessment Group model was appropriate to use for decision-making purposes.

4.99 The Committee understood that biosimilar versions of infliximab were now available in the NHS and that the scope of the appraisal had been updated to include these. It heard from the clinical experts that policies differ, but in their trusts people starting treatment may have a biosimilar. However, if a person is already on a treatment and their disease is responding, they would not be switched to a biosimilar. The clinical experts noted that few people start treatment with infliximab because it is given by infusion rather than subcutaneous injection and is associated with greater

administration costs than other TNF-alpha inhibitors. The Committee discussed comments from consultation that biosimilar products should not be considered interchangeable with the originator products. It understood that the approach adopted by NICE in this appraisal was consistent with the NICE position statement on biosimilars and that the regulatory authorities had concluded that the biosimilar infliximab products were sufficiently similar to the originator product to be granted marketing authorisation. The Committee noted that the NHS contract price for biosimilar infliximab was lower than the list price because of tendering by the NHS Commercial Medicines Unit. It noted that the prices from the NHS Commercial Medicines Unit had been included in sensitivity analyses completed by the Assessment Group (see sections 4.86 and 4.89). The Committee concluded that the ICERs for the infliximab biosimilars were a relevant consideration.

4.100 The Committee discussed the sensitivity analyses done by the Assessment Group to identify the key drivers of the cost-effectiveness results. It noted that including or excluding trials (for example, trials that included previous biological DMARD use) and including adverse events had relatively modest effects on the ICERs, compared with the assumptions about mapping of HAQ to utility, discount rates and underlying disease progression while having treatment with conventional DMARDs. The Committee, while noting concerns about the studies included by the Assessment Group in the network meta-analysis, concluded that the effect of including or excluding the trials on the ICERs was not large enough to affect decision-making in this appraisal, and that the assumptions about the progression of disease and its effect on health-related quality of life were key drivers for decision-making.

4.101 The Committee initially discussed the assumptions about underlying disease progression used in the companies'

submissions and in previous NICE technology appraisal guidance. These assumptions were a worsening in HAQ score of 0.00 per year for biological DMARDs, 0.045 for conventional DMARDs and 0.06 for palliative care for people with disease that was not responding to treatment. These changes were assumed to accrue each year until the person reached an HAQ score of 3 (that is, the worst HAQ score). The Committee heard from the Assessment Group that these assumptions were made based on a study in Finland that showed the annual change in HAQ score for the general rheumatoid arthritis population was 0.03. The Assessment Group for previous NICE technology appraisals had assumed that HAQ score during palliative care changes at twice the rate of the general population, and that for conventional DMARDs it was halfway between 0.03 and 0.06, which was 0.045. The Committee, although aware of the use of these values in previous appraisals, concluded that there was limited evidence to support these assumptions.

4.102 The Committee discussed the assumptions made by the Assessment Group about underlying disease progression for people having biological DMARDs. The Committee noted that the Assessment Group assumed a 0.00 change in HAQ score for people having biological DMARDs, which was the same as that used by the companies. The Committee noted that the Assessment Group did not rely on the assumptions from previous NICE technology appraisal guidance to obtain this value; rather, it had analysed data from the BSRBR that confirmed there was no change in HAQ score while on treatment. The Committee accepted the Assessment Group's assumption that there was no disease progression while people were having biological DMARDs.

4.103 The Committee then considered the assumptions made by the Assessment Group about underlying disease progression for

people having conventional DMARDs. It noted that an initial error had been corrected in the model, and that the model now included disease progression for patients with disease that had not responded at the start of treatment. It also noted that although the Assessment Group's report referred to this parameter as progression while on conventional DMARDs, the parameter more accurately reflected progression while on all non-biological treatments (for example, conventional DMARDs, surgery and glucocorticoids). The Committee noted that the estimate of disease progression had been obtained from an alternative source to that of the biological DMARDs; the ERAS dataset. This dataset suggested an initial decrease (improvement) in HAQ score for the first 2 years, followed by an increase (worsening) in HAQ score for the following 5 years, with a slowing down in worsening approximately 7 to 10 years after diagnosis. The Committee heard from the Assessment Group that their estimate of the rate of disease progression was higher in the first 7 years than the assumption of 0.045 made by the companies, but that it reduced after this. The Assessment Group commented that this avoided the assumption that a large proportion of patients progress to an HAQ score of 3 before death, which is not supported by observational data. The Assessment Group also stated that the original analyses from ERAS (showing the slowing down of worsening) were also supported by its analyses of the NOAR and ERAN datasets. The Committee heard from the clinical experts that, although they accepted that there was no perfect dataset available, they had concerns about the use of these data because ERAS was a general rheumatoid arthritis cohort and would not be representative of people who would be likely to use biological DMARDs. The Committee heard from the Assessment Group that it recognised that ERAS was a mixed cohort and that, rather than using the ERAS dataset as it existed, a model was developed that included

patient characteristics as covariates, so that patients with characteristics similar to those likely to have biological DMARDs were sampled. This meant that overall the Assessment Group sample had a larger proportion of people with more rapid progression of disease than in the ERAS dataset as a whole. The Committee accepted that there were limitations with the model developed by the Assessment Group for estimating the underlying progression of disease while on conventional DMARDs. However, any limitations also needed to be balanced with the limitations of the methods used for obtaining the estimates used in previous NICE technology appraisals.

4.104 The Committee considered both of the approaches used to model the underlying progression of disease while having conventional DMARDs. The Committee noted that the previous approach to modelling HAQ trajectory with conventional DMARD therapy was based on a series of assumptions that had limited evidence to support them. The Committee also noted that the Assessment Group's approach to modelling the progression of disease was informed by more evidence, but there may be limitations with using the ERAS dataset. However, the Committee considered that the Assessment Group's analysis (showing a decrease over time of the rate of underlying disease progression) had greater clinical plausibility than the linear estimates of the rate of disease progression, because observational studies do not show large proportions of people in the worst HAQ score states. The Committee accepted the Assessment Group's method for modelling disease progression while having conventional DMARDs. It concluded that the Assessment Group's model more accurately represented disease progression with conventional DMARDs than the assumptions used in previous NICE technology appraisals.

4.105 The Committee examined the different methods that had been used to obtain EQ-5D from HAQ scores. It understood that the Assessment Group had used a function from a mixture model developed using the NDB and ERAS datasets. This estimated EQ-5D using both HAQ score and pain score. The Committee noted that in response to comments on the assessment report the function had been updated, and that the model fit had been improved. It heard from the Assessment Group that it had used an alternative approach and dataset (the NDB dataset) to that used in previous appraisals and in some of the company models (Malottki et al. 2011). This was because the use of linear regression in Malottki et al to estimate EQ-5D was not appropriate, because EQ-5D scores are not normally distributed. Further, the ERAS and NDB datasets are also larger than that used in Malottki et al. and have a higher number of patients at the severe end of the HAQ scale, which is the population of greatest relevance to the appraisal. Finally, the Committee heard from the Assessment Group that the function in Malottki et al. was associated with the biggest range of EQ-5D estimated from HAQ compared with other available equations, and therefore they considered it to be an outlier. The Committee concluded that the Assessment Group's method of estimating EQ-5D from HAQ was appropriate to use in decision-making.

4.106 The Committee noted that the original NICE technology appraisal guidance had used a different set of discount rates to the appraisal review. The original guidance used discount rates of 6% for costs and 1.5% for benefits, whereas the analyses in the review used a 3.5% discount rate for both costs and benefits, as specified in the NICE guide to the methods of technology appraisal. The Committee was aware that sensitivity analyses using the previous discount rates significantly reduced the ICER. The Committee discussed the fact that the discount rates were inconsistent

between the original guidance and the review, but it considered that for recommendations being made at the same point in time the same discount rates should be used. The Committee was also aware of the economic rationale for equal discount rates for costs and benefits. The Committee also noted consultation comments and discussed whether the alternative discount rates described in section 6.2.19 of NICE guide to the methods of technology appraisal would apply to rheumatoid arthritis. It understood that the criteria in the methods guide were for use when the costs of a treatment were accrued at the beginning of treatment, but the benefits only accrued in the long term. It concluded that the circumstances described in the methods guide did not apply to ongoing treatment. The Committee concluded that using a 3.5% discount rate for both costs and benefits, in line with the current NICE methods guide, was appropriate.

4.107 The Committee noted that the Assessment Group had done an analysis using the rates of HAQ progression for people with rapid disease progression, and that this reduced the base-case ICERs for the severe active population who can have methotrexate from £41,600 to £25,300 per QALY gained. For the severe active population having monotherapy, the ICER changed from £48,300 to £29,000 per QALY gained. The Committee noted that this analysis was not based on a patient subgroup defined by a pre-specified set of characteristics; rather, it used the fastest rates of disease progression observed in each of the latent classes in the Assessment Group's analysis of HAQ progression for conventional DMARDs. The Committee discussed whether this analysis could be used as the basis for decision-making. The Committee considered that there was uncertainty in the analysis because it was not based on a set of patients defined by their characteristics. The Committee concluded that it had not been presented with sufficient clinical evidence about the characteristics of patients with rapid disease

progression, to be able to use the Assessment Group's exploratory analysis as the basis for decision-making (see section 4.94). However, it considered that such patients would be a subset of those currently having biological DMARDs (see section 4.92) and concluded that the Assessment Group's ICER for the severe active subgroup may be overestimated.

4.108 The Committee considered the most appropriate ICERs for the population with severe active rheumatoid arthritis that has not been treated with methotrexate. Based on the clinical expert comments, the Committee considered that intensive therapy with combination DMARDs was the appropriate comparator. The Committee noted that AbbVie had submitted an ICER for adalimumab plus methotrexate compared with methotrexate plus hydroxychloroquine of £70,000 per QALY gained, and that Pfizer's analysis suggested that the ICER for etanercept plus methotrexate compared with combination conventional DMARDs was £34,400 per QALY gained. The Committee noted that the Assessment Group's base-case ICER for the population who have not had methotrexate before, but who could have it, was £68,300 per QALY gained. For the population who have not had methotrexate before and who cannot have it, the ICER was £77,500 per QALY gained. The Committee, noting the clinical expert comments that there was limited clinical interest in using biological DMARDs before methotrexate, concluded that biological DMARDs were not cost effective for people who had severe active rheumatoid arthritis not previously treated with methotrexate.

4.109 The Committee considered the most appropriate ICERs for the population with severe active rheumatoid arthritis previously treated with methotrexate. The Committee accepted the use of the ERAS dataset to estimate underlying disease progression for conventional DMARDs, the Assessment Group's HAQ-to-utility mapping

function, and discount rates of 3.5%. It considered that the most plausible ICER for biological DMARDs used in severe active rheumatoid arthritis was likely to lie between the Assessment Group's base-case ICER (that is, £41,600 per QALY gained) and the Assessment Group's ICER for the exploratory analysis for the severe group with the fastest HAQ progression (that is, £25,300 per QALY gained). Noting that the upper end of this range was higher than the range of ICERs normally considered a cost effective use of NHS resources (£20,000-£30,000 per QALY gained), the Committee discussed whether there were other factors that should be taken into account in its decision-making. It noted that the biological DMARDs have significantly changed the management of rheumatoid arthritis, affecting surgery rates and hospitalisation. The Committee agreed that the biological DMARDs should be considered an innovative class of drugs. It also noted the comments from patient experts that biological DMARDs provide extensive benefits for people with rheumatoid arthritis and their families, in terms of both physical and mental health. It understood that the physical health benefits associated with biological DMARDs may encompass improvements in pain and cardiovascular health and well as benefits to the musculoskeletal system. On balance, based on the range of the most plausible ICERs, the Committee concluded that biological DMARDs in combination with methotrexate were a cost-effective use of NHS resources for people with severe active rheumatoid arthritis previously treated with methotrexate.

4.110 The Committee discussed criteria for starting and stopping treatment with biological DMARDs. It noted data from the BSRBR that not all patients having treatment with biological DMARDs are recorded as having a response to treatment. It heard from the clinical expert that stopping rules should be applied, so that patients whose disease is not responding stop having an ineffective

treatment that is not controlling disease and could potentially be causing adverse effects. The Committee understood from clinical experts that, before starting treatment with biological DMARDs, patients should have had intensive combination therapy with conventional DMARDs. It also noted that the basis of the ICERs in the Assessment Group's modelling was DAS28 and a moderate EULAR response. The Committee, although aware of the limitations of the DAS score, concluded that it was appropriate to base starting and stopping criteria on DAS28 and moderate EULAR response (because of their use in the calculation of the ICERs) plus the failure of intensive combination treatment with conventional DMARDs.

4.111 The Committee discussed the most plausible ICERs for the population with moderate active rheumatoid arthritis. It noted that the ICERs for this group were higher than those for the severe active group for the analyses presented by the Assessment Group. For the biological DMARDs used in moderate active rheumatoid arthritis, the most plausible ICER was £51,100 per QALY gained (using the EULAR main analysis), approximately £10,000 higher than the upper end of the range for the severe active population. The Committee noted that the ICER reduced to £28,500 per QALY gained when using the exploratory analysis for the moderate active group with the fastest HAQ progression. The Committee was not persuaded that the exploratory analysis for the moderate active group was as applicable to this group as to the severe active group. The Committee accepted that current clinical management includes treating severe active disease that is progressing rapidly (see section 4.92), therefore the Assessment Group's base-case ICER would be an overestimate. However, the Committee was not persuaded that expanding treatment to include moderate disease activity would also target those patients whose disease was progressing rapidly. It was not persuaded that the alternative

treatment criteria proposed could be currently used in decision-making (see section 4.95). The Committee noted the reduction in the ICER to £37,600 per QALY gained for biosimilar infliximab, but was aware of statements from clinical experts that infliximab was not frequently used in the NHS because of its mode of administration. The availability of infliximab biosimilar did not change its decision. It also understood that the benefits to physical and mental health for patients with rheumatoid arthritis and their families (sections 4.89 4.109) would also apply to moderate active disease, but noting the higher base-case ICER for the moderate active population compared to the severe active population, the Committee was not persuaded that these factors changed its decision. The Committee concluded that at current prices the biological therapies could not be considered a cost-effective use of NHS resources for patients with moderate active disease.

4.112 The Committee discussed the ICERs for biological monotherapy, noting that these were higher than those for combination therapy. The Committee heard from the Assessment Group that the higher ICERs were mainly driven by the costs of treatments given after the failure of the first biological DMARD, and less costly rituximab not being available to people who cannot take methotrexate (because it has to be given in combination with methotrexate). The Committee noted the results of the exploratory analyses of the Assessment Group, which included rituximab in the monotherapy treatment sequence. The Committee noted that these ICERs were comparable to those for combination therapy. It also noted comments from consultation that rituximab may be used in clinical practice as monotherapy, even though it is not licensed. The Committee concluded that the base-case ICERs for monotherapy were higher than those for combination therapy. However, it accepted that this was mainly because of the costs of later treatments rather than the costs or benefits associated with the first

biological DMARD. It also agreed that the minority of people with severe active rheumatoid arthritis who could not tolerate methotrexate should not be treated differently from other people with severe disease, as far as possible. The Committee concluded that biological DMARDs, for which the marketing authorisation allows, should be recommended as a cost-effective use of NHS resources when used as monotherapy for severe active disease previously treated with DMARDs.

4.113 The Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, when appraising adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept. The Appraisal Committee noted NICE's position statement about this, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept. It therefore concluded that the PPRS payment mechanism was irrelevant for the consideration of the cost effectiveness of adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept.

4.114 There were no equality issues raised during the Committee discussion.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Adalimumab, etanercept, infliximab, certolizumab pegol,	Section

	golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed	
Key conclusion		
The Committee's recommendations are: • Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept all in combination with methotrexate are recommended as options for treating rheumatoid arthritis, only if: – disease is severe, that is, a disease activity score (DAS28) greater than 5.1 and – disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs) and – the companies provide certolizumab pegol, golimumab, abatacept and tocilizumab with the discount agreed in their patient access schemes • Adalimumab, etanercept, certolizumab pegol or tocilizumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance where the criteria in section 1.1 are met. • Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. • After initial response, withdraw treatment if a moderate EULAR response is not maintained. • Start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose).		1.1–1.6, 4.108, 4.109, 4.111, 4.112

This may need to be varied for some people because of differences in the mode of administration and treatment schedules.

The Committee concluded that all the technologies were clinically effective for all subgroups, but could only consider them as a cost-effective use of NHS resources for people with severe active rheumatoid arthritis previously treated with methotrexate.

The Committee considered that the most plausible incremental cost-effectiveness ratio (ICER) for biological DMARDs used in severe active rheumatoid arthritis previously treated with methotrexate, was likely to lie between the Assessment Group's base-case ICER (that is, £41,600 per quality-adjusted life year [QALY] gained) and the Assessment Group's ICER for the severe group with the fastest Stanford Health Assessment Questionnaire (HAQ) progression (that is, £25,300 per QALY gained). The Committee accepted that patients with the fastest HAQ progression would be a subset of those currently having biological DMARDs and that the estimate of £41,600 per QALY gained may be overestimated.

For the population with moderate active rheumatoid arthritis the Assessment Group's base-case ICER for biological DMARDs was £51,100 per QALY gained approximately £10,000 higher than the base-case ICER for severe active disease. The ICER reduced in the analysis of patients with the fastest HAQ progression, but the Committee was not persuaded that expanding treatment to include moderate active disease would target patients whose disease was progressing rapidly, nor was it persuaded that alternative criteria to identify patients with the fastest HAQ progression could currently be used for decision making.

For biological monotherapy, the Committee concluded that the most plausible ICERs for both subgroups were higher than those for the

combination therapy, but it accepted that this was mainly because of the costs of later treatments. Therefore it concluded that these people should not be treated differently from other people with severe disease, as far as possible.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	Rheumatoid arthritis can affect parts of the body other than the joints and it has a significant impact on social life, employment and mental health. Biological DMARDs can enable patients to continue working. The Committee concluded that rheumatoid arthritis can have a significant effect on patients and their families.	4.89
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Biological DMARDs have significantly changed the management of rheumatoid arthritis. The Committee agreed that the biological DMARDs should be considered an innovative class of drugs. Patient experts emphasised that biological DMARDs provided extensive benefits for people with rheumatoid arthritis.	4.109

What is the position of the treatment in the pathway of care for the condition?	This is a review of technology appraisal guidance 130, 186, 224 and 280, and a partial review of technology appraisal guidance 225 and 247, appraising the use of biological DMARDs for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed.	–
Adverse reactions	Not an issue in this appraisal. This is a review of technology appraisal guidance 130, 186, 224 and 280, and a partial review of technology appraisal guidance 225 and 247. These technologies are part of established clinical practice.	–
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	There were concerns with some trials that were included and excluded in the Assessment Group's analyses. The Committee concluded that it was appropriate to consider the main analyses presented by the Assessment Group and also their sensitivity analyses using the wider set of clinical trials.	4.95, 4.96
Relevance to general clinical practice in the NHS	This is a review of technology appraisal guidance 130, 186, 224 and 280, and a part-review of technology appraisal guidance 225 and 247. These technologies are part of established clinical practice.	–

Uncertainties generated by the evidence	The Committee discussed concerns over the inclusion and exclusion criteria of the Assessment Group's analyses, in particular for Swefot, TACIT and several certolizumab pegol trials, but concluded that both the main analysis and the sensitivity analyses were appropriate. It also noted that the network meta-analysis had been updated after consultation on the assessment report and economic model.	4.95
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	There were no clinically relevant subgroups in this appraisal. This is a review of technology appraisal guidance 130, 186, 224 and 280, and a part-review of technology appraisal guidance 225 and 247. These technologies are part of established clinical practice.	–
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that the evidence of greater clinical effectiveness for biological DMARDs compared with conventional DMARDs was more compelling in disease previously treated with methotrexate and that the evidence did not suggest differential effectiveness between the biological DMARDs.	4.95

For reviews (except rapid reviews): How has the new clinical evidence that has emerged since the original appraisal (TA130, 186, 224, 280, 225 and 247) influenced the current (preliminary) recommendations?	Additional trials have been published, which were incorporated into the Assessment Group's analyses.	4.95
Evidence for cost effectiveness		
Availability and nature of evidence	The Assessment Group's model used the EULAR response measure, which was considered appropriate by the Committee and accurately reflected rheumatoid arthritis care in the UK. Using EULAR response had meant that a smaller number of trials could be taken into account, but the effect of the full set of trials was considered, by mapping ACR response data to EULAR scores when necessary.	4.97

Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee considered that the following factors introduce uncertainty into the evidence base for the cost effectiveness of biological DMARD therapies: • The Assessment Group modelled the underlying disease progression for people on conventional DMARDs on the basis of the ERAS dataset, which differed from the method used by the companies' models, which assumed linear HAQ progression of 0.045 while on conventional DMARDs, based on the assumptions used in previous NICE technology appraisals. The Committee concluded that the Assessment Group's method more accurately represented disease progression on conventional DMARDs than the assumptions used in previous NICE technology appraisals. • To obtain EQ-5D from HAQ scores the Assessment Group used a function from a mixture model developed using the NDB and ERAS datasets. This estimated EQ-5D using both HAQ score and pain score. The Committee noted that previous appraisals and some of the company models used an alternative approach and dataset (Malottki et al. 2011), but concluded that the Assessment Group's method was more appropriate to use for decision-making.	4.97, 4.100, 4.101, 4.103, 4.104, 4.106

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Assessment Group included pain and HAQ in its estimation of EQ-5D values. There were some concerns about model fit to data in the Assessment Group's model, but the Committee concluded that the Assessment Group's method of estimating EQ-5D from HAQ was appropriate to use in decision-making. No other health-related benefits have been identified that have not been captured in the QALY calculation.	4.105
Are there specific groups of people for whom the technology is particularly cost effective?	This technology appraisal included people who had had methotrexate and who had moderate active and severe active disease, and people who had never been treated with methotrexate and who had severe disease. The Committee concluded that biological DMARDs can only be considered a cost-effective use of NHS resources for the severe active rheumatoid arthritis population who had been treated with methotrexate both as monotherapy and in combination therapy.	4.108, 4.109, 4.111, 4.112

What are the key drivers of cost effectiveness?	The key driver of the cost effectiveness for biological DMARDs was the assumption about mapping of HAQ to utility, discount rates and underlying disease progression while on treatment with conventional DMARDs.	4.100
Most likely cost-effectiveness estimate (given as an ICER)	For the population with severe active rheumatoid arthritis who had not had methotrexate before, the Committee noted that the most plausible ICER was £68,300 per QALY gained for the population who could have methotrexate and £77,500 per QALY gained for the population who could not have methotrexate. The Committee considered that the most plausible incremental cost-effectiveness ratio (ICER) for biological DMARDs used in severe active rheumatoid arthritis previously treated with methotrexate, was likely to lie between the Assessment Group's base-case ICER (that is, £41,600 per quality-adjusted life year [QALY] gained) and the Assessment Group's ICER for the severe group with the fastest Stanford Health Assessment Questionnaire (HAQ) progression (that is, £25,300 per QALY gained). Assessment Group's base-case ICER for biological DMARDs was £51,100 per QALY gained for the moderate active population. This was approximately £10,000 higher than	4.108, 4.109, 4.111, 4.112

	the Assessment Group's base-case ICER for severe active disease. For biological monotherapy, the Committee concluded that the most plausible ICERs for both subgroups were higher than those for the combination therapy, but it accepted that this was mainly because of the costs of later treatments. Therefore it concluded that these people should not be treated differently from other people with severe disease, as far as possible. For people with moderate active disease previously treated with methotrexate and with severe active disease not previously treated with methotrexate, it concluded that biological DMARDs were not cost effective.	

For reviews (except rapid reviews): How has the new cost-effectiveness evidence that has emerged since the original appraisal (TA TA130, 186, 224, 280, 225 and 247)) influenced the current (preliminary) recommendations?	The Assessment Group modelled the underlying disease progression for people on conventional DMARDs on the basis of the ERAS dataset, which suggested an initial decrease in HAQ score, followed by worsening of the disease after the second year, with a slowing down in worsening over time. This differed from the method used in previous NICE appraisals, which assumed linear HAQ progression of 0.045. The method used by the Assessment Group to obtain EQ-5D values from HAQ scores and pain also differed from the method used in previous NICE technology appraisals, and it used a function from a mixture model based on NDB and ERAS datasets. The original NICE technology appraisal guidance had used a different set of discount rates to the appraisal review. The current NICE methods guide uses a 3.5% discount rate for both costs and benefits. Biosimilar versions of infliximab are now available on the NHS.	4.97, 4.100, 4.103, 4.104, 4.105, 4.106
Additional factors taken into account		
Patient access schemes (PPRS)	Four patient access schemes were taken into account, for tocilizumab, abatacept, golimumab and certolizumab pegol.	4.54
End-of-life considerations	None	–

Equalities considerations and social value judgements	There were no equality issues raised during the Committee discussion.	4.114

5 Implementation

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

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

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has rheumatoid arthritis and the doctor responsible for their care thinks that adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 The Department of Health, UCB Pharma, Merck Sharp & Dohme, Bristol–Myers Squibb and Roche have agreed that certolizumab pegol, golimumab, abatacept and tocilizumab will be available to the NHS with patient access schemes which make the drugs

available with a discount. The size of the discount is commercial in confidence. It is the responsibility of each company to communicate details of their drug's discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to [NICE to add details at time of publication]

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

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

6 Recommendations for further research

6.1 The Committee agreed that further research would be of value to investigate factors which can predict the likelihood of rapid progression of disease and response, in the presence of these factors, to treatment with biological DMARDs. Factors to investigate include:

- persistent elevation of inflammatory markers (such as C-reactive protein [CRP]) and
- presence of erosions on X-ray and
- positive for anti-citrullinated protein antibodies (ACPA) (see section 4.94).

The Committee felt that how these factors interact with each other and to what extent the likelihood of progression is affected by the use of different thresholds would be of value.

7 Related NICE guidance

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

- Abatacept for treating rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs (rapid review of technology appraisal guidance 234) NICE technology appraisal guidance 280 (2013).
- Tocilizumab for the treatment of rheumatoid arthritis (rapid review of technology appraisal guidance 198) NICE technology appraisal guidance 247 (2012).
- Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs NICE technology appraisal guidance 225 (2011).
- Golimumab for the treatment of methotrexate-naive rheumatoid arthritis (terminated appraisal) NICE technology appraisal 224 (2011).
- Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor NICE technology appraisal guidance 195 (2010).
- Certolizumab pegol for the treatment of rheumatoid arthritis NICE technology appraisal guidance 186 (2010).
- Rheumatoid arthritis NICE guideline 79 (2009).
- Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis NICE technology appraisal guidance 130 (2007).

8 Review of guidance

8.1 The guidance on this technology is considered for review by the Guidance Executive in 3 years after publication of the guidance.

NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Stevens
Chair, Appraisal Committee
August 2015

9 Appraisal Committee members and NICE project team

Appraisal Committee members

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

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

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

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne

Vice Chair of Appraisal Committee C, Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne

Professor Kathryn Abel

Director of Centre for Women's Mental Health, University of Manchester

Dr David Black

Medical Director, NHS South Yorkshire and Bassetlaw

Dr Andrew Burnett

Formerly – Director for Health Improvement and Medical Director, NHS Barnet, London

David Chandler

Lay Member

Gail Coster

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome

Honorary Professor, Department of Primary Care and Population Health, University College London

Dr Maria Dyban

GP, Kings Road Surgery, Cardiff

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Greg Fell

Consultant in Public Health, Bradford Metropolitan Borough Council

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Dr Janice Kohler

Senior Lecturer and Consultant in Paediatric Oncology, University Hospital Southampton NHS Foundation Trust

Emily Lam

Lay Member

Dr Nigel Langford

Consultant in Clinical Pharmacology and Therapeutics/Acute Physician, Leicester Royal Infirmary

Dr Allyson Lipp

Principal Lecturer, University of South Wales

Dr Andrea Manca

Health Economist and Senior Research Fellow, University of York

Henry Marsh

Consultant Neurosurgeon, St George's Hospital, London

Dr Iain Miller

Founder and Chief Executive Officer, Health Strategies Group

Dr Paul Miller

Director, Payer Evidence, AstraZeneca UK Ltd

Professor Stephen O'Brien

Professor of Haematology, Newcastle University

Dr Anna O'Neill

Deputy Head of Nursing & Health Care School/Senior Clinical University Teacher, University of Glasgow

Dr Claire Rothery

Research Fellow in Health Economics, University of York

Professor Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Tim Stokes

Senior Clinical Lecturer, University of Birmingham

Dr Paul Tappenden

Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Professor Robert Walton

Clinical Professor of Primary Medical Care, Barts and The London School of Medicine and Dentistry

Dr Judith Wardle

Lay Member

NICE project team

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

Dr Grace Jennings/Boglarka Mikudina

Technical Leads

Zoe Garrett

Technical Adviser

Lori Farrar

Project Manager

10 Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by the School of Health and Related Research (ScHARR):

- Stevenson MD, Archer R, Tosh J et al. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying anti-rheumatic drugs and after the failure of conventional disease-modifying anti-rheumatic drugs only: systematic review and economic evaluation. February, 2015
- Gibson L, Hernandez Alava M, Wailoo A. Progression of disease in people with rheumatoid arthritis treated with non-biologic therapies. Report by the Decision Support Unit. February, 2015

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

I. Companies:

- AbbVie
- Bristol–Myers Squibb
- Hospira UK*
- Pfizer
- Merck Sharp & Dohme Ltd
- Napp Pharmaceuticals*
- Roche
- UCB Pharma Ltd

* denotes that these companies were not included at the start of the appraisal and so were not invited to comment on the draft scope or assessment report; only on the Appraisal Consultation Document.

II. Professional/expert and patient/carer groups:

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

III. Other consultees:

- Department of Health
- Welsh Government

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

- Department of Health, Social Services and Public Safety for Northern Ireland
- Commissioning Support Appraisals Service
- Health Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- AstraZeneca UK
- Hospira UK
- Novartis
- Pfizer
- Arthritis Research UK
- The Work Foundation

- School of Health and Related Research (ScHARR)
- National Institute for Health Research Health Technology Assessment Programme

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Chris Deighton, Consultant Rheumatologist, nominated by British Society for Rheumatology – clinical expert
- Dr Frank McKenna, Consultant Rheumatologist, nominated by British Society for Rheumatology – clinical expert
- Professor Ernest Choy, Professor of Rheumatology, nominated by Roche Pharmaceuticals – clinical expert
- Dr Ben Parker, Consultant Rheumatologist – clinical specialist
- Ailsa Bosworth, nominated by National Rheumatoid Arthritis Society – patient expert
- Don McWilliam, nominated by Arthritis Care – patient expert

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

- AbbVie
- Bristol–Myers Squibb
- Hospira UK

- Pfizer
- Merck Sharp & Dohme Ltd
- Napp Pharmaceuticals
- Roche
- UCB Pharma Ltd