NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Committee papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL (MTA)

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Contents:

b. Amgen
    i. AR response
c. Biogen
    i. AR response
    ii. Response to CE model
d. Celltrion Healthcare
    i. AR response
e. Pfizer
    i. AR response
f. Sandoz
    i. AR response
g. British Society for Rheumatology
h. British Biosimilars Association

7. **Assessment Group report** updated post-consultation and with a minor clarification in section 6.2 following ACM1

NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance

Published: TBC
nice.org.uk/guidance/ta375

Contents

This guidance replaces TA130, TA186, TA224 and TA280.

This guidance partially replaces TA247 and TA225.

1 Recommendations

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 as 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, when 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 (see table 1). 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
Certolizumab pegol	+	–	+	+	SC
Golimumab	+	+	+	–	SC
Abatacept	+	–	+	–	IV or SC
Tocilizumab	+	+*	+	+	IV or SC*

Abbreviations: IV, intravenous infusion; MTX, methotrexate; MTX-naive, disease not previously treated with methotrexate; RA, rheumatoid arthritis; SC, subcutaneous injection; +, licensed for use; MTX-experienced, disease 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; Remsima, Napp Pharmaceuticals and Inflectra, Hospira UK), 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. The contraindications, adverse reactions and administration schedule are the same for all infliximab products (see sections 3.9 and 3.10), but both biosimilars are subject to additional monitoring in line with standard European Medicines Agency recommendations.

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 NHS list price of originator infliximab (Remicade) 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. The NHS list price of infliximab biosimilars (Remsima, Inflectra) is £377.66 per 100-mg vial (BNF, December 2015). 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

3.11 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.

3.12 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.

3.13 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, (or with the patient access scheme, £6793) and then £9295 per year. Costs may vary in different settings because of negotiated procurement discounts.

3.14 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.

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

Golimumab

3.16 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.

3.17 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.

3.18 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.

3.19 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.

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

Abatacept

3.21 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.

3.22 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.

3.23 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.

3.24 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 3.23). 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.

3.25 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.

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

Tocilizumab

3.27 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.

3.28 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.

3.29 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.

3.30 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.

3.31 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; ADA, adalimumab; CrI, credible intervals; DMARDs, disease-modifying anti-rheumatic drugs; ETN, etanercept; GOL, golimumab; IFX, infliximab; MTX, methotrexate.			

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

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 (0.53–0.73)	0.40 (0.30–0.51)	0.20 (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: ABT, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; CrI, credible intervals; CTZ, certolizumab pegol; DMARDs, disease-modifying anti-rheumatic drugs; ETN, etanercept; GOL, golimumab; IFX, infliximab; IV, intravenous; MTX, methotrexate; PBO, placebo; SC, subcutaneous; TCZ, tocilizumab.

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 (TA130) 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 the drugs 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 NICE technology appraisal guidance 130 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 (TA130), 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 NICE technology appraisal guidance 130 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 biologic 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 treated with rituximab 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 when the maximum acceptable ICER is above £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, disease activity score (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 NICE technology appraisal guidance 130 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 130 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 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 infliximab biosimilars.

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 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 did not 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 infliximab biosimilars 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 infliximab biosimilars were sufficiently similar to the originator product to be granted marketing authorisation. The Committee noted that the NHS contract price for infliximab biosimilars 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 section 4.88). 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 4.91) 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 as 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 the median, £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 the lowest bound of the ICER range of £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. It noted that the analysis was retrospective and was not based on pre-identifiable patient characteristics which could inform a decision about whether or not a treatment should be offered. The assumptions were also highly uncertain and none of them were directly linked with the work done by the DSU. It also noted that the assumptions were very favourable, such as all patients would have the worst possible trajectory. Furthermore, the Committee did not find it plausible that the £28,500 ICER would apply to approximately one third to one half of patients with moderate active disease that the measures in section 4.94 would identify. The Committee accepted that current clinical management includes treating severe active disease that is progressing rapidly (see section 4.91), 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 4.94). The Committee noted the reduction in the ICER to £37,600 per QALY gained for infliximab biosimilars, 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 biosimilars did not change its decision. It also understood that the benefits to physical and mental health for patients with rheumatoid arthritis and their families (see sections 4.89 and 4.109) would also apply to moderate active disease, but noting the higher base-case ICER for the moderate active population compared with 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

TA375	**Appraisal title: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed**	**Section**
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 as 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, when 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 within 6 months, 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). 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	1.1–1.6, 4.107–4.109, 4.111, 4.112

the exploratory analysis 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 people who could not have methotrexate 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 some that were excluded in the Assessment Group's analyses. The Committee 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.	4.95
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.	4.96
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 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 Early Rheumatoid Arthritis Study (ERAS) dataset, which differed from the method used in 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 US National Data Bank for Rheumatic Diseases (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, 4.105

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 drivers of the cost effectiveness for biological DMARDs were 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 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 QALY gained) and the Assessment Group's ICER for the severe group with the fastest HAQ progression (that is, £25,300 per QALY gained). The 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 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 people with severe disease who cannot have methotrexate 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.	4.108, 4.109, 4.111, 4.112

For reviews (except rapid reviews): How has the new cost-effectiveness evidence that has emerged since the original appraisals (TA130, 186, 224, 280, 225 and 247) influenced the current 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. Infliximab biosimilars are now available on the NHS.	4.97, 4.100, 4.101, 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, Bristol–Myers Squibb and Roche have agreed that 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. The Department of Health and Merck, Sharp & Dohme have agreed that golimumab will be available to the NHS with a patient access scheme which makes it available with a discount. This will make the 100 mg dose of golimumab available to the NHS at the same cost as the 50 mg dose. The Department of Health and UCB Pharma have agreed that certolizumab pegol will be available to the NHS with a patient access scheme. UCB Pharma will provide the first 12 weeks of certolizumab pegol free of charge, which is equivalent to 10 vials. Any enquiries from NHS organisations about the patient access scheme should be directed to the relevant company.

6 Recommendations for 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 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

Further information is available on the NICE website.

- Tocilizumab for the treatment of rheumatoid arthritis (rapid review of technology appraisal guidance 198) (2012) NICE technology appraisal guidance 247
- Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs (2011) NICE technology appraisal guidance 225
- Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (2010) NICE technology appraisal guidance 195
- Rheumatoid arthritis (2009) NICE guideline 79

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 Dillon
Chief Executive
January 2016

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.

Grace Jennings and 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 expert
- 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

ISBN: 978-1-4731-1630-6

Accreditation

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Targeted submission

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Your name	[redacted]
Organisation name	AbbVie Ltd.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

1. It is proposed that this partial review is based on the original economic model developed by the Assessment Group in TA375. See here for the Assessment Group report. The assessment Group will update the model to address a limitation which means that currently, on progression from moderate to severe disease, patients are only modelled as having conventional DMARDs not biological DMARDs as in clinical practice.

Please comment on the proposal to use the Assessment Group model from TA375 amended as above.

AbbVie agree with the use of the original health economic model amended to include a progression from moderate rheumatoid arthritis (RA) to severe RA advanced therapies.

2. In order to amend the model to address the above issue the Assessment Group will need to source information on the relationship between the change in Health Assessment Questionnaire (HAQ) score and the change in disease activity (DAS28) score.

Are you aware of any data on this relationship?

As part of the AbbVie submission to NICE for the appraisal of Upadacitinib for treating moderate to severe rheumatoid arthritis [ID1400] a HE model was submitted which included a transition of patients from moderate to severe RA. We ran a repeated measures linear mixed effects model on the upadacitinib trials' data. Only one functional form was explored, the change in DAS-28 at three or six months being regressed on the change in the HAQ at three and, for one study (the SELECT-COMPARE), at six months. The results are shown in the table 1. below:

Table 1. ∆DAS-28 from baseline as a function of ∆HAQ from baseline

	Coefficient	SE	p-value
Intercept	-1.16	0.05	<0.0001
∆HAQ	0.91	0.07	<0.0001

Abbreviations: DAS-28, disease activity score 28-joint count; HAQ, health assessment questionnaire; SE, standard error

This would suggest that as disease activity increases, measured by DAS28, so does disutility, as measured by the Health Assessment Questionnaire. To further understand this relationship, AbbVie have carried out an analysis of patient registry data from the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) to understand the rate of transition between moderate RA and severe RA based on the DAS28 definition in the real-world. [redacted]

[redacted] This data is tabulated below:

Table 2. Baseline characteristics

	N	Mean	Median	Min	Max
Follow up time from baseline to last visit (days)	[redacted]				
Age at baseline		[redacted]			
Disease duration at baseline (years)			[redacted]		
Baseline DAS score				[redacted]	
Male (%)					[redacted]

[redacted]

Table 3. Transition rate in the whole follow-up period

	Number at risk	Rate
Year 1	[redacted]	
Year 2		
Year 5		
Year 10		[redacted]
Year 12		

[redacted]

[redacted] This estimation is similar to that in the Early Rheumatoid Arthritis Network (ERAN) published data, based on a UK registry, which includes 302 moderate RA patients followed up for 2 years at which point 19% had transitioned to severe RA [Deighton et al 2010, Kiely et al 2009].

[redacted]

References

- Deighton C, Hyrich K, Ding T, Ledingham J, Lunt M, Luqmani R, et al. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. Rheumatology (Oxford). 2010.
- Kiely PD, Jayakumar K, Norton S, Williams R, Walsh D, Young A, editors. Relation between year 1 DAS28 status and 2 year disease activity, function and employment in DMARD treated RA patients in the Early Rheumatoid Arthritis Network (ERAN). Rheumatology; 2009: OXFORD UNIV PRESS GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND.

3. In TA375 the committee identified uncertainties relating to long-term disease progression for people having conventional DMARDs and the mapping from HAQ scores to EQ-5D (health-related quality of life) utility values. It based decisions on:

- Early Rheumatoid Arthritis Study data to model disease progression with conventional DMARDs rather than assume a linear progression
- Hernandez et al (2013) to calculate EQ-5D utility values

The review paper did not find any new evidence to address these uncertainties, so it is proposed that the Assessment Group analyses also use these assumptions.

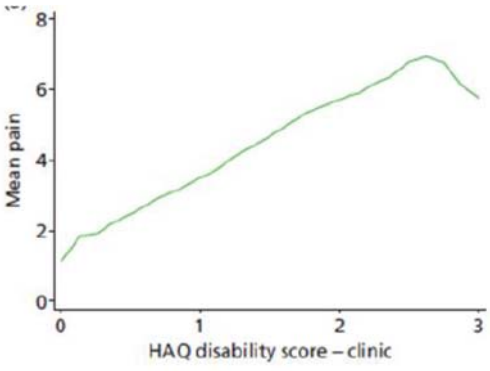
Are you aware of any new evidence in these areas?

AbbVie agree with the use of ERAS data to model progression with conventional DMARDs and found on literature search no preferential method for analysing this.

AbbVie agree broadly with the use of Hernandez et al (2013) to calculate EQ-5D utility values. In the submission to NICE for upadacitinib [ID1400] AbbVie used the Hernadez et al approach to calculate EQ-5D values. However, pain was estimated based on HAQ using individual patient data (IPD) from the Phase III upadacitinib trials for the csDMARD-IR (SELECT-NEXT, SELECT-MONOTHERAPY, SELECT-SUNRISE, SELECT COMPARE trials) and bDMARD-IR (SELECT-BEYOND) populations. Mapping using upadacitinib phase 3 trial data was preferred by AbbVie over the National Database for Rheumatic Diseases (NDB) data used in TA375. This was accepted by the appraisal committee as being an equally valid method to calculate EQ-5D utility values for the reasons detailed below:

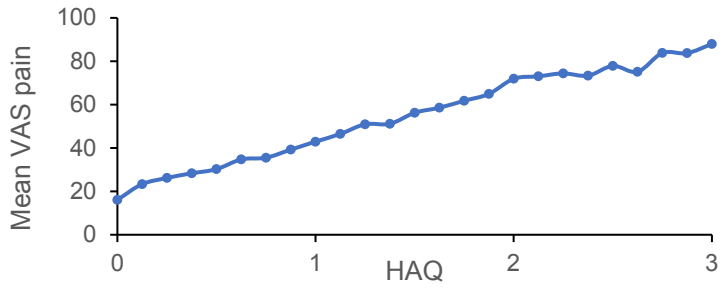
(1) The National Databank for Rheumatic Diseases (NDB) algorithm provides counterintuitive results that HAQ scores at the highest end of the spectrum (indicating lowest functionality) are associated with a reduction in pain (**Error! Reference source not found.**).

Figure 1: HAQ-to-pain map based on using NDB



(2) The use of the SELECT trial-based algorithm does not show such a counterintuitive decrease in pain scores with HAQ scores at the highest end of the spectrum as shown

Figure 2: HAQ-to-pain map based on SELECT trials



The SELECT trial-based algorithm is based upon a substantial dataset consisting of 3599 patients and 7963 observations.

Additionally, data from the AbbVie upadacitinib RA trials (see table 4.) showing the relationship between patient administered pain VAS and HAQ does not show the reduction in pain scores shown between HAQ 2.75 and 3.0 (mean values 73.6 and 80.9 mm respectively) estimated using the NDB algorithm. The values are in line with the progressive increase in pain scores with increased HAQ severity shown using the SELECT trial algorithm.

Table 4. Relationship between patient administered pain VAS and HAQ

Unique Level of HAQ-DI	N	Mean	(95% CI)	[A]	SD	Q1	Median	Q3
0	7858	10.8	(10.4,	11.1)	15.06	1.0	5.0	14.0
0.125	2091	16.7	(16.0,	17.5)	17.80	3.0	11.0	24.0
0.25	2390	19.8	(19.1,	20.6)	19.27	5.0	14.0	29.0
0.375	2177	21.9	(21.1,	22.7)	19.44	7.0	17.0	30.0
0.5	2431	23.9	(23.1,	24.7)	19.77	8.0	18.0	35.0
0.625	2246	27.4	(26.5,	28.2)	20.56	11.0	23.0	40.0
0.75	2475	29.2	(28.4,	30.1)	21.44	12.0	24.0	44.0
0.875	2462	31.9	(31.0,	32.7)	21.52	14.0	28.0	47.0
1	3586	36.6	(35.9,	37.3)	21.65	19.0	35.0	52.0
1.125	2746	38.7	(37.9,	39.5)	21.68	22.0	38.0	53.0
1.25	2708	41.5	(40.7,	42.3)	21.90	24.0	41.0	57.0
1.375	2800	44.6	(43.8,	45.5)	22.12	28.0	45.0	61.0
1.5	2790	47.6	(46.8,	48.5)	22.18	31.0	48.0	64.0
1.625	2523	51.5	(50.7,	52.4)	21.69	36.0	52.0	68.0
1.75	2309	55.0	(54.1,	55.9)	21.82	40.0	56.0	72.0
1.875	1945	59.5	(58.5,	60.4)	21.34	46.0	62.0	76.0
2	1906	64.1	(63.1,	65.0)	21.74	51.0	68.0	80.0
2.125	1013	65.0	(63.6,	66.4)	22.63	51.0	69.0	83.0
2.25	752	67.8	(66.3,	69.3)	20.98	55.0	71.5	84.0
2.375	592	68.9	(67.3,	70.5)	20.02	56.0	73.0	84.0
2.5	431	72.0	(70.1,	74.0)	20.66	61.0	76.0	88.0
2.625	335	70.0	(67.7	72.3)	21.55	57.0	74.0	88.0

2.75	178	73.6	(70.4,	76.7)	21.22	62.0	79.0	90.0
2.875	98	73.6	(68.6	78.5)	24.80	52.0	83.5	93.0
3	79	80.9	(77.0	84.8)	17.42	70.0	85.0	96.0

Further details on the SELECT trial-based algorithm

Method

Patients with moderately and severely active RA from the upadacitinib phase 3 clinical trials (SELECT NEXT, SELECT COMPARE, SELECT MONO, SELECT SUNRISE, and SELECT BEYOND) were included in this analysis. Observed HAQ, VAS pain and EQ-5D values reported at baseline, 3 months, and 6 months (for COMPARE only) and were used for the evaluation [Genovese, 2018, Burmester, 2018, Smolen JS, 2019, AbbVie, 2019].

The SELECT trials collected EQ-5D-5L. As NICE currently does not recommend using the EQ-5D-5L valuation set to estimate utility inputs for economic models, the EQ-5D-5L values were mapped to EQ-5D-3L using the Van Hout et al. (2012) mapping function recommended by NICE.

Two approaches were used to derive VAS pain values by HAQ scores:

- Trial-derived HAQ-to-pain mapping: HAQ-to-pain mapping derived based on the observed VAS pain values and HAQ scores from phase 3 clinical trials of upadacitinib. The tofacitinib submission [TA480] used the same approach with tofacitinib clinical trial data.
- Literature reported HAQ-to-pain mapping: HAQ-to-pain mapping reported in TA375 that was established using the US NDB and UK ERAS data.

Next, EQ-5D was predicted based on patients' HAQ, age, sex, and VAS pain using the Hernandez approach. EQ-5D values were predicted separately using the trial-derived and literature-reported pain values.

The predictability of the two HAQ-to-pain mapping approaches was compared:

- Trajectories of the average observed EQ-5D values from the upadacitinib trials, predicted EQ-5D using the trial-derived pain values, and predicted EQ-5D using literature-reported pain values were plotted by HAQ scores.
- Predictive properties including mean absolute error (MAE) and root mean squared error (RMSE) were summarized (where lower scores indicate better predictive properties).

Results

When HAQ is lower than 0.5, the predicted EQ-5D based on both the trial-derived and the literature-reported HAQ-to-pain mapping algorithms showed similar trends as the observed

EQ-5D. As HAQ scores increase and EQ-5D scores decrease, both approaches perform worse than in the lower HAQ values. However, the pattern of the EQ-5D predictions using trial-derived HAQ-to-pain mapping is more consistent with the observed data, compared to the predictions using the alternative approach (see Figure 3. below).

The findings in the plot were consistent with the predictive properties (see Table 5. below). The trial-derived HAQ-to-pain mapping approach had a smaller MAE (trial-derived vs literature: 0.125 vs. 0.128) and RMSE (0.172 vs. 0.180) than the alternative approach.

Figure 3. Average EQ-5D by HAQ score

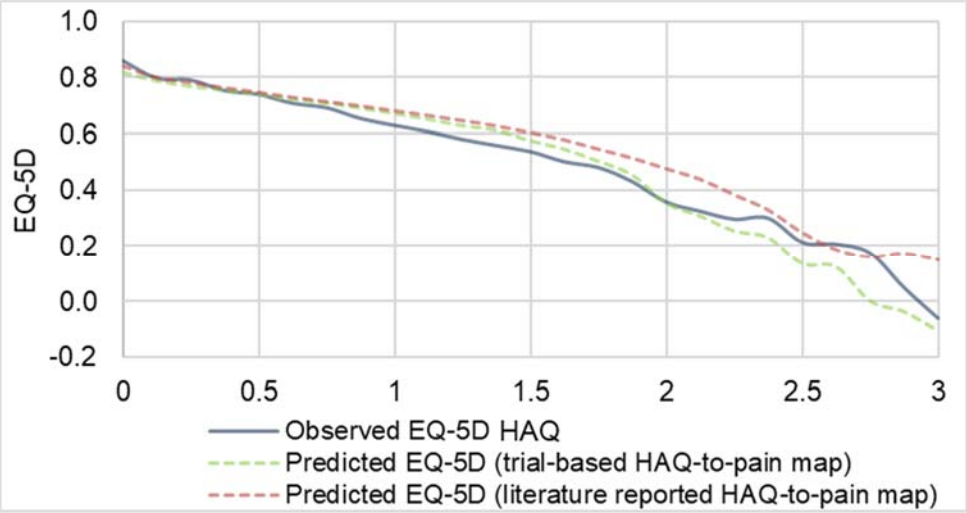


Table 5. Predictive properties of each mapping approach

Approach	Mean EQ-5D	MAE	RMSE
Observed EQ-5D	0.567	-	-
Predicted EQ-5D based on trial-derived HAQ-to-pain map	0.580	0.125	0.172
Predicted EQ-5D based on TA375 reported HAQ-to-pain map	0.620	0.128	0.180
Abbreviations: HAQ = health assessment questionnaire disability index; MAE = mean absolute error; RMSE = root mean squared error			

Conclusion

Based particularly on the counterintuitive pain scores using the NDB approach which are reduced at more severe HAQ scores, the algorithm using the SELECT trial data which did not show such a counterintuitive trend is the preferred option by AbbVie and was confirmed to be an equally valid method by the Appraisal Committee.

Additionally, data from the SELECT trials showing the relationship between HAQ and patients' measurement of pain on a VAS supports the relationship at higher HAQ scores demonstrated by the SELECT trial algorithm over that seen with the NDB one.

4. If you are the manufacturer of one of the interventions, please provide details of your product(s) including price and any confidential discounts.

The list price for Humira is £704.28 per pack (containing two 40mg pens or syringes). The annual cost for an RA patient at this price is £9,155.64 (based on 13 packs per year).

The company has a commercial arrangement (CMU confidential discount) that makes Humira available to the NHS at £[redacted]. The annual cost for an RA patient at this price is £[redacted]. This discounted price is offered by AbbVie under the Adalimumab Framework for 2020-2022 and AbbVie is the only supplier awarded for existing patients across all regions covered by the framework. As a result, this is the only discounted price appropriate for use by NICE in assessing cost-effectiveness since other available adalimumab discounted prices do not align with the Methods Guide.

According to the current Methods Guide (Section 5.5.2), the default position is to use a technology's list price and to deviate from that only if there are reduced prices that meet certain specific criteria, i.e. they are transparent and consistently available nationally across the NHS for a guaranteed period of time.

Importantly, all adalimumab biosimilar products are subject to regional allocation, therefore cannot be considered consistently available across the NHS at a nationally available price.

The Methods Guide also requires selecting and evaluating evidence (including with respect to costs) that avoids selection bias (e.g., at Section 3.3.11). This principle would be at risk if the adalimumab price selected for the purpose of the MTA was not national, transparent, and consistently available across the NHS.

5. Please provide any other comments on the potential for a change in the recommendations for moderate active disease.
None.
6. Are there any potential equality issues that should be taken into account when considering these treatments?
None.

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Targeted evidence submission

Prepared by:

October 2020

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Your name	[redacted]
Organisation name	Amgen Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Please note this document contains two sections – the completed targeted evidence submission, followed on p. 9 by an Appendix with further detail on the health condition and clinical effectiveness considerations

1. It is proposed that this partial review is based on the original economic model developed by the Assessment Group in TA375. See here for the Assessment Group report. The assessment Group will update the model to address a limitation which means that currently, on progression from moderate to severe disease, patients are only modelled as having conventional DMARDs not biological DMARDs as in clinical practice. **Please comment on the proposal to use the Assessment Group model from TA375 amended as above.**
It is appropriate for the Assessment Group to use the original economic model for TA375. In addition, the proposed change to the Assessment Group model does reflect clinical practice, given that as a result of TA375 and subsequent NICE technology appraisals, biological disease-modifying anti-rheumatic drugs (bDMARDs) are now recommended by NICE in severe disease. However, this is a substantial change to the original TA375 model, and as such it will be important to minimise uncertainty associated with the key required adaptations, in particular: • Treatment sequencing in moderate and severe RA for both the intervention and standard of care arms • Disease progression while on conventional disease-modifying antirheumatic drugs (cDMARD) or bDMARDs • Implementation of the relationship between HAQ progression and Disease Activity Score-28 [DAS28] To understand and validate the impact of this proposed change on the model results, the Assessment Group should also present results using the original TA375 model (i.e. without the proposed change).
2. In order to amend the model to address the above issue the Assessment Group will need to source information on the relationship between the change in Health Assessment Questionnaire (HAQ) score and the change in disease activity (DAS28) score. **Are you aware of any data on this relationship?**
In recent NICE appraisals in RA (TA485, ID1400) the relationship between change in HAQ and change in DAS28 has been estimated from the relevant pivotal trials for the intervention. For the purposes of this appraisal, it would be appropriate to

estimate this relationship from clinical evidence for standard of care treatment (i.e. cDMARD therapy) in moderate and severe RA.

3. In TA375 the committee identified uncertainties relating to long-term disease progression for people having conventional DMARDs and the mapping from HAQ scores to EQ-5D (health-related quality of life) utility values. It based decisions on:

- Early Rheumatoid Arthritis Study data to model disease progression with conventional DMARDs rather than assume a linear progression
- Hernandez et al (2013) to calculate EQ-5D utility values

The review paper did not find any new evidence to address these uncertainties, so it is proposed that the Assessment Group analyses also use these assumptions.

Are you aware of any new evidence in these areas?

Amgen are not aware of any new evidence in these areas.

4. If you are the manufacturer of one of the interventions, please provide details of your product(s) including price and any confidential discounts.

Amgevita is a biosimilar version of the Tumour Necrosis Factor alpha (TNFα) inhibitor adalimumab. It received marketing authorisation from the European Medicines Agency (EMA) in March 2017 and is approved in all indications for which the reference product is approved, including the treatment of adult patients with moderate to severe RA following inadequate response to DMARDs, and severe, active and progressive RA in adults not previously treated with methotrexate.[1] Details of its dosing, administration and list price are summarised in Table 1.

Table 1: Technology being appraised

UK approved name and brand name	Amgevita (biosimilar Adalimumab)
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	**Rheumatoid Arthritis:** Amgevita in combination with methotrexate, is indicated for:[1] ▪ The treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate ▪ The treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. Amgevita can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

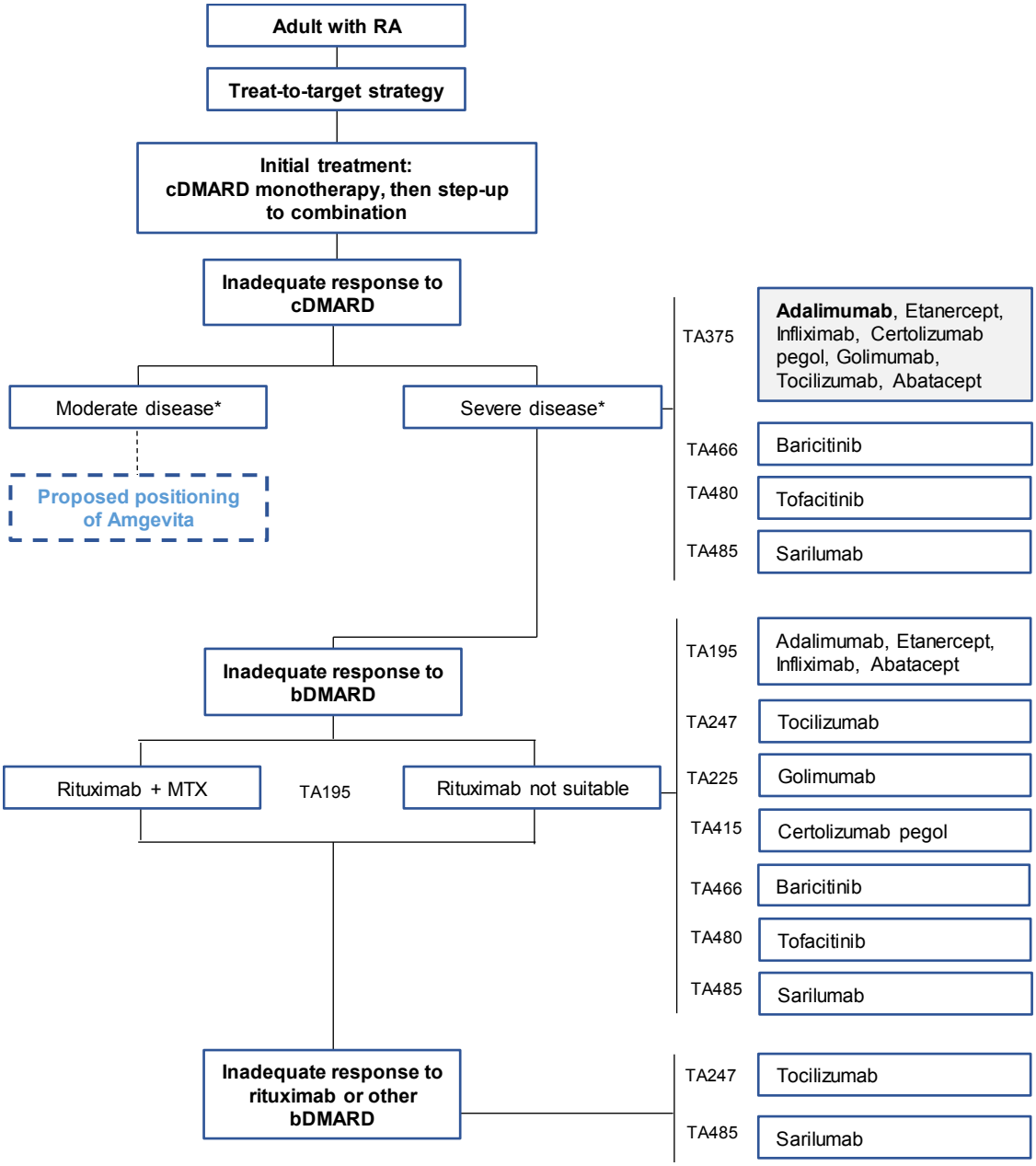
	Amgevita reduces the rate of progression of joint damage as measured by x-ray and improves physical function, when given in combination with methotrexate.	
		Source
Acquisition cost (excluding VAT)*	For 2 x 40 mg/0.8 mL pre-filled syringes/pens: ▪ Confirmed list price: £633.60 [redacted]	BNF (2020)[2] [redacted]
Method of administration (including homecare provision)	Subcutaneous injection (self-administered); [redacted]	Amgevita SmPC[1] [redacted]
Dosage	40 mg every other week (recommended)	Amgevita SmPC[1]
Average length of a course of treatment **Anticipated average interval between courses of treatments** **Anticipated number of repeat courses of treatments**	Adalimumab is received continuously. Available data suggest clinical response is usually achieved within 12 weeks of treatment. NICE TA375 recommends continued treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy.	Amgevita SmPC[1] NICE TA375[3]
Dose adjustments	Dose adjustments are permitted in the SmPC for Amgevita monotherapy in patients experiencing a decrease in their response to Amgevita 40 mg every other week.	Amgevita SmPC[1]

* Indicate whether this acquisition cost is a confirmed or anticipated list price. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the list price of each intervention should be presented.

Footnotes: [redacted]

The current treatment pathway for RA in England and Wales based on NICE guidance is summarised in Figure 1 (see the Appendix for further details), alongside the proposed positioning of the Amgevita in the treatment pathway.

Figure 1: Current RA treatment pathway based on existing NICE guidance



Footnotes: *Moderate disease: DAS28 3.2-5.1; Severe disease: DAS28>5.1.
Abbreviations: bDMARD: biological disease-modifying anti-rheumatic drug; cDMARD: conventional disease-modifying anti-rheumatic drug; MTX: methotrexate; RA: rheumatoid arthritis.
Source: NICE Pathways: Drug treatment for RA.[4]

5. Please provide any other comments on the potential for a change in the recommendations for moderate active disease.

Permitting people with moderate RA (defined as DAS28 score of 3.2 to 5.1) to remain with uncontrolled disease activity is not clinically desirable or appropriate and results in substantial and sustained disability and functional decline, negatively affecting quality of life.[5-10] At least 10–15% of RA patients in the UK fail to respond

to cDMARD treatment and require further treatment options to achieve disease control.[3, 11, 12]

TNFα inhibitors such as adalimumab have demonstrated consistent efficacy across both moderate and severe RA;[13] as such, both UK and European guidelines recommend the early use of TNFα inhibitors in patients with moderate activity disease.[10, 14] However, the current NICE treatment pathway limits treatment options in moderate RA to cDMARDs and denies access to bDMARDs,[4, 15] leaving moderate RA patients exposed to the significant risks of disease progression, irreversible joint damage, and associated consequences. There is a clear and pressing unmet need for access to bDMARDs such as adalimumab to improve disease control and quality of life among patients with persistently moderate DAS28 in spite of standard of care cDMARD treatment.

In 2016 NICE TA375 recommended adalimumab as an option (among other specific bDMARDs) for use in patients with severe RA whose disease has not responded to intensive therapy with a combination of cDMARDs. Use of adalimumab for the treatment of moderate RA was not recommended because it was not considered to be cost-effective, although the Committee concluded that adalimumab was more clinically effective compared to standard of care cDMARD therapy in this patient population.[3] This is supported by patient registry data, including data from the British Society For Rheumatology Biologics Register, demonstrating that TNFα inhibitors have demonstrated consistent efficacy across both moderate and severe RA.[13, 16]

Since NICE TA375 was issued, Amgevita and other biosimilar versions of adalimumab have become available at markedly reduced prices compared with the originator adalimumab, resulting in significant cost savings to the NHS. As such, Amgevita (and other TNFα inhibitors biosimilars) are highly likely to be cost-effective early in the treatment pathway and provide an opportunity to optimise clinical management of moderate RA by increasing patient access to adalimumab. Indeed, clinical evidence[13, 16] suggests that the likelihood of achieving the NICE-recommended treatment goals, and realising the benefits associated with achieving these, is greater if TNFα inhibitors such as adalimumab are initiated before patients progress to severe activity disease. This change to the treatment pathway would be expected to reduce the morbidity and quality of life impairment associated with persistent moderate disease activity, and improve disease management across RA as a whole by reducing the number of patients progressing to severe RA.

A positive recommendation from NICE for adalimumab in moderate RA would also align the NICE recommendation for adalimumab and Amgevita with their full marketing authorisation and enable RA patients to benefit from bDMARD treatment at an earlier stage of disease. This would also align NICE guidance to British Society for Rheumatology and EULAR guidelines, which have both long

recommended the early use of TNFα inhibitors in RA patients with moderate disease.[10, 14]

As described above, Amgevita is highly likely to be cost-effective early in the treatment pathway. Furthermore, using highly conservative assumptions, the budget impact of extending the use of adalimumab to patients with moderate RA is likely to be small, manageable and comfortably below the NHS England budget impact test limit of £20 million per year within any of the first three years. Overall, Amgevita should, therefore, be recommended for use in patients with moderate RA.

More details on unmet need in moderate RA and the budget impact analysis can be found in the Appendix and Budget Impact Template, respectively.

6. Are there any potential equality issues that should be taken into account when considering these treatments?

No equality issues related to the use of adalimumab in moderate RA are foreseen.

References

1. EMC. Amgevita 40 mg solution for injection in pre-filled pen. Available at [accessed 26 August 2020]: https://www.medicines.org.uk/emc/product/9546/smpc.
2. BNF 2020. Adalimumab medicinal forms. Available at [accessed 26 August 2020]: https://bnf.nice.org.uk/medicinal-forms/adalimumab.html.
3. NICE 2016. TA375: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. Available at [accessed 26 August 2020]: https://www.nice.org.uk/guidance/ta375.
4. NICE 2020. NICE Pathways: Drug treatment for rheumatoid arthritis. Available at [accessed 26 August 2020]: https://pathways.nice.org.uk/pathways/rheumatoid-arthritis.
5. Nikiphorou E, Norton SJ, Carpenter L, Walsh DA, Creamer P, Dixey J, et al. Remission vs low disease activity: function, quality of life and structural outcomes in the Early Rheumatoid Arthritis Study and Network. Rheumatology (Oxford, England). 2020;59(6):1272-80.
6. Kiely P, Walsh D, Williams R, Young A. Outcome in rheumatoid arthritis patients with continued conventional therapy for moderate disease activity--the early RA network (ERAN). Rheumatology (Oxford, England). 2011;50(5):926-31.
7. Nikiphorou E, Norton S, Young A, Carpenter L, Dixey J, Walsh DA, et al. Association between rheumatoid arthritis disease activity, progression of functional limitation and long-term risk of orthopaedic surgery: combined analysis of two prospective cohorts supports EULAR treat to target DAS thresholds. Annals of the rheumatic diseases. 2016;75(12):2080-6.
8. Combe B, Logeart I, Belkacemi MC, Dadoun S, Schaeverbeke T, Daurès JP, et al. Comparison of the long-term outcome for patients with rheumatoid arthritis with

persistent moderate disease activity or disease remission during the first year after diagnosis: data from the ESPOIR cohort. Annals of the rheumatic diseases. 2015;74(4):724-9.
9. Conaghan PG, Hensor EMA, Keenan A-M, Morgan AW, Emery P, Consortium tY. Persistently moderate DAS-28 is not benign: loss of function occurs in early RA despite step-up DMARD therapy. Rheumatology. 2010;49(10):1894-9.
10. Deighton C, Hyrich K, Ding T, Ledingham J, Lunt M, Luqmani R, et al. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. Rheumatology. 2010;49(6):1197-9.
11. Bluett J, Sergeant JC, MacGregor AJ, Chipping JR, Marshall T, Symmons DPM, et al. Risk factors for oral methotrexate failure in patients with inflammatory polyarthritis: results from a UK prospective cohort study. Arthritis Research & Therapy. 2018;20(1):50.
12. Hope HF, Hyrich KL, Anderson J, Bluett J, Sergeant JC, Barton A, et al. The predictors of and reasons for non-adherence in an observational cohort of patients with rheumatoid arthritis commencing methotrexate. Rheumatology (Oxford, England). 2020;59(1):213-23.
13. Hyrich KL, Deighton C, Watson KD, Symmons DP, Lunt M. Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity. Rheumatology (Oxford, England). 2009;48(10):1323-7.
14. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Annals of the rheumatic diseases. 2020;79(6):685-99.
15. NICE 2018. NG100: Rheumatoid arthritis in adults: management. Available at [accessed 26 August 2020]: https://www.nice.org.uk/guidance/ng100.

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

TECHNOLOGY APPRAISAL

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Appendix

Prepared by:

AMGEN

October 2020

File name	Version	Contains confidential information	Date
Amgen_ID2710_Targeted Evidence Submission_REDACTED	1.0	CIC information has been redacted	01/10/2020

Contents

List of tables and figures

1 Technology being appraised

Amgevita is a biosimilar version of the Tumour Necrosis Factor alpha (TNFα) inhibitor adalimumab. It received marketing authorisation from the European Medicines Agency (EMA) in March 2017 and is approved in all indications for which the reference product is approved, including the treatment of adult patients with moderate to severe rheumatoid arthritis (RA) following inadequate response to disease-modifying antirheumatic drugs (DMARDs), and severe, active and progressive RA in adults not previously treated with methotrexate.[1] Details of its dosing, administration and list price are summarised in Table 1.

Table 1: Technology being appraised

UK approved name and brand name	Amgevita (biosimilar Adalimumab)	
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	**Rheumatoid Arthritis:** Amgevita in combination with methotrexate, is indicated for:[1] ▪ The treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate ▪ The treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. Amgevita can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Amgevita reduces the rate of progression of joint damage as measured by x-ray and improves physical function, when given in combination with methotrexate.	
		Source
Acquisition cost (excluding VAT)*	For 2 x 40 mg/0.8 mL pre-filled syringes/pens: ▪ Confirmed list price: £633.60 [redacted]	BNF (2020)[2] [redacted]
Method of administration (including homecare provision)	Subcutaneous injection (self-administered); [redacted]	Amgevita SmPC[1] [redacted]
Dosage	40 mg every other week (recommended)	Amgevita SmPC[1]

Average length of a course of treatment	Adalimumab is received continuously. Available data suggest clinical response is usually achieved within 12 weeks of treatment. NICE TA375 recommends continued treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy.	Amgevita SmPC[1] NICE TA375[3]
Anticipated average interval between courses of treatments		
Anticipated number of repeat courses of treatments		
Dose adjustments	Dose adjustments are permitted in the SmPC for Amgevita monotherapy in patients experiencing a decrease in their response to Amgevita 40 mg every other week.	Amgevita SmPC[1]
* Indicate whether this acquisition cost is a confirmed or anticipated list price. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the list price of each intervention should be presented.		

Footnotes: [redacted]

In 2016 NICE TA375 recommended adalimumab as an option (among other specific biological DMARDs [bDMARDs]) for use in patients with severe RA (defined as patients with a Disease Activity Score-28 [DAS28] >5.1) whose disease has not responded to intensive therapy with a combination of conventional DMARDs (cDMARDs). However, use of adalimumab for the treatment of moderate RA (defined as DAS28 score of 3.2 to 5.1) was not recommended because it was not considered to be cost-effective, although the Committee concluded that adalimumab was more clinically effective compared to standard of care cDMARD therapy in this patient population.[3]

Since NICE TA375 was issued, Amgevita and other biosimilar versions of adalimumab have become available at significantly reduced prices compared with the originator adalimumab. The recommendation for use of the originator adalimumab in patients with severe RA extends to Amgevita and other adalimumab biosimilar versions. However, given their significantly lower prices, Amgevita (and other TNFα inhibitors biosimilars) are highly likely to be cost-effective early in the treatment pathway and provide an opportunity to optimise clinical management of moderate RA by increasing patient access to adalimumab, improving disease management across RA as a whole. NICE is therefore conducting a partial review of NICE TA375, focused on patients with moderate disease only.[17]

In line with NICE's proposed pragmatic approach to the review of NICE TA375,[17] this is a short, succinct Appendix in support of Amgevita in the treatment of patients with

moderate RA, to be considered alongside the Targeted Evidence Submission and the Budget Impact Template.

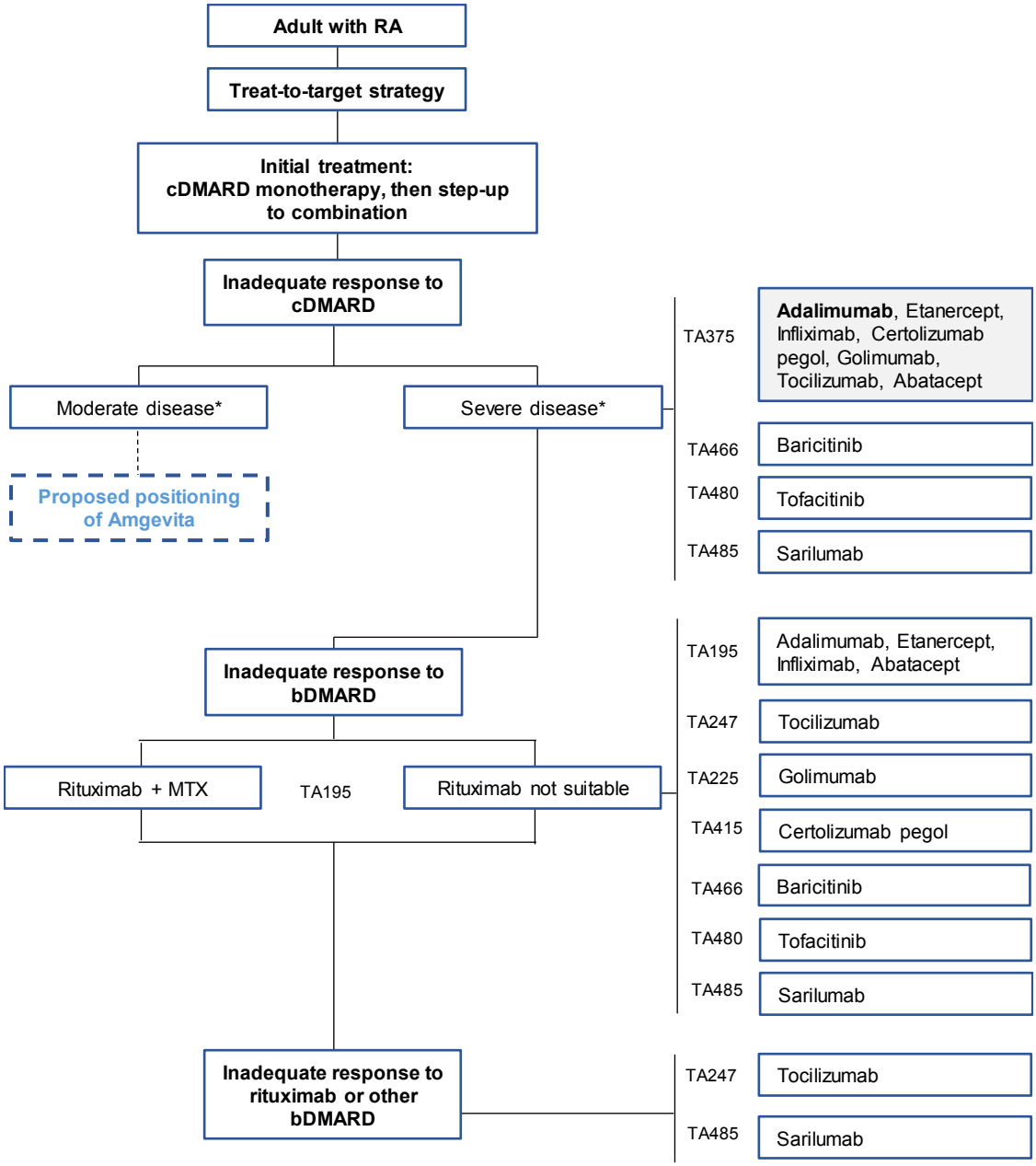
2 Health condition and position of the technology in the treatment pathway

2.1 Rheumatoid arthritis treatment pathway

RA is an inflammatory disease largely affecting synovial joints. It typically affects the small joints of the hands and the feet, and usually both sides equally and symmetrically, although any synovial joint can be affected. It is a systemic disease and so can affect the whole body, including the heart, lungs and eyes. Approximately one-third of people who develop RA stop work as a result of their disease within 2 years of onset, and this increases thereafter.[15] The most recent peer-reviewed estimates of the prevalence and incidence of RA in the UK are 0.67% and 3.81/10,000 person-years, respectively, based on an analysis of Clinical Practice Research Datalink data from 1990–2014.[18] In England, this equates to nearly 300,000 prevalent RA patients and over 16,700 newly incident patients annually.[18, 19] RA is therefore associated with a wide range of complications and presents a significant burden, for people with the disease and also for carers, the NHS and society in general.

There is no cure for RA. The main aims of management are to suppress disease activity and induce disease remission, prevent loss of function, control joint damage, maintain pain control and enhance self-management, and ultimately improve patient quality of life. The NICE Clinical Guideline Rheumatoid arthritis in adults: Management (NICE NG100) recommends a treat-to-target strategy in which the aim is to induce remission (defined as a DAS28 score <2.6), or at least low disease activity (DAS28 score of 2.6 to <3.2) where remission is not possible. The current treatment pathway indicates initial treatment is cDMARD monotherapy, with step up to combination of cDMARDs where necessary. Treatment with bDMARDs, such as TNFα inhibitors including adalimumab, is currently only available in England and Wales for patients with inadequate response to cDMARDs and with severe active disease.[4, 15] The current treatment pathway for RA in England and Wales based on NICE guidance is summarised in Figure 1, alongside the proposed positioning of Amgevita in the treatment pathway.

Figure 1: Current RA treatment pathway based on existing NICE guidance



Footnotes: *Moderate disease: DAS28 3.2-5.1; Severe disease: DAS28>5.1.
Abbreviations: bDMARD: biological disease-modifying anti-rheumatic drug; cDMARD: conventional disease-modifying anti-rheumatic drug; MTX: methotrexate; RA: rheumatoid arthritis.
Source: NICE Pathways: Drug treatment for RA.[4]

2.2 Significant unmet needs in moderate RA

Summary

- Permitting people with moderate RA to remain with uncontrolled disease activity is not clinically desirable or appropriate and results in substantial and sustained disability and functional decline, negatively affecting quality of life[5-10]
- At least 10–15% of RA patients in the UK fail to respond to cDMARD treatment and require further treatment options to achieve disease control[3, 11, 12]
- TNFα inhibitors such as adalimumab have demonstrated consistent efficacy across both moderate and severe RA;[13] as such both UK and European guidelines recommend the early use of TNFα inhibitors in patients with moderate activity disease[10, 14]
- However, the current NICE treatment pathway limits treatment options in moderate RA to cDMARDs and denies access to bDMARDs,[4, 15] leaving moderate RA patients exposed to the significant risks of disease progression, irreversible joint damage, and associated consequences
- There is a clear and pressing unmet need for access to bDMARDs such as adalimumab in moderate RA, to improve disease control and quality of life among patients with persistently moderate DAS28 in spite of standard of care cDMARD treatment

Failure to achieve early, tight control of disease activity with cDMARDs among patients with moderate RA results in persistent, poor disease control and substantial and sustained disability and functional decline, negatively affecting quality of life.[6-10]

For example, the Early RA Network (ERAN) is a prospective observational cohort of newly diagnosed RA patients that are monitored and treated according to local practice in England, Wales and Ireland. This study found that patients with moderate disease who failed to achieve remission (DAS28 score <2.6) or low disease activity (DAS28 score <3.2) after two years of cDMARD therapy also had high HAQ scores.[6] Other data from ERAN and another prospective cohort of RA patients in England (Early RA Study, ERAS) also show that persistent moderate disease activity is associated with greater progression in HAQ scores over time and, using orthopaedic surgery episodes as a surrogate marker, significantly greater risk of joint destruction compared with either low disease activity or remission states.[7] Comparable observational data from French and regional UK cohorts demonstrate persistent moderate disease activity is associated with deteriorating HAQ scores, increased radiographic progression, reduced function, and reduced workdays.[8, 9] Indeed, the

British Society for Rheumatology has noted that persistent moderate disease activity translates into radiological progression, functional decline and loss of work in a manner similar to that with more severe disease activity.[10]

Therefore permitting people with moderate RA to remain with uncontrolled disease activity is not clinically desirable or appropriate. In line with this, according to European League Against Rheumatism (EULAR) guidelines and as endorsed by NICE, any disease activity state higher than either remission or low disease activity is regarded as inadequate control mandating a therapeutic change.[5] EULAR RA guidelines consider cDMARD treatment failure meriting a change in treatment approach as failure to improve outcomes within 3 months and to achieve the treatment target at 6 months.[14] It is estimated that at least 10–15% of RA patients in the UK fail to respond to cDMARD treatment;[3, 11, 12] for example, clinical experts advised the Committee during the TA375 appraisal that 15% of RA patients do not respond to intensive combination therapy with cDMARDs, and that these patients are likely to have disease that progresses more quickly with worse outcomes.[3] These patients require alternative treatment options to achieve disease control and avoid the morbidity and quality of life impairment associated with persistent disease activity.

EULAR guidelines describe that the increasing number of effective biologics has improved the likelihood of reaching the treatment target for individuals with RA.[14] For example, data from the British Society For Rheumatology Biologics Register (BSRBR) has shown that TNFα inhibitors have demonstrated consistent efficacy across both moderate and severe RA.[13] Furthermore, US patient registry data indicate that greater proportions of moderate RA patients treated with bDMARDs achieve remission or low disease activity compared to severe RA patients.[16] As such, the British Society for Rheumatology and EULAR have both long since recommended the early use of TNFα inhibitors in patients with moderate activity disease,[10, 14] and patients with moderate disease in other European countries have benefited from access for many years.[6] Collectively, these data suggest that the likelihood of achieving the NICE-recommended treatment goals, and realising the benefits associated with achieving these, is greater if TNFα inhibitors such as adalimumab are initiated before patients progress to severe activity disease.

However, as per the current NICE treatment pathway (Figure 1), patients with moderate RA have only cDMARDs available with which to try to achieve the NICE-recommended target of remission or at least low disease activity and do not have access to bDMARDs until progression to severe disease.[4, 15] As described above, at least 10–15% of RA patients in the UK fail to respond to cDMARD treatment; [3, 11, 12] moderate RA patients failing to respond to cDMARD therapy have no alternative therapy options and therefore continue to suffer the consequences of moderate disease activity and increased likelihood of progression to severe disease, compared

to patients who have reached the treatment target. As such, there is a clear and pressing unmet need for access to bDMARDs such as adalimumab to improve disease control and quality of life among patients with persistently moderate DAS28 in spite of standard of care cDMARD treatment. The existing treatment pathway in England, which limits treatment options for patients with moderate RA to cDMARDs and denies access to bDMARDs, [4, 15] leaves these patients exposed to the significant risks of disease progression, irreversible joint damage, and associated consequences.

3 Clinical effectiveness considerations

3.1 Amgevita biosimilarity with originator adalimumab

The NICE Technology Appraisal Proposal paper for the review of NICE TA375 indicated that, having reviewed new evidence since TA375 was issued, it is the price reductions in available bDMARDs that may change the existing recommendations. A pragmatic approach using the Assessment Group's economic model from TA375 will be used to model the new prices of the bDMARDs in patients with moderate disease.[17]

No changes in the clinical evidence base for adalimumab that would materially change the conclusions of its efficacy and safety in patients with RA were identified in the Proposal paper. The extensive clinical evidence in support of adalimumab in the treatment of moderate and severe RA is already well documented and available to NICE and its Assessment Group. This evidence applies equally to Amgevita, as a licensed biosimilar version of adalimumab. Therefore, and in line with the proposal by NICE that a short, succinct submission be made by manufacturers,[17] we have omitted a discussion of the extensive clinical evidence in support of the efficacy and safety of adalimumab. As Amgevita is already well established in use in the NHS in England, we provide only a brief overview of its clinical development programme.

Amgevita was licensed as a biosimilar version of the originator adalimumab on the basis of a robust clinical development programme that included two comparative clinical studies and a clinical pharmacology study in healthy volunteers. The comparative clinical studies compared Amgevita against originator adalimumab in patients with moderate-to-severe RA[20, 21] and in patients with moderate-to-severe psoriasis[22, 23] (Table 2).

Table 2: Summary of comparative clinical studies of Amgevita vs originator adalimumab

	Interventions	Outcomes reported	Primary endpoint results	Safety results
Rheumatoid arthritis[20, 21]				
To assess the clinical efficacy, safety and immunogenicity of AMGEVITA compared with ADA for the treatment of adult patients with moderate to severe RA who were MTX-IR Double-blind, equivalence RCT *Follow-up*: 2 weeks; 8 weeks; **24 weeks**	AMGEVITA 40 mg SC Q2W + MTX N = 264	*Primary endpoint* • ACR20 response rate *Secondary endpoints* • DAS28-CRP • ACR20, ACR50, ACR70 response (RR and RD) • AE incidence	**ACR20 response rate, n (%)** • 24 weeks, 194 (74.6) *ACR20 response rate, RR (90% CI)* 1.039 (0.954, 1.133)	**Overall safety and AEs, n (%)** • Any TEAEs, 132 (50.0) • SAEs, 10 (3.8) • AEs leading to discontinuation of drug, 5 (1.9) • AEs leading to study discontinuation, 7 (2.7) • ***AEs of Interest***: • Infection, 61 (23.1) • Malignancies, 1 (0.4) • Hypersensitivity, 14 (5.3) • Hematological reactions, 5 (1.9) • Heart failure, 1 (0.4) • Liver enzyme rise, 13 (4.9) • ISRs, 6 (2.3)
	ADA[a] 40 mg SC Q2W + MTX N = 262		**ACR20 response rate, n (%)** • 24 weeks, 189 (72.4)	**Overall safety and AEs, n (%)** • Any TEAEs, 143 (54.6) • SAEs, 13 (5.0) • AEs leading to discontinuation of drug, 2 (0.8) • AEs leading to study discontinuation, 2 (0.8) • ***AEs of Interest***: • Infections, 68 (26.0) • Malignancies, 1 (0.4) • Hypersensitivity 10 (3.8) • Hematological reactions, 5 (1.9) • Heart failure, 2 (0.8) • Liver enzyme rise, 10 (3.8) • ISRs, 13 (5.0)
Psoriasis[22, 23]				
To compare the efficacy and safety of AMGEVITA with ADA for the treatment of moderate to severe psoriasis (in patients who were IR to ≥1 conventional systemic therapy) Double-blind RCT	AMGEVITA 40 mg SC Q2W N = 175	*Primary endpoint:* • % improvement in PASI score *Secondary endpoints:* • PASI 50, PASI 75, PASI 90, PASI 100 • Physician Global Assessment • Mean change in affected	**% PASI improvement, %** • 16 weeks, 80.9	**TEAEs 0-16 weeks, n (%):** • Any TEAEs, 117 (67.2) • Grade ≥3 AEs, 8 (4.6) • SAEs, 6 (3.4) • Discontinuation due to TEAEs, 7 (4.0) • TRAEs 43 (24.7) ***AEs occurring in ≥5% of patients*** *0-16 weeks* • Nasopharyngitis, 25 (14.4); headache, 13 (7.5); URTI, 9 (5.2)

	Interventions	Outcomes reported	Primary endpoint results	Safety results
(patients with PASI ≥50 at 16 weeks were eligible to continue study: patients in the ADA group were re-randomised to continue ADA or transition to AMGEVITA) *Follow up*: **16 weeks;** 20 weeks (post-transition); 32 weeks (post-transition); 52 weeks (post-transition)	ADA[a] 40 mg SC Q2W N = 175	body surface area • TEAE incidence (after transition) • Antidrug antibody rate	**% PASI improvement, %** • 16 weeks, 83.1	**TEAEs 0-16 weeks, n (%):** • Any TEAEs, 110 (63.6) • Grade ≥3 AEs, 5 (2.9) • SAEs, 5 (2.9) • TEAEs leading to discontinuation, 5 (2.9) • TRAEs, 43 (24.9) ***AEs occurring in ≥5% of patients*** • Nasopharyngitis, 27 (15.6); headache, 18 (10.4); URTI, 9 (5.2)

Footnotes: [a]The comparator adalimumab was a previous formulation of Humira®; the formulation of Humira® has since changed.
Abbreviations: ACR: American College of Rheumatology; ADA; adalimumab; AE: adverse event; CI: confidence interval; DAS28-CRP: Disease Activity Score-28 with CRP; MTX: methotrexate; IR: inadequate response; ISR: injection site reaction; PASI: Psoriasis Area and Severity Index; Q2W: once every 2 weeks; RCT: randomised controlled trial; RD: risk difference; RR: relative risk; SAE: serious AE; SC: subcutaneous; TEAE: treatment-emergent AE; TRAE: treatment-related AE; URTI: upper respiratory tract infection.

In adult subjects with RA, 74.6% of subjects in the Amgevita group and 72.4% in the adalimumab group met the primary endpoint of ACR20 response at week 24 (Relative risk 1.04 [95% CI: 0.95-1.13]). The incidence of binding antibodies was 38.3% in the ABP 501 group and 38.2% in the adalimumab group. Results from an open-label extension study, which included a combination of subjects who continued on Amgevita from the parent study and those who transitioned from adalimumab to Amgevita, found that safety was consistent with the known safety profile for adalimumab and that efficacy was maintained.[20, 21]

In adult subjects with psoriasis, the PASI percent improvement from baseline was 80.9% in the Amgevita group and 83.1% in the adalimumab group at week 16 (least-squares mean difference: -2.18 [95% CI -7.39, 3.02]), which fell within the predefined equivalence margin of ±15. Through week 16, the incidence of subjects with binding antibodies was 55.2% in the Amgevita group and 63.6% in adalimumab group. There was no negative impact on safety, efficacy, or immunogenicity in patients who transitioned from adalimumab to Amgevita compared with those who continued treatment with adalimumab.[22, 23]

Adverse events were comparable between the Amgevita and adalimumab arms in both comparative clinical studies in terms of frequency, type, and severity, and mean injection-site pain ratings were lower in patients treated with Amgevita compared with those who received subcutaneous injections of adalimumab at each study visit.[i, 20-23]

In summary, no clinically meaningful differences in analytical, functional, non-clinical, pharmacokinetic, immunogenicity, efficacy, and safety profiles were observed between Amgevita and adalimumab.[24]

3.2 Amgevita compared with other biosimilar versions of adalimumab

By definition, the clinical efficacy and safety of licensed biosimilar medicines and their originator products are considered sufficiently similar that there are no clinically meaningful differences. There may, however, be potential differences in presentations and formulations that make some products more suitable than others. For example, pain related to subcutaneous injection can be influenced by various factors, including the formulation (e.g. citrate buffer), injection volume and needle size and sharpness.[25] Humira® and Amgevita have a citrate-free formulation, in contrast to Imraldi® and Idacio® which contain citrate.[1, 26-28]

Continual use of biological agents that target specific components of the immune response is highly effective in reducing disease symptoms, slowing the rate of disease progression, and improving physical function and quality of life measures in patients with inflammatory diseases.[29] However, drug shortages that lead to nonadherence to prescribed therapy (i.e. patients miss scheduled doses) not only limit the effectiveness of the therapy but are also associated with poor clinical outcomes[30] and a substantial economic burden.[31] Amgen's end-to-end supply chain control has led to 99% on-time, in-full (OTIF) deliveries in Europe since 2012.[32] [redacted]

4 Budget impact analysis

The patient population included in the budget impact analysis is all adult patients with moderate RA. Among these patients, patients with an inadequate response to cDMARDs are assumed to be eligible for adalimumab treatment, in line with the marketing authorisations for adalimumab and Amgevita.[1] The patient population included in the analysis is wider than the population in the scope (adults with moderate RA, whose disease has responded inadequately to, or who are intolerant

[i]The comparator adalimumab was a previous formulation of Humira®; the formulation of Humira® has since changed.

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710] – Targeted Evidence Submission Form

of cDMARDs). This approach was taken to estimate the budget impact of introducing adalimumab across moderate RA as a whole. Full details of the budget impact analysis can be found in the Budget Impact Template.

Without the introduction of adalimumab into the moderate RA setting, the current annual budget impact of the treatment of moderate RA is estimated as £10,394,862 (i.e. cost in year 0).

Following the introduction of adalimumab treatment in moderate RA, the net budget impact compared to year 0 is estimated to be £[redacted] in year 1 rising to £[redacted] in year 3 (Table 3). The treatment pathway costs attributed to Amgevita specifically are estimated as £[redacted] in year 1 rising to £[redacted] in year 3 (Table 3). As such, in this conservative analysis the estimated net budget impact is not expected to exceed £20 million in any of the first three years of adalimumab use in moderate RA in the NHS in England.

Overall, using highly conservative assumptions, the budget impact of extending the use of adalimumab to patients with moderate RA is likely to be small, manageable and comfortably below the NHS England budget impact test limit of £20 million per year within any of the first three years.

Table 3: Expected budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5
Moderate RA patients	132,335	139,450	146,603	153,796	161,028
Patients eligible for adalimumab	10,587	11,156	11,728	12,304	12,882
Patients treated with adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of treatment pathway without adalimumab	£10,982,012	£11,572,396	£12,166,032	£12,762,937	£13,363,129
Cost of treatment pathway with adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact of adalimumab[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients able to receive Amgevita	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated with Amgevita	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment pathway costs attributed to Amgevita specifically[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a]Compared to cost of treatment pathway without adalimumab in year 0: £10,394,862. Values are rounded to the nearest integer.

5 Conclusion

The existing treatment pathway for RA in England, which limits treatment options for patients with moderate RA to cDMARDs and denies access to bDMARDs, leaves these patients exposed to the significant risks of disease progression, irreversible joint damage, and associated consequences.

Amgevita is a biosimilar version of the TNFα inhibitor adalimumab. Data from the BSRBR has shown that TNFα inhibitors have demonstrated consistent efficacy across both moderate and severe RA,[13] and US patient registry data indicate that greater proportions of moderate RA patients treated with bDMARDs achieve remission or low disease activity compared to severe RA patients.[16] The clinical case for the use of TNFα inhibitors such as Amgevita in patients with moderate RA is therefore highly compelling.

Due to the markedly reduced cost of Amgevita compared with the originator adalimumab, Amgevita is highly likely to be cost-effective early in the treatment pathway and provides an opportunity to optimise clinical management of moderate RA by increasing patient access to adalimumab. Indeed, clinical evidence[13, 16] suggests that the likelihood of achieving the NICE-recommended treatment goals, and realising the benefits associated with achieving these, is greater if TNFα inhibitors such as adalimumab are initiated before patients progress to severe activity disease. This change to the treatment pathway would be expected to reduce the morbidity and quality of life impairment associated with persistent moderate disease activity, and improve disease management across RA as a whole by reducing the number of patients progressing to severe RA. Furthermore, using highly conservative assumptions, the budget impact of extending the use of adalimumab to patients with moderate RA is likely to be small, manageable and comfortably below the NHS England budget impact test limit of £20 million per year within any of the first three years.

Amgevita should, therefore, be recommended for use in patients with moderate RA.

6 References

1. EMC. Amgevita 40 mg solution for injection in pre-filled pen. Available at [accessed 26 August 2020]: https://www.medicines.org.uk/emc/product/9546/smpc.
2. BNF 2020. Adalimumab medicinal forms. Available at [accessed 26 August 2020]: https://bnf.nice.org.uk/medicinal-forms/adalimumab.html.
3. NICE 2016. TA375: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. Available at [accessed 26 August 2020]: https://www.nice.org.uk/guidance/ta375.
4. NICE 2020. NICE Pathways: Drug treatment for rheumatoid arthritis. Available at [accessed 26 August 2020]: https://pathways.nice.org.uk/pathways/rheumatoid-arthritis.
5. Nikiphorou E, Norton SJ, Carpenter L, Walsh DA, Creamer P, Dixey J, et al. Remission vs low disease activity: function, quality of life and structural outcomes in the Early Rheumatoid Arthritis Study and Network. Rheumatology (Oxford, England). 2020;59(6):1272-80.
6. Kiely P, Walsh D, Williams R, Young A. Outcome in rheumatoid arthritis patients with continued conventional therapy for moderate disease activity--the early RA network (ERAN). Rheumatology (Oxford, England). 2011;50(5):926-31.
7. Nikiphorou E, Norton S, Young A, Carpenter L, Dixey J, Walsh DA, et al. Association between rheumatoid arthritis disease activity, progression of functional limitation and long-term risk of orthopaedic surgery: combined analysis of two prospective cohorts supports EULAR treat to target DAS thresholds. Annals of the rheumatic diseases. 2016;75(12):2080-6.
8. Combe B, Logeart I, Belkacemi MC, Dadoun S, Schaeverbeke T, Daurès JP, et al. Comparison of the long-term outcome for patients with rheumatoid arthritis with persistent moderate disease activity or disease remission during the first year after diagnosis: data from the ESPOIR cohort. Annals of the rheumatic diseases. 2015;74(4):724-9.
9. Conaghan PG, Hensor EMA, Keenan A-M, Morgan AW, Emery P, Consortium tY. Persistently moderate DAS-28 is not benign: loss of function occurs in early RA despite step-up DMARD therapy. Rheumatology. 2010;49(10):1894-9.
10. Deighton C, Hyrich K, Ding T, Ledingham J, Lunt M, Luqmani R, et al. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. Rheumatology. 2010;49(6):1197-9.
11. Bluett J, Sergeant JC, MacGregor AJ, Chipping JR, Marshall T, Symmons DPM, et al. Risk factors for oral methotrexate failure in patients with inflammatory polyarthritis: results from a UK prospective cohort study. Arthritis Research & Therapy. 2018;20(1):50.
12. Hope HF, Hyrich KL, Anderson J, Bluett J, Sergeant JC, Barton A, et al. The predictors of and reasons for non-adherence in an observational cohort of patients with rheumatoid arthritis commencing methotrexate. Rheumatology (Oxford, England). 2020;59(1):213-23.
13. Hyrich KL, Deighton C, Watson KD, Symmons DP, Lunt M. Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity. Rheumatology (Oxford, England). 2009;48(10):1323-7.

14. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Annals of the rheumatic diseases. 2020;79(6):685-99.
15. NICE 2018. NG100: Rheumatoid arthritis in adults: management. Available at [accessed 26 August 2020]: https://www.nice.org.uk/guidance/ng100.
16. Kavanaugh A, Keystone E, Greenberg JD, Reed GW, Griffith JM, Friedman AW, et al. Benefit of biologics initiation in moderate versus severe rheumatoid arthritis: evidence from a United States registry. Rheumatology (Oxford, England). 2017;56(7):1095-101.
17. NICE 2019. Review of TA375; Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. Available at [accessed 26 August 2020]: https://www.nice.org.uk/guidance/ta375/evidence/review-proposal-paper-pdf-6904907822.
18. Abhishek A, Doherty M, Kuo CF, Mallen CD, Zhang W, Grainge MJ. Rheumatoid arthritis is getting less frequent-results of a nationwide population-based cohort study. Rheumatology (Oxford, England). 2017;56(5):736-44.
19. Office for National Statistics 2020. Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2019. Available at [accessed 26 August 2020]: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2019estimates.
20. Cohen S, Genovese MC, Choy E, Perez-Ruiz F, Matsumoto A, Pavelka K, et al. Efficacy and safety of the biosimilar ABP 501 compared with adalimumab in patients with moderate to severe rheumatoid arthritis: a randomised, double-blind, phase III equivalence study. Annals of the rheumatic diseases. 2017;76(10):1679-87.
21. Cohen S, Pablos JL, Pavelka K, Müller GA, Matsumoto A, Kivitz A, et al. An open-label extension study to demonstrate long-term safety and efficacy of ABP 501 in patients with rheumatoid arthritis. Arthritis Res Ther. 2019;21(1):84.
22. Papp K, Bachelez H, Costanzo A, Foley P, Gooderham M, Kaur P, et al. Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: A randomized, double-blind, multicenter, phase III study. Journal of the American Academy of Dermatology. 2017;76(6):1093-102.
23. Papp K, Bachelez H, Costanzo A, Foley P, Gooderham M, Kaur P, et al. Clinical similarity of the biosimilar ABP 501 compared with adalimumab after single transition: long-term results from a randomized controlled, double-blind, 52-week, phase III trial in patients with moderate-to-severe plaque psoriasis. The British journal of dermatology. 2017;177(6):1562-74.
24. EMA. Amgevita: EPAR - Product Information. Available at [accessed 26 August 2020]: https://www.ema.europa.eu/en/medicines/human/EPAR/amgevita.
25. Nash P, Vanhoof J, Hall S, Arulmani U, Tarzynski-Potempa R, Unnebrink K, et al. Randomized Crossover Comparison of Injection Site Pain with 40 mg/0.4 or 0.8 mL Formulations of Adalimumab in Patients with Rheumatoid Arthritis. Rheumatology and therapy. 2016;3(2):257-70.

26. EMC. Humira 40 mg solution for injection in pre-filled pen. Available at [accessed 26 August 2020]: https://www.medicines.org.uk/emc/product/7986/smpc.
27. EMC. Idacio 40 mg solution for injection in pre-filled pen. Available at [accessed 26 August 2020]: https://www.medicines.org.uk/emc/product/11307/smpc.
28. EMC. Imraldi 40 mg solution for injection in pre-filled pen. Available at [accessed 26 August 2020]: https://www.medicines.org.uk/emc/product/9594/smpc.
29. Curtis JR, Singh JA. Use of biologics in rheumatoid arthritis: current and emerging paradigms of care. Clinical therapeutics. 2011;33(6):679-707.
30. Bluett J, Morgan C, Thurston L, Plant D, Hyrich KL, Morgan AW, et al. Impact of inadequate adherence on response to subcutaneously administered anti-tumour necrosis factor drugs: results from the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate cohort. Rheumatology (Oxford, England). 2015;54(3):494-9.
31. Hughes DA, Bagust A, Haycox A, Walley T. The impact of non-compliance on the cost-effectiveness of pharmaceuticals: a review of the literature. Health Economics. 2001;10(7):601-15.
32. Schipper R, Middelkoop K, Biniass B, Hippenmeyer J. Assessment of drug supply reliability in Europe by evaluating on time in full (OTIF) delivery. Poster presented at BOPA conference; Abstract 32. 2018.

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Targeted submission

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Your name	[redacted]
Organisation name	Biogen Idec Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links to disclose

1. It is proposed that this partial review is based on the original economic model developed by the Assessment Group in TA375. See here for the Assessment Group report. The assessment Group will update the model to address a limitation which means that currently, on progression from moderate to severe disease, patients are only modelled as having conventional DMARDs not biological DMARDs as in clinical practice.

Please comment on the proposal to use the Assessment Group model from TA375 amended as above.

The model structure based on EULAR states is appropriate

The original economic model developed by the Assessment Group in TA375 is appropriate.

Despite clinical trials defining clinical response according to the American College of Rheumatology (ACR) criteria, a European League Against Rheumatism (EULAR)-based approach should be adopted to align with its use in clinical practice.

EULAR thresholds on the disease activity (DAS28) score are used to determine severity of a patient's rheumatoid arthritis (RA). According to the EULAR thresholds, a DAS28 score of <2.6 indicates disease remission, patients with a DAS28 score of ≤3.2 are classified as having low disease activity, those with a DAS28 score >3.2 and ≤5.1 are classified as having moderate disease activity and those with a DAS28 score of >5.1 are assessed as high disease activity or severe disease.[1] For the purpose of decision making, recommendations for patients classified as having moderate disease should be made based on a DAS28 score >3.2 and ≤5.1.

The cost of treating RA with anti-TNFs in moderate disease will be partially offset by an anticipated reduction in anti-TNF treatment in severe disease when compared to current usage. Additionally, based on clinical opinion, the gap between treatments when used in moderate disease is longer than when in severe disease, therefore the burden of treatment can be reduced by introducing anti-TNF treatment earlier in the disease. This should be considered within the construct of the economic model.

The original economic model did not consider a wider societal perspective. However, the focus of the review on moderate disease will consider earlier initiation of treatment with anti-TNFs in the disease pathway. By initiating treatment earlier, patients are able to maximise the benefit of treatment before their disease worsens; once RA has become severe, it is very difficult for patients to reverse progression.[2] A significant proportion of patients affected by RA are of working age and there is a need to ensure patients are supported to continue participating in the workforce by offering clinically effective treatments early on in their disease. For this reason, a wider societal perspective considering productivity losses, including caregiver burden should be included in the economic model.

The analysis should consider comparisons between molecules, with recommendations made for each brand that are deemed cost-effective in this review.

Prior to the current availability of biosimilar anti-TNFs indicated for RA, the original economic model assessed and made recommendations according to molecule (i.e. adalimumab, etanercept and infliximab); there were fewer brands associated with each molecule and, as such, recommendations were not made by brand. For example, in contrast to the market then, there are now multiple licenced brands available on the BNF for the adalimumab molecule (e.g. Imraldi and Humira). The Company asks that following this review, products that are considered cost-effective are recommended by brand name and not by molecule name. Recommendations by brand would ensure that there remains a diverse anti-TNF treatment market in England and Wales without the market becoming saturated. This diversity helps to

maintain a sustainable and competitive industry, which will ultimately offer improved value for money to the NHS.

Should recommendations be made only according to molecule rather than brand, there is the potential for new brands to be developed, potentially rendering recommendations from this review void. Recommendations should be durable and those with potential to undermine sustainability, such as those which potentially shrink the market leading to monopoly, should be avoided.[3] Therefore, only brands considered in this partial review of TA375 and deemed cost-effective should be recommended.

There is robust evidence to support clinical equivalence of originator products and biosimilars for the treatment of RA, therefore it would not be possible to demonstrate differential efficacy within the same molecule.[4–6] As such, there is a preference to have a number of cost effective brands recommended for each molecule. This will then allow physicians to choose from a range of brands that are deemed cost effective within this review.

Recommendations for a specified range of anti-TNF treatments would provide patients and healthcare professionals (HCP) with choice, enabling patients to find the treatment that is most suited to their needs and lifestyle based on clinical evidence, HCP experience, and patient preferences. In turn, this availability of choice is expected to improve patient adherence to treatment which is correlated with better clinical outcomes.[7,8]

A recommendation should be made to endorse cycling of anti-TNFs

With more biosimilar products available, and at lower prices than when compared in the original review, there is the opportunity to cycle through (sequentially use) alternative anti-TNF treatments before switching to a treatment with a new mechanism of action (MoA) such as janus kinase (JAK) inhibitors, which are less cost-effective than anti-TNFs. As such, the possibility of cycling through at least two anti-TNF biologics should be reflected within the economic model.

It is noted that the framework of evaluating the treatment pathway in the original assessment group model does not consider cycling of all anti-TNF agents before progressing to treatments with an alternative MoA such as JAK inhibitors and interleukin (IL)-6 inhibitors.

The guidelines from EULAR and recommendations from other specialist bodies, such as the Regional Medicines Optimisation Committee (RMOC), recognise cycling anti-TNF agents as an appropriate treatment option after the first anti-TNF fails in suitable patients, i.e. secondary non-responders.[9,10] The British Society for Rheumatology Biologics Registry (BSRBR) has shown that, as with any biologic, a proportion of patients will not respond to first-choice anti-TNFs, meaning treatment choices are important from a clinical and economic perspective in the second line.[11]

Data from clinical trials and registries, supported by the notion recognised in the EULAR guidelines and the RMOC statement, show a significant proportion of patients regain clinical remission or good disease control with the sequential use of anti-TNFs following secondary failure of the first.[12–16] This extension of the RA treatment pathway can help limit the risk of patients developing refractory disease.[17] By cycling through two or three treatments with the same MoA, HCPs can extend the treatment window for anti-TNFs and delay moving onto products with a different MoA such as JAK inhibitors and interleukin (IL)-6 inhibitors.

Finally, it is noted that treatments should be assessed independently of their citrate content status, in line with the current NHS England adalimumab tender.[18]

2. In order to amend the model to address the above issue the Assessment Group will need to source information on the relationship between the change in Health Assessment Questionnaire (HAQ) score and the change in disease activity (DAS28) score.

Are you aware of any data on this relationship?

No comment.

3. In TA375 the committee identified uncertainties relating to long-term disease progression for people having conventional DMARDs and the mapping from HAQ scores to EQ-5D (health-related quality of life) utility values. It based decisions on:

- Early Rheumatoid Arthritis Study data to model disease progression with conventional DMARDs rather than assume a linear progression
- Hernandez et al (2013) to calculate EQ-5D utility values

The review paper did not find any new evidence to address these uncertainties, so it is proposed that the Assessment Group analyses also use these assumptions.

Are you aware of any new evidence in these areas?

No comment.

4. If you are the manufacturer of one of the interventions, please provide details of your product(s) including price and any confidential discounts.

Pricing information

Product information for Benepali, Flixabi, and Imraldi can be found in Table 1, Table 2 and Table 3, respectively. For further prescribing information, please refer to the Summary of Product Characteristics (SmPC) for each product.

Table 1: Benepali (etanercept) product information

Product Information	Details
Pharmaceutical Formulation:	Benepali 50mg solution for injection pre-filled pen[19] Benepali 50mg solution for injection pre-filled syringe[20] Benepali 25mg solution for injection in pre-filled syringe[21]
Indication in rheumatoid arthritis (SmPC)[19,21]	Benepali (etanercept) in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate. Benepali can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Benepali is also indicated in the treatment of severe, active and progressive RA in adults not previously treated with methotrexate.

	Benepali, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.
Method of administration and dosage (SmPC):	The recommended dose is 50mg administered subcutaneously once weekly.[19,20] Alternatively, 25mg may be administered subcutaneously twice weekly.[21]
Dosage adjustments (SmPC):	No dose adjustments are required.[19–21]
List Price (£)[22]:	Benepali 50mg/1ml solution for injection pre-filled pen (x4): £656.00 Benepali 50mg/1ml solution for injection pre-filled syringes (x4): £656.00 Benepali 25mg/0.5ml solution for injection pre-filled syringes (x4): £328.00
Commercial Price (with Biogen's homecare support service):	Benepali 50mg/1ml solution for injection pre-filled pen (x4): £[redacted] Benepali 50mg/1ml solution for injection pre-filled syringes (x4)[redacted] Benepali 25mg/0.5ml solution for injection pre-filled syringes (x4): £[redacted]
Commercial Price (without Biogen's homecare support service):	Benepali 50mg/1ml solution for injection pre-filled pen (x4): £[redacted] Benepali 50mg/1ml solution for injection pre-filled syringes (x4): £[redacted] Benepali 25mg/0.5ml solution for injection pre-filled syringes (x4): £[redacted]

Table 2: Flixabi (infliximab) product information

Product Information	Details
Pharmaceutical Formulation:[23]	Flixabi 100 mg powder for concentrate for solution for infusion.
Indication in rheumatoid arthritis (SmPC) [23]	Flixabi (infliximab), in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in: • Adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate. • Adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs. In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated.

Method of administration and dosage (SmPC):[23]	Flixabi should be administered intravenously over a 2-hour period. Flixabi infusions should be administered by qualified healthcare professionals trained to detect any infusion-related issue. 3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Flixabi must be given concomitantly with methotrexate.
Dosage adjustments (SmPC):[23]	If a patient has an inadequate response or loses response, consideration may be given to increase the dose step-wise by approximately 1.5 mg/kg, up to a maximum of 7.5 mg/kg every 8 weeks. Alternatively, administration of 3 mg/kg as often as every 4 weeks may be considered. If adequate response is achieved, patients should be continued on the selected dose or dose frequency.
List Price (£):	£377.00 per 100mg vial[24]
Commercial Price	[redacted] per 100mg vial

Table 3: Imraldi (adalimumab) product information

Product Information	Details
Pharmaceutical formulation:[25]	Imraldi 40 mg solution for injection in pre-filled pen. Imraldi 40 mg solution for injection in pre-filled syringe.
Indication in rheumatoid arthritis (SmPC):[25]	Imraldi (adalimumab) in combination with methotrexate, is indicated for: • The treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate has been inadequate. • The treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. Imraldi can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.
Method of administration and dosage (SmPC):[25]	The recommended dose of Imraldi for adult patients with rheumatoid arthritis is 40 mg/0.8ml solution for injection pre-filled pens/syringes administered subcutaneously every other week as a single dose. Methotrexate should be continued during treatment with Imraldi.
Dosage adjustments (SmPC):[25]	In monotherapy, some patients who experience a decrease in their response to Imraldi 40 mg every other week dosing may benefit from an increase in dosage to 40 mg adalimumab every week or 80 mg every other week.
List Price (£):[26]	Imraldi 40mg/0.8ml solution for injection pre-filled pens (x2): £633.85 Imraldi 40mg/0.8ml solution for injection pre-filled syringes (x2): £633.85
Commercial Price (with Biogen's	Imraldi 40mg/0.8ml solution for injection pre-filled pens (x2): [redacted] Imraldi 40mg/0.8ml solution for injection pre-filled syringes (x2): [redacted]

homecare support service):	
Commercial Price (without Biogen's homecare support service):	Imraldi 40mg/0.8ml solution for injection pre-filled pens (x2): [redacted] Imraldi 40mg/0.8ml solution for injection pre-filled syringes (x2): [redacted]

Biogen homecare support service

As part of Biogen's commitment to delivering value beyond price, a range of tailored services are available to patients who use the homecare support service. [redacted]

[redacted]

Evidence suggests that increasing a patient's ability to manage their own long-term health condition may have a positive impact on reducing hospitalisation, increasing medication adherence, and improving health outcomes.[7,8,27] [redacted]

5. Please provide any other comments on the potential for a change in the recommendations for moderate active disease.

Biogen supports the partial review of TA375 for patients with moderate, active RA. RA is a chronic progressive autoimmune disease which has substantial impacts on patients, family, and the wider society. Ensuring patients with moderate disease have earlier access to anti-TNFs will help minimise the societal, clinical, and humanistic impact already associated with RA.

Economic burden

Diseases of the musculoskeletal system are the fourth largest expenditure on the NHS, with rheumatoid arthritis costing above an estimated £700 million in 2012.[29] Due to the chronic nature of RA, care is

ongoing and the costs of care increase with progression of disease. In addition to direct health care costs, RA poses a wider economic burden beyond the healthcare sector; a report conducted by the National Rheumatoid Arthritis Society (2010) calculated that productivity losses due to RA cost the UK economy £8 billion a year. [30]

A study in the EU estimated that the total average cost per patient was €4,737 per patient. As functional status decline, it was shown that the average expenditure across all direct cost categories increased. In less severe patients, the total amount spent per patient was €3,225 compared to €8,403 per patient in severe patients. Of the €8,403 spent per patient per year with more severe RA, nearly a third of spending was drugs.[31]

Clinical burden of disease

It is estimated that up to 60% of patients with RA have moderate disease, though this proportion varies across literature, and are therefore unable to access clinically effective anti-TNF treatments based on current recommendations in the UK.[32] The UK remains a region with low access to biologic DMARDs compared to several countries across Europe and there remains a significant unmet need for patients with moderate RA.[32]

Data from registries such as the British Society for Rheumatology Biologics Register for RA (BSRBR-RA) support the evidence base of favourable clinical outcomes in patients with moderate disease activity and illustrate how early treatment responses within the first six months can be predictive of long-term outcomes.[33,34]

As highlighted within the EULAR guidelines, treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.[9] Initiating more effective treatments, including the anti-TNF treatments currently under review, in patients with moderate RA will mean that patients have a better chance of successfully sustaining remission or low disease activity.[35]

Humanistic burden of disease

Patients with moderate disease activity exhibit progression of joint damage and have impaired quality of life, physical function, work and daily activities.[36] As patients remain within moderate RA, damage to joints progresses; currently, it is only once patients meet a threshold defining severe RA (DAS28 score >5.1) that they can access more effective options such as anti-TNFs.[37]

Making effective treatments available earlier could sustain quality of life in patients with moderate RA since progression of joint damage is likely to be slowed or inhibited by efficacious therapies.[35,38] Moreover, if patients enter remission, progression can be halted.[38] Halting the development of joint damage, which leads to pain and inflammation,[39] will prolong the ability of patients to perform their usual daily activities, maximising their quality of life.

Patients with moderate disease activity can also have high levels of disability despite being in moderate disease and these patients are likely to continue to have high levels of disability over subsequent years.[40] Therefore, making available anti-TNF treatments to patients with moderate disease is likely to reduce the progression of disability.

Social burden of disease

Moreover, reducing the impact of disability amongst patients with moderate RA will ensure that patients are able to stay in gainful employment for longer.

As highlighted in the 'Work Matters' report by the National Rheumatoid Arthritis Society (NRAS), the unemployment figures for those with RA, including those that stopped working or retired early due to RA, is more than four times greater than the general population (17.3% vs 4.3%, respectively).[30]

The authors note that this figure has decreased since the previous survey in 2007 and propose that this is due to earlier access to effective treatments. With treatments made available earlier still in the disease pathway, it is hoped that the proportion of patients unable to work due to their disease will reduce further still and offer benefits to both patients and the broader economy.

Approximately one–third of people stop work because of RA within two years of its onset and this increases thereafter, highlighting the need to support this group of patients to delay disease progression with early intervention and remain active in the workforce.[41]

6. Are there any potential equality issues that should be taken into account when considering these treatments?

RA disproportionately affects women; RA is between two to four times more common in women than in men.[42] Subsequently, a recommendation to withhold anti-TNF treatment in moderate RA will have a greater negative impact on women than men.

References

1. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]- Final Scope. at <https://www.nice.org.uk/guidance/gid-ta10586/documents/final-scope>
2. Evidence supporting the benefit of early intervention in rheumatoid arthritis. at <https://www.jrheum.org/content/jrheumsupp/66/3.full.pdf>
3. Schneider PJ & Reilly MS. Policy recommendations for a sustainable biosimilars market: lessons from Europe - GaBI Journal. 2020. at <http://gabi-journal.net/policy-recommendations-for-a-sustainable-biosimilars-market-lessons-from-europe.html>
4. Weinblatt ME, Baranauskaite A, Niebrzydowski J, *et al.* Phase III Randomized Study of SB5, an Adalimumab Biosimilar, Versus Reference Adalimumab in Patients With Moderate-to-Severe Rheumatoid Arthritis. *Arthritis & Rheumatology (Hoboken, NJ)* 2018. 70: 40–48.
5. European Medicines Agency. Imraldi Committee for Medicinal Products for Human Use (CHMP) Assessment Report. 2017. at <https://www.ema.europa.eu/en/medicines/human/EPAR/imraldi>
6. Emery P, Vencovský J, Sylwestrzak A, *et al.* Long-term efficacy and safety in patients with rheumatoid arthritis continuing on SB4 or switching from reference etanercept to SB4. *Ann Rheum Dis* 2017. doi:10.1136/annrheumdis-2017-211591

7. NHS England. NHS England » Patient activation and PAM FAQs. at <https://www.england.nhs.uk/personalisedcare/supported-self-management/patient-activation/pa-faqs/#Q15>
8. Hibbard J & Gilburt H. Supporting people to manage their health. 2014. at <https://www.kingsfund.org.uk/publications/supporting-people-manage-their-health>
9. Smolen JS, Landewé RBM, Bijlsma JWJ, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Annals of the Rheumatic Diseases* 2020. 79: 685–699.
10. Updated RMOC Advisory statement: Sequential Use of Biologic Medicines. *SPS - Specialist Pharmacy Service* at <https://www.sps.nhs.uk/articles/rmoc-advisory-statement-sequential-use-of-biologic-medicines/>
11. Soliman MM, Ashcroft DM, Watson KD, *et al.* Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2011. 70: 583–589.
12. Soliman MM, et al. in (Ann Rheum Dis., 2011). 70:583–9:
13. Bombardieri S et al. in (Rheumatology, 2007). 46:1991–9:
14. Bessette et al. in (Rheumatology Ther, 2017). 4;391-404:
15. Hyrich KL, et al. in (Rheumatology, 2008). 47:100–5:
16. 7. CK *et al.* in (Ann Rheum Dis, 2015). 74:890–6:
17. Kearsley-Fleet L, Davies R, Cock DD, *et al.* Biologic refractory disease in rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Annals of the Rheumatic Diseases* 2018. 77: 1405–1412.
18. NHS England. Data on file. Confidential NHS England tender document for adalimumab. 2020.
19. EMC. Benepali 50 mg solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC). at <https://www.medicines.org.uk/emc/product/1987/smpc>
20. EMC. Benepali 50 mg solution for injection in pre-filled syringe - Summary of Product Characteristics (SmPC). at <https://www.medicines.org.uk/emc/product/8032/smpc#gref>
21. EMC. Benepali 25 mg solution for injection in pre-filled syringe - Summary of Product Characteristics (SmPC). at <https://www.medicines.org.uk/emc/product/2708/smpc>

22. Anonymous. Benepali. *European Medicines Agency* 2018. at <https://www.ema.europa.eu/en/medicines/human/EPAR/benepali>

23. EMC. Flixabi 100 mg powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC). at <https://www.medicines.org.uk/emc/medicine/32130#gref>

24. NICE. BNF: British National Formulary - infliximab, NICE. at <https://bnf.nice.org.uk/drug/infliximab.html>

25. EMC. Imraldi 40 mg solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC). at <https://www.medicines.org.uk/emc/product/9594/smpc#gref>

26. NICE. BNF: British National Formulary - adalimumab, NICE. at <https://bnf.nice.org.uk/medicinal-forms/adalimumab.html>

27. Deeny S, Thorlby R & Steventon A. Reducing emergency admissions: Unlocking the potential of people to better manage their long-term conditions. *The Health Foundation* 2018. at <https://www.health.org.uk/publications/reducing-emergency-admissions-unlocking-the-potential-of-people-to-better-manage-their-long-term-conditions>

28. Hibbard JH, Stockard J, Mahoney ER, *et al.* Development of the Patient Activation Measure (PAM): Conceptualizing and Measuring Activation in Patients and Consumers. *Health Serv Res* 2004. 39: 1005–1026.

29. Bowman SJ & Guest L. The national clinical audit for rheumatoid and early inflammatory arthritis. *Clin Med (Lond)* 2016. 16: 500–501.

30. NRAS - National Rheumatoid Arthritis Society. Work Matters - A UK wide survey of adults with Rheumatoid Arthritis and Juvenile Idiopathic Arthritis on the impact of their disease on work. 2017. at <https://www.nras.org.uk/publications/work-matters>

31. Huscher D, Merkesdal S, Thiele K, *et al.* Cost of illness in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and systemic lupus erythematosus in Germany. *Ann Rheum Dis* 2006. 65: 1175–1183.

32. Kaló Z, Vokó Z, Östör A, *et al.* Patient access to reimbursed biological disease-modifying antirheumatic drugs in the European region. *Journal of Market Access & Health Policy* 2017. 5: 1345580.

33. Hyrich KL, Deighton C, Watson KD, *et al.* Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity. *Rheumatology (Oxford)* 2009. 48: 1323–1327.

34. Hamann PDH, Pauling JD, McHugh N, *et al.* Early response to anti-TNF predicts long-term outcomes including sustained remission: an analysis of the BSRBR-RA. *Rheumatology (Oxford)* 2020. 59: 1709–1714.

35. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, *et al.* Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2005. 52: 3381–3390.

36. Ceccarelli F, Massafra U, Perricone C, *et al.* Anti-TNF treatment response in rheumatoid arthritis patients with moderate disease activity: a prospective observational multicentre study (MODERATE). *Clin Exp Rheumatol* 2017. 35: 24–32.

37. NICE. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor | TA195. 2010. at <https://www.nice.org.uk/guidance/TA195>

38. van der Heijde D, Klareskog L, Landewé R, *et al.* Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2007. 56: 3928–3939.

39. Suresh E. Diagnosis of early rheumatoid arthritis: what the non-specialist needs to know. *J R Soc Med* 2004. 97: 421–424.

40. Pan Y, Norton S, Gwinnutt JM, *et al.* Not all moderate disease is the same – Identification of disability trajectories among patients with rheumatoid arthritis and moderate disease activity. *PLoS One* 2019. 14:

41. Conditions (UK) NCC for C. *Rheumatoid Arthritis*. (Royal College of Physicians (UK), 2009). at <https://www.ncbi.nlm.nih.gov/books/NBK51812/>

42. Prevalence and incidence | Background information | Rheumatoid arthritis | CKS | NICE. at <https://cks.nice.org.uk/topics/rheumatoid-arthritis/background-information/prevalence-incidence/>

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Targeted submission

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Your name	[redacted]
Organisation name	Celltrion
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

1. It is proposed that this partial review is based on the original economic model developed by the Assessment Group in TA375. See here for the Assessment Group report. The assessment Group will update the model to address a limitation which means that currently, on progression from moderate to severe disease, patients are only modelled as having conventional DMARDs not biological DMARDs as in clinical practice.

Please comment on the proposal to use the Assessment Group model from TA375 amended as above.

- **If it is assumed that the highest tender price for infliximab submitted previously in TA375 represented less than a 40% discount to the Remicade list price, then it should be possible to achieve an ICER in the £20k to £30k range for all mDAS patients without restricting to the fast-progressing subgroup.**

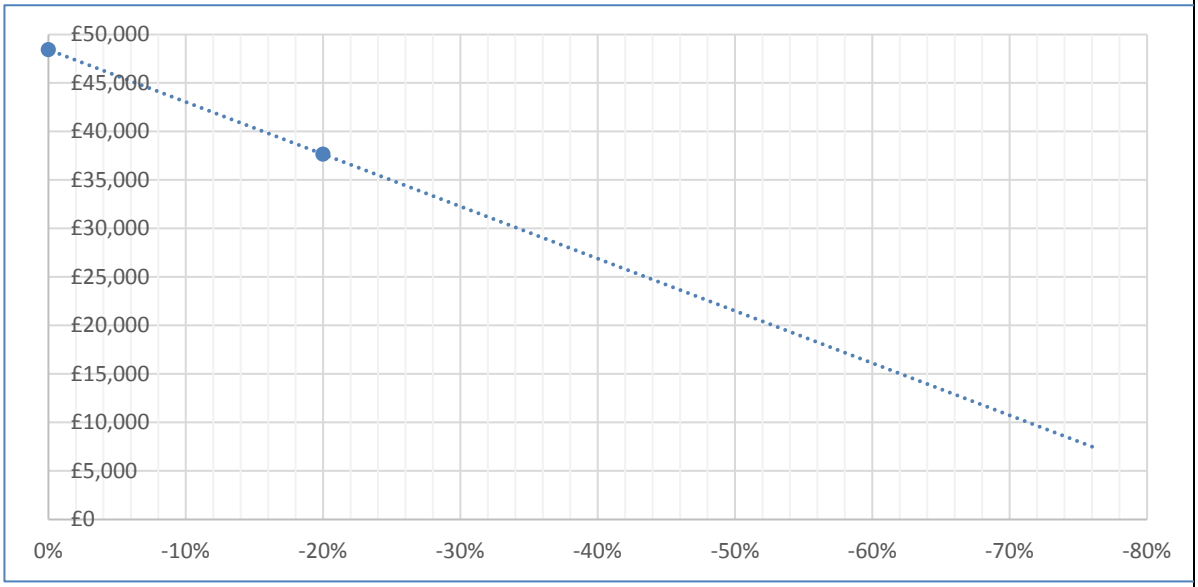
NICE considers a range of likely ICERs when deciding on whether a treatment can be recommended for use by the NHS or not. In TA375, NICE considered the ICER for biosimilar infliximab to be £48,424 based on the NHS list price of £419.62 per 100 mg vial for Remicade. Based on the revised AG model, below shows the ICERs for the mDAS population, using different prices for infliximab.

Drug name (brand name)	Average cost pp at list price	Patient population	ICER (£ per QALY gained)
Not applicable (median)	Not applicable (median)	Overall mDAS	51,100
		Fast progressors	28,500
Originator infliximab (Remicade)	£10,070 in first year, then £8,812 in subsequent years[a]	Overall mDAS	48,424
		Fast progressors	26,641
Biosimilar infliximab (Remsima, Inflectra)	£9,063 in first year, then £7,930 in subsequent years[a]	Overall mDAS	37,658 (highest NHS tender price)
		Fast progressors	20,462 (highest NHS tender price)

In the absence of access to the model, a linear extrapolation has been assumed based on the available ICER information reported by the AG. For this extrapolation it is necessary to assume what percentage discount to Remicade is represented by the highest tender price ICER (£37,658). The highest tender price is unknown because it could have been offered by either Napp or Hospira and has been redacted. However, it is known that the highest tender price must be lower than the Remsima list price (£377: 10% discount to Remicade) and higher than the lowest tender price offered by Napp (£215: 49% discount to Remicade). We have therefore run scenarios assuming that the ICER for the highest tender price for mDAS patients is based on a 20%, 30% or 40% discount to the Remicade list price.

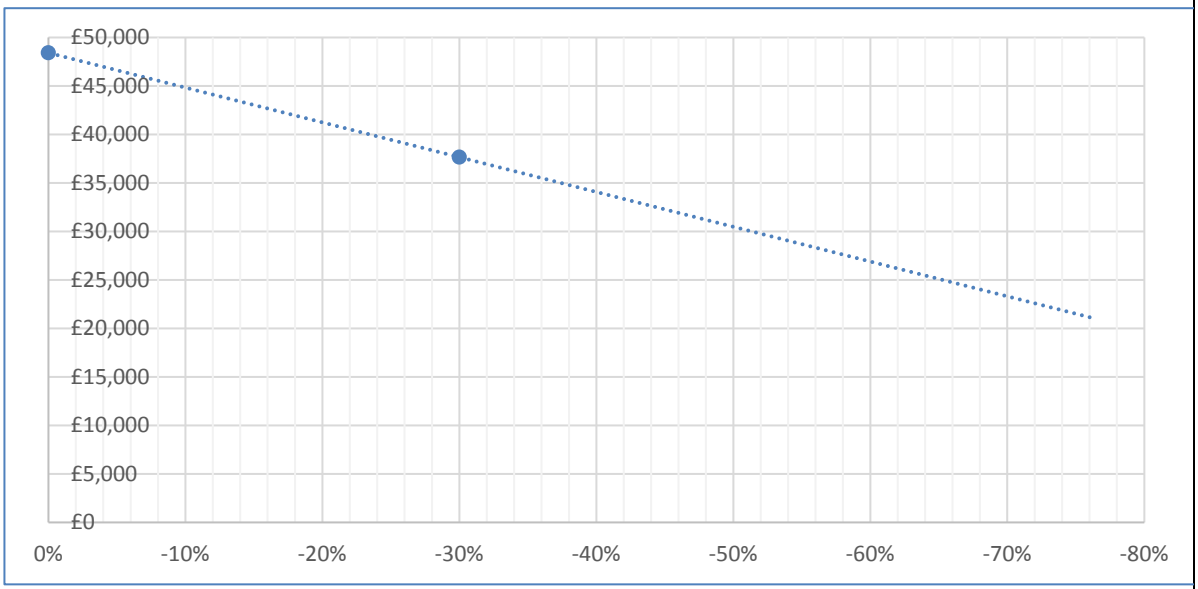
Please note that the in-market discount currently applicable is in the region of 85% from list price. At this price level the ICER is within the range to allow usage in patients with moderate disease.

Figure 1: ICER for infliximab by percentage reduction in price vs Remicade list price for mDAS population (assuming highest tender price represents 20% reduction: £335.70)



Based on a linear extrapolation from the reported ICERs and an assumed 20% discount highest tender price vs Remicade list price, it is estimated that an approximate 34% price reduction for Remsima vs the Remicade list price would give an ICER of less than £30,000 for the mDAS patient population. A price reduction of around 53% vs the Remicade list price would give an ICER of less than £20,000. Therefore, a price of around £197 to £277 per vial would be needed to support a positive NICE recommendation of Remsima for the total mDAS population. At a price of £100 per vial (76% discount vs Remicade list price) the ICER is estimated to be £7,513.

Figure 2: ICER for infliximab by percentage reduction in price vs Remicade list price for mDAS population (assuming highest tender price represents 30% reduction: £293.73)

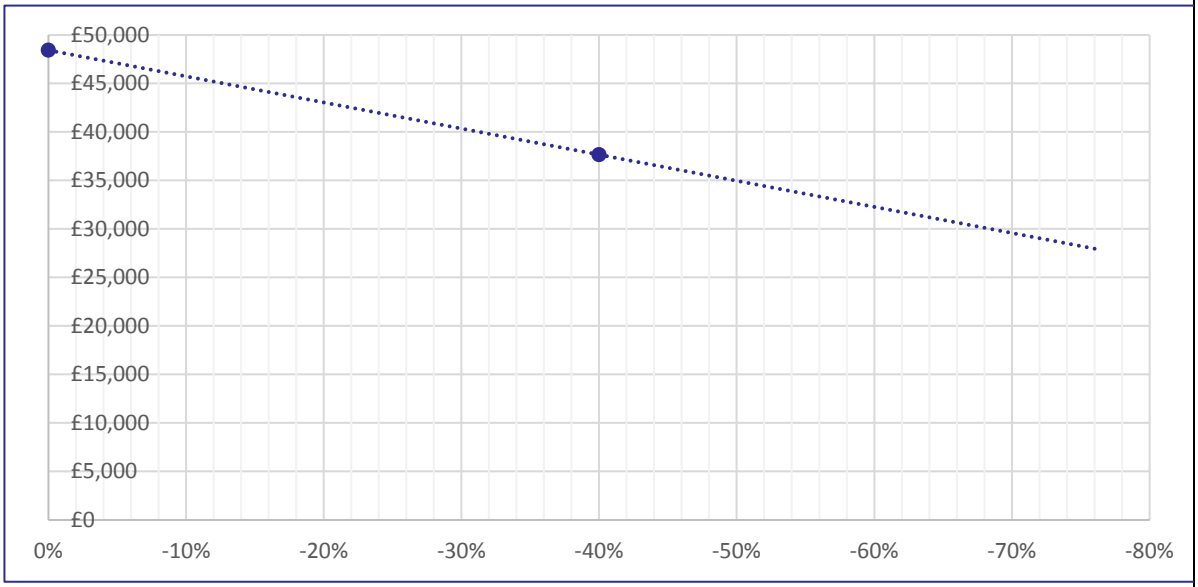


Based on a linear extrapolation from the reported ICERs and an assumed 30% discount highest tender price vs Remicade list price, it is estimated that an approximate 52% price reduction for

Remsima vs the Remicade list price would give an ICER of less than £30,000 for the mDAS patient population. A price reduction of around 80% vs the Remicade list price would give an ICER of less than £20,000. Therefore, a price of around £84 to £201 per vial would be needed to support a positive NICE recommendation of Remsima for the total mDAS population. At a price of £100 per vial (76% discount vs Remicade list price) the ICER is estimated to be £21,150.

Please note that current in-market price of Remsima 100mg vials is available on request - £[redacted] per vial.

Figure 3: ICER for infliximab by percentage reduction in price vs Remicade list price for mDAS population (assuming highest tender price represents 40% reduction: £251.77)



Based on a linear extrapolation from the reported ICERs and an assumed 40% discount highest tender price vs Remicade list price, it is estimated that an approximate 69% price reduction for Remsima vs the Remicade list price would give an ICER of less than £30,000 for the mDAS patient population. A price of below £130 per vial would be needed to support a positive NICE recommendation of Remsima for the total mDAS population. At a price of £100 per vial (76% discount vs Remicade list price), the ICER is estimated to be £27,969.

These ICERs are mean estimates for all mDAS patients. If a subgroup strategy is pursued where eligibility requirements for access to biologic therapy beyond the DAS28 exist (i.e. to identify fast progressors), price reductions of this magnitude will not be necessary. For fast progressors in the mDAS group receiving biosimilar infliximab, the ICER estimate was £20,462 at the highest tender price. This issue will be discussed further; however, it should be noted that these criteria will need to be pre-specified and supported by a robust evidence base and stakeholder agreement.

If the above extrapolations are accurate and it is assumed that the highest tender price for infliximab submitted previously in TA375 represented less than a 40% discount to the Remicade list price, then it should be possible to achieve an ICER in the £20k to £30k range for all patients without restricting to the fast-progressing subgroup.

2. In order to amend the model to address the above issue the Assessment Group will need to source information on the relationship between the change in Health Assessment Questionnaire (HAQ) score and the change in disease activity (DAS28) score. **Are you aware of any data on this relationship?**
No, we are not aware of any such data.
3. In TA375 the committee identified uncertainties relating to long-term disease progression for people having conventional DMARDs and the mapping from HAQ scores to EQ-5D (health-related quality of life) utility values. It based decisions on: • Early Rheumatoid Arthritis Study data to model disease progression with conventional DMARDs rather than assume a linear progression • Hernandez et al (2013) to calculate EQ-5D utility values The review paper did not find any new evidence to address these uncertainties, so it is proposed that the Assessment Group analyses also use these assumptions. **Are you aware of any new evidence in these areas?**
No, we are not aware of any new evidence in these areas.
4. If you are the manufacturer of one of the interventions, please provide details of your product(s) including price and any confidential discounts.

Product: Remsima.
This product is available in 100mg vials for reconstitution and subsequent intravenous injection.

Pricing:
List price is £377.66 per vial.
This product is subject to NHSE CMU Regional and Devolved Nation framework commissioning and hence in-market pricing is significantly lower than list price.
In-market pricing is subject to change with revised frameworks.
The below in-market pricing is confidential and agreed with NHS CMU (North of England Region, Midlands and East of England Region, South of England Region, London Region), NHS Scotland and NHS HSC Northern Ireland and NHS Wales.
Current in-market pricing for this product, across the whole of the UK is available on request - £[redacted].
There is no Patient Access Scheme.
There is no change in pricing based on any factor, such as indication or disease state or volume of stock ordered.

Please note that on 1st March 2020, Celltrion Healthcare UK Limited launched the first and only subcutaneous version of infliximab – Remsima SC®.

5. Please provide any other comments on the potential for a change in the recommendations for moderate active disease.

Fast-progressing subgroup

Future health economic research should focus on whether there are subgroups within the mDAS population that can be prospectively identified as at risk of faster HAQ progression. For patients who have failed combination therapy and have a DAS28 > 3.2, certain criteria were suggested by the clinical experts in TA375:

- Persistent elevation of inflammatory markers.
- Presence of erosions on x-ray.
- Positive for ACPAs.

However, the NICE Committee and Appeal Panel considered that these factors had not been prospectively modelled for use as prognostic factors for fast HAQ progression. It will be challenging to find evidence supporting the rates of HAQ progression for this subgroup, as ACPA testing was not conducted in the ERAS study used to inform the AG model estimates of HAQ progression. A systematic literature search for data assessing the evidence linking prognostic factors to disease progression in mDAS patients could be conducted in advance of any future submission to NICE. This review should also assess the evidence to support the hypothesis that the treatment effect of bDMARDs is not reduced when treating patients with these prognostic factors.

A systematic review was performed in the year of 2019 January with the aim of identifying prognostic factors in patients with moderately active rheumatoid arthritis (RA), at greater risk of progression

Few remarks on the fast progressors are:

- Within patients with moderate RA, both high C reactive protein levels and rheumatoid factor (RF) positivity at baseline, joint damage and GSUS score were factors contributing to the risk of significant radiographic progression (SRP), despite methotrexate (MTX) treatment.[1]
- MBDA (multi-biomarker disease activity) score enhanced the ability of conventional risk factors (i.e. serological status, SJC [0–28], CRP and DAS28-CRP) to predict radiographic progression in patients with established RA receiving non-biologic DMARDs.[2]
- Patients who remain in low- or high-moderate DAS in the first 5 years of disease, despite conventional DMARD therapy, have similar risks for joint failure and surgery as those with persistently high DAS. This is highly relevant in health systems where the use of biologic DMARDs is restricted based on DAS thresholds and moderate RA is excluded.[3]
- Patients with early RA with persistent moderate disease activity during the first year had a worse outcome than patients who achieved sustained clinical remission. Persistent moderate disease activity affects long-term structure, remission rate and functional and work disability. Such patients may benefit from intensive treatment.[4]
- Patients on a worse trajectory who may benefit from more intensive treatment could potentially be identified earlier in the disease the group of patients with moderate disease activity.[5]

Celltrion also conducted Advisory Board Meeting with KOLs and below is a brief summary on the fast progressors:

- It is apparent in clinical practice that there is a subpopulation within moderately active RA who are under-treated and who will benefit the most if the current thresholds for the use of biologics are lowered.
- Identifying succinctly worse progressors is still problematic, although there are many factors to suggest a poor prognosis. Yet, there is a lack of data on moderately active patients at the risk of greater progression likely to benefit from bDMARDs.
- There are risk factors, associations, but no definitive algorithm or definitive disease activity measures to identify subgroups who will have worst prognosis.
- In the short term (prior to a review) that prospectively identifying these sub groups for the purposes of guidance is not possible. However, in the long term it is important to identify possible sub-groups which could inform future guidelines.
- It would be beneficial for a consortium to analyse the clinical trial databases to explore the efficacy of bDMARDs in moderate patients, and to support definitions of which groups benefit most from treatment.

Potential mDAS subgroups are:

- The patients with DAS ≥ 4.2 who have failed at least 2 conventional DMARDs should be tried on bDMARD.
- Upcoming systematic review identified three prognostic factors in moderately-active RA patients at greater risk of disease progression
    a. positive Power Doppler: PDUS ≥ 1

b. DAS28 ≥ 4.2

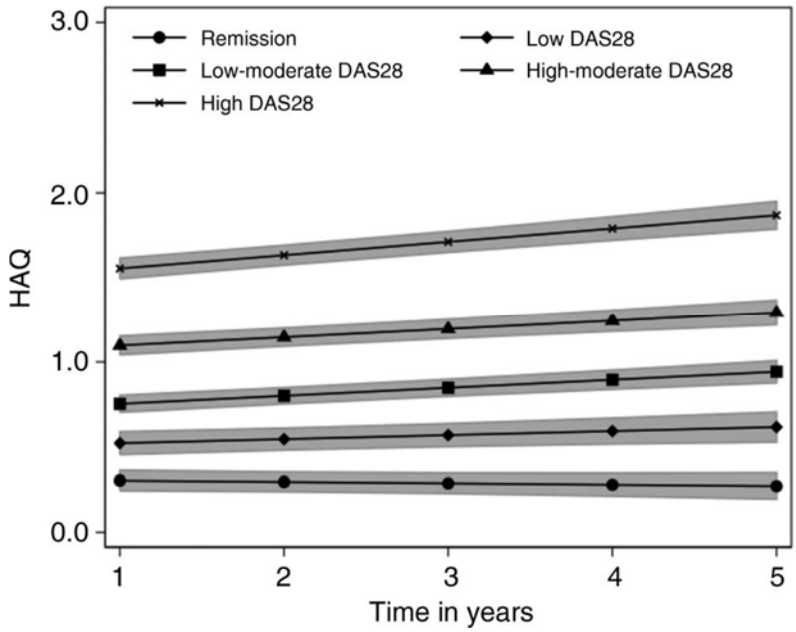
c. Presence of anti-CCP

- Other factors that would indicate potential to treat with bDMARDs or worse progression:
  a. DAS >3.2 and ≤ 5.1patients who cannot be controlled or require high levels of steroids
  b. Osteoporosis
  c. Blood tests
  d. Rheumatoid factor, anti-CCP
  e. Ultrasound to confirm active disease

6. Are there any potential equality issues that should be taken into account when considering these treatments?

In the UK, the majority of RA is diagnosed in people of working age. The debilitating nature of RA as the disease progresses, often results in disability and patients having to leave work due to this. The loss of function combined with the day-to-day pain of living with RA places a significant health-related quality of life (HRQoL) burden on patients[6,7] and caregivers.[8] Mental health can also be affected, with some patients developing depression as the disease progresses.[9,10] An association between RA disease activity, functional limitation and long-term risk of orthopaedic surgery was reported by Nikiphorou and colleagues. The requirement for major orthopaedic surgery was significantly more prevalent in mDAS patients than in those in the remission category.[11] Figure 4,[12] shows the progression of functional impairment (measured by HAQ) over time for patients within the different DAS28 categories. The data were collected from two multicentre longitudinal study cohorts in the UK: the Early Rheumatoid Arthritis Study (ERAS); and the Early RA Network (ERAN).[13]

Figure 4: Health Assessment Questionnaire (HAQ) progression by disease activity score (DAS28) category



Shaded areas indicate 95% CIs.

In 2009, TNF inhibitor therapy was shown to improve the Health Assessment Questionnaire (HAQ) score in UK patients with RA over a period of 12 months regardless of baseline DAS28, suggesting that TNF inhibitor treatment offers a clinical benefit to patients with moderate disease activity[14]. Similar beneficial effects of TNF inhibitor treatment in patients with moderate disease activity have been reported across Central [15] and Western Europe.[16] Variation in the initiation of TNF inhibitor therapy across EU countries was described in 2009 by Emery and colleagues. Clinical guidelines from Spain and Sweden were found to recommend the use of bDMARDs for RA with moderate disease activity.[17] A study using data from the Anti-Rheumatic Treatment in Sweden (ARTIS) register revealed that treatment with a bDMARD resulted in similar reductions in lost workdays for patients with mDAS (40%; p<0.001) and hDAS (42%; p<0.001) at baseline.[18] In a cross-sectional study among 46 European countries, significant differences in criteria for prescription of bDMARDs were reported.[19] In addition, countries with lower socioeconomic status tended to have more stringent criteria for patient eligibility.[20] Early access to bDMARDs is therefore highly variable between countries. In the UK, treatment with infliximab is currently only available to patients with high disease activity (DAS28 > 5.1). Early and effective treatment intervention during moderate disease activity could potentially relieve the heavy burden that RA places on patients and caregivers.

[1] Fautrel et al. Identifying patients with rheumatoid arthritis with moderate disease activity at risk of significant radiographic progression despite methotrexate treatment. 2015

[2] Li et al., 2016. Relationship of multi-biomarker disease activity score and other risk factors with radiographic progression in an observational study of patients with rheumatoid arthritis. Rheumatology, 55(2), 357-366

[3] Nikiphorou et al., 2015. OP0179 Different Levels of Moderate Disease in Rheumatoid Arthritis (RA) are Associated with Varying Risk for Joint Destruction and Failure. Time to Update Das Cut-Offs for Biologic Dmard Use? Annals of the Rheumatic Diseases, 74(Suppl 2), 139-139

[4] Combe et al., 2015.). Comparison of the long-term outcome for patients with rheumatoid arthritis with persistent moderate disease activity or disease remission during the first year after diagnosis: data from the ESPOIR cohort. Annals of the Rheumatic Diseases, 74(4), 724-729.

[5] Norton et al., 2018. SAT0110 Trajectories of functional disability in patients with early inflammatory polyarthritis and moderate disease activity: results from the early rheumatoid arthritis network and norfolk arthritis register. Annals of the Rheumatic Diseases, 77(Suppl 2), 917-918

[6] Matcham F, Scott IC, Rayner L, Hotopf M, Kingsley GH, Norton S, et al. The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis. Semin Arthritis Rheum. 2014;44(2):123-30.

[7] Hernandez Alava M, Wailoo A, Wolfe F, Michaud K. The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis. Rheumatology (Oxford). 2013;52(5):944-50

[8] Coskun Benlidayi I, Gokcen N, Sariyildiz A, Sarpel T. They have got the blues: patient's mood- and disease activity-related psychological burden of rheumatoid arthritis on caregivers. International journal of psychiatry in clinical practice. 2018:1-6.

[9] Deb A, Dwibedi N, LeMasters T, Hornsby JA, Wei W, Sambamoorthi U. Burden of Depression among Working-Age Adults with Rheumatoid Arthritis. Arthritis. 2018;2018:8463632.

[10] McBain H, Shipley M, Newman S. The impact of appearance concerns on depression and anxiety in rheumatoid arthritis. Musculoskeletal care. 2013;11(1):19-30.

[11] Nikiphorou E, Norton S, Young A, Carpenter L, Dixey J, Walsh DA, et al. Association between rheumatoid arthritis disease activity, progression of functional limitation and long-term risk of orthopaedic surgery: combined analysis of two prospective cohorts supports EULAR treat to target DAS thresholds. Annals of the Rheumatic Diseases. 2016;75(12):2080

[12] Ibid

[13] Ibid

[14] Hyrich KL, Deighton C, Watson KD, Consortium BCC, Symmons DPM, Lunt M, et al. Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity. Rheumatology (Oxford, England). 2009;48(10):1323-7.

[15] Smolen JS, Nash P, Durez P, Hall S, Ilivanova E, Irazoque-Palazuelos F, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. Lancet. 2013;381(9870):918-29.

[16] Ceccarelli F, Massafra U, Perricone C, Idolazzi L, Giacomelli R, Tirri R, et al. Anti-TNF treatment response in rheumatoid arthritis patients with moderate disease activity: a prospective observational multicentre study (MODERATE). Clinical and experimental rheumatology. 2017;35(1):24-32.

[17] Emery P, Van Vollenhoven R, Ostergaard M, Choy E, Combe B, Graninger W, et al. Guidelines for initiation of anti-tumour necrosis factor therapy in rheumatoid arthritis: similarities and differences across Europe. Annals of the Rheumatic Diseases. 2009;68(4):456

[18] Olofsson T, Johansson K, Eriksson JK, van Vollenhoven R, Miller H, Petersson IF, et al. Does disease activity at start of biologic therapy influence work-loss in RA patients? Rheumatology. 2016;55(4):729-34

[19] Putrik P, Ramiro S, Kvien TK, Sokka T, Uhlig T, Boonen A. Variations in criteria regulating treatment with reimbursed biologic DMARDs across European countries. Are differences related to country's wealth? Ann Rheum Dis. 2014;73(11):2010-21.

[20] Ibid

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Targeted submission

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Your name	[redacted]
Organisation name	Fresenius Kabi Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

1. It is proposed that this partial review is based on the original economic model developed by the Assessment Group in TA375. See here for the Assessment Group report. The assessment Group will update the model to address a limitation which means that currently, on progression from moderate to severe disease, patients are only modelled as having conventional DMARDs not biological DMARDs as in clinical practice. **Please comment on the proposal to use the Assessment Group model from TA375 amended as above.**
We support the decision to update the model to account for the identified limitation. Many people with Rheumatoid Arthritis (RA) with moderate disease activity (MDA) are often started on conventional DMARDs (cDMARDs) for which clinical treatment decisions on disease progression may include a biological DMARD (bDMARD). There will be few patients with MDA, who are treatment naïve and therefore the rationale to include bDMARD as the second step is reasonable. NICE in TA375 has already highlighted the clinical effectiveness of bDMARDS in MDA. Up to one third of patients with MDA may be fast progressors and could therefore be currently sub-optimally treated without access to bDMARDs.[1] Furthermore, there is evidence to suggest that the administration of bDMARDs to people with MDA leads to improved outcomes compared to methotrexate alone.[2-4] A registry-based study from the United States also demonstrated that patients offered bDMARDS experienced greater improvements in disease activity with a higher proportion achieving a remission compared to those with severe RA.[5] The cost of biosimilars has fallen since the original MTA and the assessment group (AG) will need to take account of the latest tender prices rather than the NHS list prices as shown in, for example MIMS, BNF or BNF on-line. The actual price paid by the NHS is likely to be commercial-in-confidence and may differ from manufacturer to manufacturer. In order to gain a more accurate estimate of the ICERs, it is suggested that it will be necessary to apply discounts to the current NHS list price ranging from 10%-90% in incremental steps or to seek the commercial in confidence prices from each manufacturer. References for Section 1 1. BSR appeal-letter 2. Hyrich KL, Deighton C, Watson KD, Control B, Consortium C. Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity. 2009;1323–7. 3. Emery P, Genovese MC, Van Vollenhoven R, Sharp JT, Patra K, Sasso EH. Less radiographic progression with adalimumab plus methotrexate versus methotrexate monotherapy across the spectrum of clinical response in early

rheumatoid arthritis. J Rheumatol. 2009;36(7):1429–41.

4. Smolen JS, Nash P, Durez P, Hall S, Ilivanova E, Irazoque-palazuelos F, et al. Maintenance , reduction , or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. Lancet 2013;381(9870):918–29.

5. Kavanaugh A, Keystone E, Greenberg JD, Reed GW, Griffith JM, Friedman AW, et al. Benefit of biologics initiation in moderate versus severe rheumatoid arthritis: Evidence from a United States registry. Rheumatol. 2017;56(7):1095–101.

2. In order to amend the model to address the above issue the Assessment Group will need to source information on the relationship between the change in Health Assessment Questionnaire (HAQ) score and the change in disease activity (DAS28) score.

Are you aware of any data on this relationship?

We are aware of the following data which investigates the relationship between the change in HAQ score and change in DAS28 score.

The changes in disease activity (DAS) may not always lead to improvements in function as measured by HAQ as this will depend on the level of disability the patient may have when the initial measurements were taken. The relationship between DAS and HAQ is not a simple linear function.[1]

DAS28 does not always reflect HAQ-DI (disease index) as patients with a low DAS28 score can still have active/residual disease. The correlation varies with time, age and presence of rheumatoid factor.[1]

Minimum Clinically Important Difference (MCID) used in clinical studies can vary significantly depending on the source used, a more robust ratio has been proposed.[2]

DAS28 and HAQ-DI should not preferentially be used to generate utilities and careful consideration of the EQ-5D or SF-6D scores is needed when assessing biologic medicines. The authors commented on the differences in utility gain as calculated by SF-6 and EQ-5D and question how to handle uncertainty. A mapping method was reported in this study and the authors also refer to other studies which derive utilities from HAQ-DI.[3]

A correlation between biomechanical tests, HAQ and DAS was presented at EULAR. The authors suggest that there is a direct relationship between increased disability as assessed by biomechanical parameters with increasing HAQ scores, as well as disease activity and structural damage in RA patients.[4]

A number of authors have questioned the use of the individual parameters and suggest that the use of HAQ and DAS28 although widely used could be supplemented by other markers / tests in order to identify patients with faster disease

progression. TA375 review proposal paper (2016) agrees with the authors and has highlighted the need for more research into markers that would predict the likelihood of rapid disease progression[5]

Subsequent research has been carried out into markers and these include:

- Anti-citrullinated peptide antibodies. (ACPA) [6-9]
- C-reactive protein (CRP).[10-11]
- Erythrocyte sedimentation rate (ESR).[8,10]
- MRI.[12,13]

A recent UK study suggested that there are varying degrees of disease progression and disability in RA patients diagnosed with moderate disease activity. The study aimed to identify trajectory groups over a three-year period. The authors state that patients with low DAS28 scores (<3.2), who thus fail to meet the current NICE criteria for access to bDMARDS, have poor long-term outcomes.[14]

The objective of the research was to identify those patients with worse long-term outcomes who may benefit from more aggressive therapy. The authors identified seven HAQ trajectory groups in patients with MDA, this heterogenous population has a range of potential long-term outcomes. The authors state: "*This study indicates that some patients with RA and MDA have high levels of disability and these patients are likely to continue having high disability over subsequent years. These patients should be identified and may benefit from more aggressive therapy, such as biologic therapy, despite their moderate disease activity".*

Furthermore, there is evidence to suggest that the administration of bDMARDS to people with MDA leads to improved outcomes compared to methotrexate alone. [Section 1 references]

References for Section 2

1. Boyd TA, Bonner A, Thorne C, Boire G, Hitchon C, Haraoui B, et al. The Relationship Between Function and Disease Activity as Measured by the HAQ and DAS28 Varies Over Time and by Rheumatoid Factor Status in Early Inflammatory Arthritis (EIA). Results from the CATCH Cohort. Open Rheumatol J. 2013;7(1):58–63.
2. Behrens F, Koehm M, Schwaneck EC, Schmalzing M, Gnann H, Greger G, et al. Use of a "critical difference" statistical criterion improves the predictive utility of the Health Assessment Questionnaire-Disability Index score in patients with rheumatoid arthritis. BMC Rheumatol. 2019;3(1):1–9.
3. Adams R, Walsh C, Veale D, Bresnihan B, FitzGerald O, Barry M. Understanding the relationship between the EQ-5D, SF-6D, HAQ and disease activity in inflammatory arthritis. Pharmacoeconomics. 2010;28(6):477–87.
4. Nuñez-Cornejo Piquer C, Nuñez-Cornejo Palomares C, Ivorra Cortes J, Grau E, Chalmeta Verdejo I, Molina Almela C, et al. AB0230 Relationship between Haq, DAS28 and Radiological Damage with Functional Capacity of the Hand in Rheumatoid Arthritis. Ann Rheum Dis. 2014 1;73(Suppl 2):879-880.

5. TA375. NICE Technology Appraisal Review Proposal paper arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. 2019
6. Fedele AL, Petricca L, Tolusso B, Alivernini S, Canestri S, Di Mario C, et al. Interleukin-6 and IgA-rheumatoid factor are crucial for baseline erosiveness, and anti-citrullinated peptide antibodies for radiographic progression in early rheumatoid arthritis treated according to a treat-to-target strategy. Scand J Rheumatol. 2018;47(5):351–9.
7. Steiner G, Sieghart D, Alasti F, Studenic P, Perkmann T, Horn T, et al. AB0217 The prognostic value of iga autoantibodies (rheumatoid factor and acpa) for prediction of therapeutic responses to anti-tnf therapy in patients with rheumatoid arthritis. Ann Rheum Dis. 2017 Jun 1;76(5):1124.
8. Joo Y Bin, Kim Y, Park Y, Kim K, Ryu JA, Lee S, et al. Biological function integrated prediction of severe radiographic progression in rheumatoid arthritis: a nested case control study. Arthritis Res Ther. 2017;19(1):244.
9. Koga T, Okada A, Fukuda T, Hidaka T, Ishii T, Ueki Y, et al. Anti-citrullinated peptide antibodies are the strongest predictor of clinically relevant radiographic progression in rheumatoid arthritis patients achieving remission or low disease activity: A post hoc analysis of a nationwide cohort in Japan. PLoS One. 2017;12(5):1–13.
10. Koga T, Okada A, Fukuda T, Hidaka T, Ishii T, Ueki Y, et al. Prognostic Factors Toward Clinically Relevant Radiographic Progression in Patients with Rheumatoid Arthritis in Clinical Practice. Med (United States). 2016;95(17):1–8.
11. Smolen JS, Van Vollenhoven RF, Florentinus S, Chen S, Suboticki JL, Kavanaugh A. Predictors of disease activity and structural progression after treatment with adalimumab plus methotrexate or continued methotrexate monotherapy in patients with early rheumatoid arthritis and suboptimal response to methotrexate. Ann Rheum Dis. 2018;77(11):1566–72.
12. Baker J, Conaghan P, Emery P, Baker D, Ostergaard M. Repository copy of Relationship of Patient-Reported Outcomes with MRI Measures in Rheumatoid Arthritis. MJ Publ Gr Ltd Eur Leag Against Rheum. 2017;76(3):486–90.
13. Peterfy C, Strand V, Tian L, Østergaard M, Lu Y, Dicarlo J, et al. Short-term changes on MRI predict long-term changes on radiography in rheumatoid arthritis : an analysis by an OMERACT Task Force of pooled data from four randomised controlled trials. 2016;1–6.
14. Pan Y, Norton S, Id JMG, Id LK, Deborah P, Symmons M, et al. Not all moderate disease is the same – Identification of disability trajectories among patients with rheumatoid arthritis and moderate disease activity. 2019;1–11.

3. In TA375 the committee identified uncertainties relating to long-term disease progression for people having conventional DMARDs and the mapping from HAQ scores to EQ-5D (health-related quality of life) utility values. It based decisions on:

- Early Rheumatoid Arthritis Study data to model disease progression with conventional DMARDs rather than assume a linear progression

- Hernandez et al (2013) to calculate EQ-5D utility values

The review paper did not find any new evidence to address these uncertainties, so it is proposed that the Assessment Group analyses also use these assumptions.

Are you aware of any new evidence in these areas?

We would like to refer you to the comments above in Section 2.

4. If you are the manufacturer of one of the interventions, please provide details of your product(s) including price and any confidential discounts.

Idacio®▼ (adalimumab)
List price:

- £633.86 (pre-filled pen and pre-filled syringe, box of 2)

Tender pricing:

- [redacted] (pre-filled pen and pre-filled syringe, box of 2)
- [redacted] (pre-filled pen and pre-filled syringe, box of 2) plus Calea homecare service

List price:

- £316.93 (vial, box of 1)

Tender pricing:

- [redacted] (vial, box of 1)

5. Please provide any other comments on the potential for a change in the recommendations for moderate active disease.

No further comments to those already provide above and in previous responses

6. Are there any potential equality issues that should be taken into account when considering these treatments?

We are not aware of any equality issues that are relevant to this submission

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Targeted submission

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Your name	[redacted]
Organisation name	Pfizer Ltd.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

1. It is proposed that this partial review is based on the original economic model developed by the Assessment Group in TA375. See here for the Assessment Group report. The assessment Group will update the model to address a limitation which means that currently, on progression from moderate to severe disease, patients are only modelled as having conventional DMARDs not biological DMARDs as in clinical practice.

Please comment on the proposal to use the Assessment Group model from TA375 amended as above.

Pfizer agrees with the proposal to explore multiple modelling methodologies in order to establish the cost-effectiveness of treatments in moderate rheumatoid arthritis (RA) based on disease severity and affiliated factors. To date, two main modelling methods are known that were accepted by NICE;

- the TA375 Assessment Group method (1), which doesn't model and account for differences between moderate and severe disease
- the TA480 Pfizer method, which models disease progression based on disease severity, including a transition of treatment paradigm from moderate to severe pathway (2) This method was subsequently used and accepted in later technology appraisals, for example TA485 sarilumab for moderate to severe RA, ID1400 upadacitinib for treating moderate to severe RA.

In both options the underpinning assumptions, for example disease progression assumptions, patient demographics, length or treatment choice of sequences in both treatment arms, amongst others, will impact the results and the interpretation of the results, and therefore should be carefully considered, next to simply adjusting for the acquisition cost changes of treatments since the original TA375 appraisal.

It should be noted that any presumed changes to the economic modelling methods and assumptions in the current TA375 review will affect any technology appraisal conclusions that followed TA375, namely TA466, TA480 and TA485, since NICE and ERG recommended and advocated the methods and assumptions used in TA375 for subsequent technology appraisals and based their decision making on these technologies with reference to TA375.

[redacted]

[redacted]

References:

1. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (TA375); https://www.nice.org.uk/guidance/ta375 ; accessed 29/09/2020

2. Tofacitinib for moderate to severe rheumatoid arthritis (TA480); https://www.nice.org.uk/guidance/ta480 ; accessed 29/09/2020

2. In order to amend the model to address the above issue the Assessment Group will need to source information on the relationship between the change in Health Assessment Questionnaire (HAQ) score and the change in disease activity (DAS28) score.

Are you aware of any data on this relationship?

During the single technology appraisal TA480 of tofacitinib in rheumatoid arthritis, tofacitinib's first indication, Pfizer generated and presented a substantial amount of information on this topic to aid the decision making for moderate RA during the appraisal. For example, Pfizer did extensive [redacted], which was acknowledged by the ERG as a robust analysis.

The information presented by Pfizer to NICE during TA480 is still unpublished and therefore classed as academic in confidence.

[redacted]

However, the following publication may provide some additional information;

- James M Gwinnutt, Kimme L Hyrich, Mark Lunt, RAMS Co-Investigators, Anne Barton, Suzanne M M Verstappen, Long-term outcomes of patients who rate symptoms of rheumatoid arthritis as 'satisfactory', Rheumatology, Volume 59, Issue 8, August 2020, Pages 1853–1861, https://doi.org/10.1093/rheumatology/kez497

3. In TA375 the committee identified uncertainties relating to long-term disease progression for people having conventional DMARDs and the mapping from HAQ scores to EQ-5D (health-related quality of life) utility values. It based decisions on:

- Early Rheumatoid Arthritis Study data to model disease progression with conventional DMARDs rather than assume a linear progression
- Hernandez et al (2013) to calculate EQ-5D utility values

The review paper did not find any new evidence to address these uncertainties, so it is proposed that the Assessment Group analyses also use these assumptions.

Are you aware of any new evidence in these areas?

According to Pfizer's knowledge, the mixture model by Hernandez et al. (2013) is still the most relevant methodology for the calculation of EQ-5D utility values from HAQ scores. The Hernández model combines distributions in a mixture model to provide an estimate of EQ-5D based on patients HAQ-DI score, pain on a visual analogue scale (VAS), age and sex. However, it should be noted that in TA375 the Assessment Group model assigned patients the expected pain score associated with their HAQ-DI score and used this relationship to estimate pain and subsequently predict EQ-5D.

Rather than assigning expected pains scores to HAQ-DI scores, Pfizer used patient level data during the single technology appraisal of tofacitinib for RA (TA480), to establish a better pain and HAQ-DI score relationship and subsequently used the Hernández model approach for EQ-5D calculations.

This new relationship between HAQ-DI and VAS pain was estimated using patient-level data from the Phase III tofacitinib ORAL trials: Standard, Scan, Sync, Solo, Start and Step, which included a total of 4273 randomised patients with 6 to 24 months trial durations. In TA480 better prediction of EQ-5D scores has been established. The method was validated by the ERG during TA480 and accepted by the Appraisal Committee. The information presented by Pfizer to NICE during TA480 is still unpublished and therefore classed as academic in confidence.

[redacted]

4. If you are the manufacturer of one of the interventions, please provide details of your product(s) including price and any confidential discounts.

	SKU	Pack of	List Price	Confidential Net Price
Inflectra® (infliximab)	100mg vial	1	£377.66	[redacted]
Enbrel® (etanercept)	10 mg powder and solvent for solution for injection for paediatric use	4	£143.00	[redacted]
	25 mg powder and solvent for solution for injection	4	£357.50	[redacted]
	25 mg solution for injection in pre-filled syringe	4	£357.50	[redacted]
	25mg Myclic Pre filled Pen	4	£357.50	[redacted]
	50 mg solution for injection in pre-filled pen	4	£715.00	[redacted]
	50 mg solution for injection in pre-filled syringe	4	£715.00	[redacted]
Xeljanz® (tofacitinib)	5mg Tabs	56	£690.03	[redacted]
	10mg Tabs	56	£1380.06	[redacted]
	11mg Tabs	28	£690.03	[redacted]

In line with consideration listed in question 5 and question 6 of this document, for completeness Pfizer has included the Xeljanz® (tofacitinib) confidential discount in this submission.

5. Please provide any other comments on the potential for a change in the recommendations for moderate active disease.

Overall, Pfizer welcomes the review of TA375 for the moderate RA subgroup as it signals a potential positive step change for patients with RA who may benefit from the earlier introduction of advanced treatments in the treatment pathway. However, it is regretful that this targeted guidance review excludes other established advanced treatments, that became available after the publication of TA375, recommended by NICE in severe RA and are licenced for the treatment of moderate to severe RA;

- TA466 – Baricitinib – Janus kinase (JAK) inhibitor
- TA480 – Tofacitinib - Janus kinase (JAK) inhibitor

- TA485 – Sarilumab – IL-6 inhibitor

As the Appraisal Committee concluded across all RA appraisals; it is important to have a range of treatment options in rheumatoid arthritis, since rheumatoid arthritis is a chronic lifetime condition that can severely reduce quality of life and conventional DMARDs such as methotrexate are inadequate therapy for many people. Therefore, it is contradictory not to include all licenced treatment options in this review for moderate RA.

This exclusion will restrict patient and clinician choice and may create a more complex treatment pathway dictated by a restricted NICE review of a much broader pathway instead of conducting a comprehensive multiple technology appraisal, which is inclusive of all licensed treatment options.

Also, the following points should be considered for the guidance review and its potential recommendation;

1. TA375 review does not fully consider the treat to target paradigm

   The recent NICE Clinical Guideline NG100 (Rheumatoid arthritis in adults: management) acknowledges the treat-to-target paradigm, which is supported by a wealth of recent evidence and reflects EULAR RA treatment guidelines. However, reimbursement is predominately based on the NICE TA375 guidance, which enforces restrictions on the disease modifying biologic and targeted treatments limiting their use to the severe RA population (DAS28>5.1). This restriction results in a divergence of guidance from NICE between NG100 and TA375, resulting in sub-optimal treatment outcomes for patients. If the treat-to-target approach as recommended in NG100 and outlined in recent publications is incorporated into the TA375 review, the clinical and cost-effectiveness conclusions are likely to be positively influenced due to additional QALY gains and cost-savings (1-7)

2. TA375 does not fully account for predictors of response

   During the NICE TA375 appraisal process the committee requested further research into potential predictors of response for patients with an increased risk of disease, such as the subgroup of rapid disease progressors. Such evidence is now available and is likely to further inform the clinical and cost-effectiveness analysis for decision making. This is underpinned by the recent NICE NG100, which highlights sub-groups in the treat-to-target strategies, how these should be identified, monitored and treated. Specifically, NG100 recommends remission as the treatment aim for people with presence of anti-CCP antibodies or erosions on X-ray at baseline assessment, for people with active RA, defined by increased C-reactive protein (CRP) and disease activity. For those with higher disease activity NG100 also recommends more frequent monitoring visits. Further to the NG100 listed identifiers of risk groups, several recent

publications provide new evidence on the prediction of response based on established clinical markers (8-17). Considering these predictors in the economic analysis is likely to alter the cost-effectiveness conclusion from TA375.

3. TA375 review may adversely result in limiting the treatment options for moderate RA patients

   - *Restricted access of established treatments for moderate RA*

   As mentioned above, new medicines, have become available since TA375. Baricitinib, tofacitinib and sarilumab, are licenced for the treatment of moderate to severe RA and have been recommended by NICE for severe RA (TA466, TA480 and TA485, respectively).

   Limiting the list of included technologies to TA375 technologies will restrict patient and clinician choice and may create a more complex treatment pathway dictated by a restricted NICE review, which is out of step with a much broader pathway comprising multiple mode of actions. Conducting a comprehensive multiple technology appraisal would therefore aid to simplify guidance across both moderate and severe disease.

   According to EULAR recommendations, 32% of the total RA population in the European region is eligible for biological DMARD treatment. However, only an average 59% of this EULAR-eligible population remains eligible after applying national reimbursement criteria (from 86% in 'high access' to 13% in 'low-access' countries). UK is amongst the low access countries, because NICE guideline only recommends the use of biological DMARDs in people with severe RA. (18)

   In addition, patients with sustained moderate disease activity in the first 5 years of disease, despite conventional DMARD therapy, still remain at high risk of joint failure and surgery. (18) This poses important management challenges in health systems where restrictions exist in the use of biologic DMARDs, which are based on DAS28 levels and exclude moderate RA. The results demonstrate that any therapy that keeps patients in low disease activity or remission states is beneficial in terms of long-term outcomes, which supports the review of all established therapies in RA, rather a selected few. (19)

   - *Pricing consideration within TA375 review and restricting access to TNFi biosimilars only*

   In the consultation paper issued by NICE in May 2019 it argues that; *Although TA375 included biosimilar infliximab, since its publication, new biosimilars for adalimumab and etanercept have become available and there have been*

changes in the confidential prices paid by NHS England for all treatments considered in TA375. The availability of cheaper treatments may reduce the committee's preferred ICER to £20,000 to £30,000 per QALY gained for people with moderate active disease (that is, the range that is considered a cost-effective use of NHS resources).

Leaving aside that changes in confidential discounts equally apply to technologies appraised in RA since TA375, it shall be noted that three of the seven technologies appraised by NICE in TA375 are now available as biosimilars, of which all three are TNFi. As it stands, it is potentially likely that only biosimilar prices may be deemed to be considered cost-effective, which will in effect make no other mode of action other than TNFi available to patients with moderate disease. This will affect patient and clinician treatment choice since there will be patients for whom TNFi's are contraindicated or whom do not tolerate or respond to TNFi's.

Furthermore, as per NICE consultation paper, rituximab, which is licenced in severe RA only, will be considered at confidential discounted price. This is likely to aid the cost-effectiveness of the technologies assessed in TA375, of which rituximab is not one, yet rituximab is included in the treatment sequence aiding QoL and cost benefits to TA375 technologies. This in turn is likely to equally positively affect the cost effectiveness of technologies that were appraised in RA after TA375, further reinforcing the need to include these more recent technologies in this appraisal, as otherwise unequal appraisal methods are applied by NICE across technology appraisals.

- Methodological issues of a restricted review of moderate RA within the current limited TA375 review

In the current TA375 review NICE have decided to change process and include treatment prices other than List or confidential patient access schemes. To measure cost-effectiveness of a technology in TA375 sequences are applied, which means that the costs and benefits of not only one but up to four biologics are incurred in any given sequence. Based on this, the costs and benefits of down-stream sequence technologies, such as rituximab and tocilizumab and potentially JAKs, are likely to reduce the ICERs for the technology explored in TA375 review, rather than established by the individual technology itself. This is unlikely to be considered by the ERG nor the committee given the statement made in the consultation paper, that '*availability of cheaper treatments may reduce the committee's preferred ICER to £20,000 to £30,000 per QALY gained for people with moderate active disease'.* This reinforces the need for inclusion of all available licenced and NICE recommended, and established treatments in RA into the TA375 review, as otherwise the treatment sequence in the current TA375 review will not reflect the treatment pathway that is

available for patients in the NHS and creates an uneven playfield across for advanced treatments in RA. Given the change in NICE process for TA375 review, it is therefore highly likely that technologies in moderate to severe RA that became available post TA375 could be deemed cost-effective at the £20,000 to £30,000 per QALY thresholds. It is therefore imperative for NICE to conduct and present scenario analyses for the technologies of TA466, TA480 and TA485 to explore the impact of the current change in NICE process.

- Restricted patient choice of oral alternative within advanced therapies

Excluding the orally administered JAK inhibitors from the review of TA375 limits advanced treatment options for patients and unnecessarily restricts the available biological DMARD options to injectables only for patients with moderate RA. This may negatively affect patients' life for a number of reasons. For example the methodology of administration and requirement for cold storage may limit work, education and travel options.

This restriction of patient choice is further amplified since the management of RA, a chronic life-time illness, is grounded in shared decision making. For various reasons, such as needle phobia, patients have a strong preference towards orally administered treatments versus injectables as it has been found by studies conducted in this area. (20)

- Patient outcome inequality compared across international league tables

Although EULAR guidelines advocate the treat-to-target approach, which is recommended by NICE NG100, the restriction of biologics to severe RA only in TA375 results in inequitable outcomes for UK patients compared to other developed countries (6. 21, 22). International comparisons, class the UK as a low access country for biologics, which correlates to worse outcomes for UK patients. Data demonstrates that UK patients on average have higher DAS28 and HAQ values, and lower DAS28 remission rates, than those in other Western countries (21, 22). As outlined above, by considering the treat-to-target approach and complications of delayed treatment within the economic analysis, it is likely that the conclusions from TA375 would be altered. Pfizer appreciates that the current TA375 review may address this inequality to some extent, although a holistic review and inclusion of all advanced treatments would be in the patients' and clinical interest.

References:

1. Versteeg GA, Steunebrink LM, Vonkeman HE, ten Klooster PM, van der Bijl AE, van de Laar MA. Long-term disease and patient-reported outcomes of a

continuous treat-to-target approach in patients with early rheumatoid arthritis in daily clinical practice. Clinical rheumatology. 2018 May 1;37(5):1189-97.

2. Brinkmann GH, Norvang V, Norli ES, Grøvle L, Haugen AJ, Lexberg ÅS, Rødevand E, Bakland G, Nygaard H, Krøll F, Widding-Hansen IJ. Treat to target strategy in early rheumatoid arthritis versus routine care–A comparative clinical practice study. InSeminars in arthritis and rheumatism 2018 Jul 25. WB Saunders.

3. Nikiphorou E, Norton S, Young A, Carpenter L, Dixey J, Walsh D, Kiely P. O07 Treating rheumatoid arthritis to target: is low disease activity good enough?. Rheumatology. 2018 Apr 1;57(suppl_3):key075-189.

4. Martin NH, Ibrahim F, Tom B, Galloway J, Wailoo A, Tosh J, Lempp H, Prothero L, Georgopoulou S, Sturt J, Scott DL. Does intensive management improve remission rates in patients with intermediate rheumatoid arthritis?(the TITRATE trial): study protocol for a randomised controlled trial. Trials. 2017 Dec;18(1):591.

5. Pavelka K, Akkoç N, Al-Maini M, Zerbini CA, Karateev DE, Nasonov EL, Rahman MU, Pedersen R, Dinh A, Shen Q, Vasilescu R. Maintenance of remission with combination etanercept–DMARD therapy versus DMARDs alone in active rheumatoid arthritis: results of an international treat-to-target study conducted in regions with limited biologic access. Rheumatology international. 2017 Sep 1;37(9):1469-79.

6. Taylor PC, Alten R, Reino JJ, Caporali R, Bertin P, Sullivan E, Wood R, Piercy J, Vasilescu R, Spurden D, Alvir J. Factors influencing the use of biologic therapy and adoption of treat-to-target recommendations in current European rheumatology practice. Patient preference and adherence. 2018;12:2007.

7. Van Vollenhoven RF, Lee EB, Fallon L, Zwillich SH, Wilkinson B, Chapman D, Demasi R, Keystone E. Tofacitinib in Rheumatoid Arthritis: Lack of Early Change in Disease Activity Predicts a Low Probability of Achieving Low Disease Activity at Month 6. Arthritis care & research. 2018 Apr 26

8. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, Nam J, Ramiro S, Voshaar M, van Vollenhoven R, Aletaha D. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Annals of the rheumatic diseases. 2017 Jun 1;76(6):960-77.

9. Smolen JS, Szumski A, Koenig AS, Jones TV, Marshall L. Predictors of remission with etanercept-methotrexate induction therapy and loss of remission with etanercept maintenance, reduction, or withdrawal in moderately active

rheumatoid arthritis: results of the PRESERVE trial. Arthritis research & therapy. 2018 Dec;20(1):8.

10. Szücs G, Gaál J, Géher P, Gömöri E, Kovács A, Kovács L, Nagy K, Posta E, Tamási L, Tóth E, Varga E. FRI0731 Assessing the risk of rapid radiologic progression in hungarian rheumatoid arthritis patients.

11. Papadopoulos N, Gkagkalis A, Konstantinidou E, Mentesidou L, Tzatzagou G, Galanopoulou V. AB0259 Predictors of high disease activity in a cohort of greek patients with acpa positive early rheumatoid arthritis. Annals of the Rheumatic Diseases. 2017 Jun 1;76:1139.

12. Kaine J, Kivitz AJ, Mysler E, Iikuni N, Fan H, Diehl A, Paulissen J, Murray CW. Baseline Characteristics of Methotrexate Inadequate Responder Patients with RA Who Achieved Low Disease Activity with Tofacitinib Monotherapy. InARTHRITIS & RHEUMATOLOGY 2018 Sep 1 (Vol. 70). 111 RIVER ST, HOBOKEN 07030-5774, NJ USA: WILEY.

13. Van Vollenhoven RF, Lee EB, Fallon L, Zwillich SH, Wilkinson B, Chapman D, Demasi R, Keystone E. Tofacitinib in Rheumatoid Arthritis: Lack of Early Change in Disease Activity Predicts a Low Probability of Achieving Low Disease Activity at Month 6. Arthritis care & research. 2018 Apr 26.

14. Verschueren P, De Cock D, Corluy L, Joos R, Langenaken C, Taelman V, Raeman F, Ravelingien I, Vandevyvere K, Lenaerts J, Geens E. Effectiveness of methotrexate with step-down glucocorticoid remission induction (COBRA Slim) versus other intensive treatment strategies for early rheumatoid arthritis in a treat-to-target approach: 1-year results of CareRA, a randomised pragmatic open-label superiority trial. Annals of the rheumatic diseases. 2017 Mar 1;76(3):511-20.

15. Fautrel B, Nab HW, Brault Y, Gallo G. Identifying patients with rheumatoid arthritis with moderate disease activity at risk of significant radiographic progression despite methotrexate treatment. RMD open. 2015 Jul 1;1(1):e000018.

16. Nikiphorou E, Norton S, Young A, Carpenter L, Dixey J, Walsh DA, Kiely P. Association between rheumatoid arthritis disease activity, progression of functional limitation and long-term risk of orthopaedic surgery: combined analysis of two prospective cohorts supports EULAR treat to target DAS thresholds. Annals of the rheumatic diseases. 2016 Mar 15:annrheumdis-2015.

17. Accortt NA, Lesperance T, Liu M, Rebello S, Trivedi M, Li Y, Curtis JR. Impact of Sustained Remission on the Risk of Serious Infection in Patients With Rheumatoid Arthritis. Arthritis care & research. 2018 May;70(5):679-84.

18. Nikiphorou E, Carpenter L, Norton S, Dixey J, Kiely P, Walsh D, Young A. Eventual Joint Failure and Surgery Rates in Rheumatoid Arthritis Remain High in Patients with Moderate Disease Activity in the First 5 Years of Disease.: 1841. Arthritis & Rheumatology. 2014 Oct 1;66.

19. J Mark Access Health Policy. 2017; 5(1): 1345580. Published online 2017 Jul 5. doi: 10.1080/20016689.2017.1345580

20. Taylor PC, Betteridge N, Brown TM, Woolcott J, Kivitz AJ, Zerbini C, Whalley D, Olayinka-Amao O, Chen C, Dahl P, Ponce de Leon D, Gruben D, Fallon L. Treatment Mode Preferences in Rheumatoid Arthritis: Moving Toward Shared Decision-Making. Patient Prefer Adherence. 2020;14:119-131 https://doi.org/10.2147/PPA.S220714

21. Bergstra SA, Branco JC, Vega-Morales D, Salomon-Escoto K, Govind N, Allaart CF, Landewé RB. Inequity in access to bDMARD care and how it influences disease outcomes across countries worldwide: results from the METEOR-registry. Annals of the rheumatic diseases. 2018 Oct 1;77(10):1413-20.

22. Kaló Z, Vokó Z, Östör A, Clifton-Brown E, Vasilescu R, Battersby A, Gibson E. Patient access to reimbursed biological disease-modifying antirheumatic drugs in the European region. Journal of market access & health policy. 2017 Jan 1;5(1):1345580

6. Are there any potential equality issues that should be taken into account when considering these treatments?

- People with needle fear or needle phobia

Patients with fear of needles (needle-phobia) could be excluded from accessing treatment for moderate RA, in case the JAK inhibitors do not get recommended alongside the review of TA375.

Research found that the majority of children reported needle fear, while prevalence estimates for needle fear ranged from 20-50% in adolescents and 20–30% in young adults. (1) In general, needle fear decreased with increasing age. Both needle fear and needle phobia were more prevalent in females than males. Needle

fear is common when undergoing venipuncture, blood donation, and in those with chronic conditions requiring injection.

Another survey found that 45% of RA patients reported some degree of needle-phobia (8%: extremely, 14%: very, and 23%: somewhat). Furthermore, at least 20% of RA patients report that they would not consider using a medication that required self-injection. Needle anxiety goes beyond physical pain. Some patients dislike the stigma of sickliness associated with needle usage, while others are afraid of not being able to properly self-administer injections. Parents living with children in the household also fear that children may accidentally stumble across a needle-based device and hurt themselves. (1)

Self-injection is also associated with a number of challenges. These include needle phobia, fear and anxiety, concerns about pain, stinging and other injection site reactions, patient lack of confidence, incorrect administration, medication non-adherence, and the struggle to use a self-injection device while suffering from arthritic pain and swelling of the hands. (2)

References:

1. McLennon J, Rogers M A.M. The fear of needles: A systematic review and meta-analysis. Journal of Clinical Nursing. 2019 Jan; 75 (1):30-42

2. Schwartzman & Morgan, 2004; Keininger & Coteur, 2011; Schiff et al., 2017

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Targeted submission

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Your name	[redacted]
Organisation name	Sandoz Limited, UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None known

1. It is proposed that this partial review is based on the original economic model developed by the Assessment Group in TA375. See here for the Assessment Group report. The assessment Group will update the model to address a limitation which means that currently, on progression from moderate to severe disease, patients are only modelled as having conventional DMARDs not biological DMARDs as in clinical practice.

Please comment on the proposal to use the Assessment Group model from TA375 amended as above.

Sandoz would welcome an update to the current model to address the limitation that on progression from moderate to severe disease, patients are only modelled as having conventional synthetic DMARDS (csDMARDs) and not biologic DMARDS (bDMARDS) as in clinical practice.

Since the original publication of TA375, there have been different modelling scenarios used throughout clinical research and practice. Two are notable for their status, conclusions and suggestions for further research:

The US Institute for Clinical and Economic Review (2017) Targeted immune modulators for rheumatoid arthritis: Effectiveness & value technical report, was heavily criticized for comparing immunomodulators to conventional DMARDs which did not optimally prevent disease progression and were not the current standard of care and for overestimation of disease progression in the absence of biologic therapies. In the ICER model, csDMARD patients would progress to a HAQ of 2.1 over lifetime, which appeared inconsistent with the substantial disease burden in the pre-biologic era.

The 2016 Health Technology Assessment (NIHR) for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only, measured clinical effectiveness and cost-effectiveness of biologic disease-modifying antirheumatic drugs (bDMARDs) compared with conventional disease-modifying antirheumatic drugs (csDMARDs) in individuals with rheumatoid arthritis. Fifty-two clinical trials provided data on American College of Rheumatology and/or European League Against Rheumatism responses for bDMARDs .These data were synthesised to produce coherent results. NIHR showed that bDMARDs were more effective than csDMARDs and further interrogation of the database indicated that historical assumptions regarding disease progression while on csDMARDs were far too pessimistic. Results from the cost-effectiveness analyses indicated typical cost per QALY of ≥ £40,000. These are higher than values reported by the National Institute for Health and Care Excellence as thresholds for an intervention to be considered cost-effective. At the time, NIHR identified that the reduction in HAQ (positive response to treatment) was greater in the company submissions than seen in the BSBR database NIHR had used in their calculations. If the greater HAQ reductions for bDMARDS (positive response to treatment) had been used by NHIR, this would have had the effect of reducing the Incremental cost Ratio (*ICER) as HAQ is linked to utility and to disease –related cost. It is now four years since this original assessment, and it is well known that the BSRBR-RA cohort is enriched for high baseline activity and does not include early arthritis patients .This dataset is therefore not fully representative of a cohort on which to base a cost effectiveness model of moderate RA, and Sandoz think this fact should be considered in NICE's future modelling scenarios.

*ICER is the incremental change in costs /incremental change in health outcomes.

Sandoz would ask NICE to consider the principles used in The US Innovation and Value project that has produced an **IVI-RA model** which is a discrete-time individual patient simulation that simulates outcomes for individual patients. Model cycles are 6-months long, which is consistent with clinical trial evidence.

References:
The US Institute for Clinical and Economic Review (2017) Targeted immune modulators for rheumatoid arthritis (https://icer-review.org/wp-content/uploads/2016/08/NE_CEPAC_RA_Evidence_Report_FINAL_040717.pdf) Institute for Clinical and Economic Review (2017). Targeted immune modulators for rheumatoidarthritis: Effectiveness & value. Technical report).

Stevenson, M., Archer, R., Tosh, J., Simpson, E., Everson-Hock, E., Stevens, J., Hernandez-Alava,M., Paisley, S., Dickinson, K., Scott, D., et al. (2016). Adalimumab, etanercept, iniximab,certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only:systematic review and economic evaluation. Health Technology Assessment, 20(35):1{610.

The US Innovation and Value project IVI-RA Model v2.0 as proposed by Incerti and Jansen **https://www.thevalueinitiative.org/**

2. In order to amend the model to address the above issue the Assessment Group will need to source information on the relationship between the change in Health Assessment Questionnaire (HAQ) score and the change in disease activity (DAS28) score.

Are you aware of any data on this relationship?

Earlier research in RA (Bansback et al, Scott et al) has suggested that the mean HAQ score over time is J-shaped with an initial improvement after treatment commencement followed by an insidious decline in patients with early RA. However, the focus of most of these studies is on the average change over time in the total study population calculating mean changes in HAQ score over time or applying simple linear regression models to determine the association between disease duration and HAQ progression. However, in most studies, the change in HAQ scores over time has been measured at the group level. Few studies had attempted to identify subgroups defined in terms of their HAQ trajectory in RA patients or considered their validity across cohorts. In a study, Norton et al included patients with early RA recruited to the Early Rheumatoid Arthritis Study (ERAS) and followed up for 10 years, latent growth mixture modelling (LGMM) was used to determine whether the study population comprises distinct subgroups of patients with differing trajectories of functional disability. Previously, Wolfe et al had previously identified three patterns of individual courses:

- Patients who had a high HAQ score at baseline and remained high
- Patients with fluctuating HAQ scores over time to be associated with variability in inflammation and
- Pain over time and patients who started low and remained low.

To address the problem of multi-nominal heterogeneity as found in RA populations, Norton et al using the LCGM technique, found that, age, gender, and the DAS28 were found to be relevant to the way the population was defined and are therefore important determinants of the HAQ trajectory and that in general, identification of distinct groups of patients who are at risk of poor outcomes may help to target therapy to those who are most likely to benefit in the clinic.

Sandoz would also ask NICE to consider the principles used in The US Innovation and Value project that has produced an **IVI-RA model** (see question 1 above). The model simulates the progression of the health assessment questionnaire disability index (HAQ), a measure of functional status in RA.Serious infection rates and changes in HAQ score during the first 6 months from baseline are based on clinical trial evidence. The change in HAQ can be modelled indirectly as a function of the American College of Rheumatology (ACR) response to treatment, the European League Against Rheumatism (EULAR) response to treatment, or directly as a function of the treatment. Patients switch treatment during the initial 6 months if they have a serious infection. After the first 6 months on a new treatment, the HAQ score progresses over time at a rate based on observational data. Progression can either be assumed to be linear (Wolfe and Michaud 2010; Michaud et al. 2011) or modelled using a non-linear mixture model (Norton et al. 2014/13) described above.

References:

Nick Bansback, Adam Young, Alan Brennan and Josh Dixey (2006).A prognostic model for functional outcome in early rheumatoid arthritis. The Journal of Rheumatology August 2006, 33 (8) 1503-1510
Scott DL, Pugner K, Kaarela K, Doyle DV, Woolf A, Holmes J, et al. The links between joint damage and disability in rheumatoid arthritis. Rheumatology (Oxford) 2000;39:122–32.

Norton, S., Fu, B., Scott, D. L., Deighton, C., Symmons, D. P., Wailoo, A. J., Tosh, J., Lunt, M.,Davies, R., Young, A., et al. (2014). Health assessment questionnaire disability progression in early rheumatoid arthritis: systematic review and analysis of two inception cohorts. In Seminars in arthritis and rheumatism, volume 44, pages 131{144. Elsevier.

Wolfe, F. and Michaud, K. (2010). The loss of health status in rheumatoid arthritis and the effect of biologic therapy: a longitudinal observational study. Arthritis research & therapy, 12(2):R35.

Michaud, K., Wallenstein, G., and Wolfe, F. (2011). Treatment and non-treatment predictors of health assessment questionnaire disability progression in rheumatoid arthritis: a longitudinal study of 18,485 patients. Arthritis care & research, 63(3):366{372

Norton, S., Fu, B., Scott, D. L., Deighton, C., Symmons, D. P., Wailoo, A. J., Tosh, J., Lunt, M.,Davies, R., Young, A., et al. (2014). Health assessment questionnaire disability progression in early rheumatoid arthritis: systematic review and analysis of two inception cohorts. In Seminars in arthritis and rheumatism, volume 44, pages 131{144. Elsevier.

Norton, S., Sacker, A., Dixey, J., Done, J., Williams, P., and Young, A. (2013). Trajectories of functional limitation in early rheumatoid arthritis and their association with mortality. Rheumatology, page ket253

3. In TA375 the committee identified uncertainties relating to long-term disease progression for people having conventional DMARDs and the mapping from HAQ scores to EQ-5D (health-related quality of life) utility values. It based decisions on:

- Early Rheumatoid Arthritis Study data to model disease progression with conventional DMARDs rather than assume a linear progression
- Hernandez et al (2013) to calculate EQ-5D utility values

The review paper did not find any new evidence to address these uncertainties, so it is proposed that the Assessment Group analyses also use these assumptions.

Are you aware of any new evidence in these areas?

Sandoz would support the algorithm used in the 4 compartment mixture model developed by Hernandez-Alava et al. (2013). This is also cited in 2019 in the IVI-RA Model v2.0 as proposed by Incerti and Jansen

The mixture model approach offers a flexible framework for complex distributions like EQ-5D and allows for consideration of patient subgroups as the relationship between HAQ and pain to EQ-5D is very different within the 4 compartments of the model. Additionally this model has an improved fit at the end of the EQ-5D distribution. Previous cost-effective analyses focused on changes in HAQ due to treatment, but this study demonstrated that better estimates of the benefits of treatment in terms of QALYs would be gained if HAQ and pain were simultaneously considered.

References:

The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis
Monica Hernandez Alava, Allan Wailoo, Fred Wolfe and Kaleb Michaud Rheumatology 2013;52:944_950
doi:10.1093/rheumatology/kes400 Advance Access publication 21 January 2013

The US Innovation and Value project IVI-RA Model v2.0 as proposed by Incerti and Jansen
https://www.thevalueinitiative.org/

4. If you are the manufacturer of one of the interventions, please provide details of your product(s) including price and any confidential discounts.

Medicine	Strength	Quantity	Brand	List Price	Discount Tender Price
Infliximab	100 mg	1 vial	Zessly	£377.66	[redacted]
Etanercept	50mg/ml	4 pens/pfs*	Erelzi	£643.50	[redacted]**
Etanercept	25mg/ml	4 pens/pfs*	Erelzi	£328.00	[redacted]**
Adalimumab	50mg/ml	2 pens/pfs*	Hyrimoz	£646.18	[redacted]**

* Pre-filled syringe; **Prices are exclusive of homecare

5. Please provide any other comments on the potential for a change in the recommendations for moderate active disease.

Sandoz would like to comment on the potential for change in the current recommendations for the treatment of moderate RA under the following headings:

Treatment in the UK is largely out of step with other European countries and the US, and there is now sufficient evidence that a revision is necessary.

Treating rheumatoid arthritis (RA) to target (T2T) is an internationally agreed standard of good practice which is founded on the principle that rapid attainment of remission or low disease activity can halt joint damage and maintain good quality of life. Both the American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis (ACR) and the European League against Rheumatism (EULAR) guidelines for the management of RA are based on the treat to target (T2T) principle and recommend the use of both conventional synthetic disease modifying antirheumatic drugs (csDMARDs) and biologic DMARDS (bDMARDs) to achieve this. Some countries and healthcare systems including the UK, restrict the use of bDMARDs to patients with a disease activity score (DAS) of 5.1 or more and this is above the highest T2T goal. A recent systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis demonstrated that existing trials comparing biologic DMARDs have shown similar efficacy, regardless of the underlying mode of action The British Society of Rheumatology Biologics Register for RA (BSRBR-RA) launched in 2001, is a source of UK prospective, longitudinal observational data. This is useful for examining the safety and long-term effectiveness of biologic agents in patients. As biologics use in England and Wales is driven by NICE guidelines (persistent high disease activity i.e. DAS28 score >5.1 despite treatment with at least two csDMARDS, one of which should be MTX, unless contraindicated), the BSRBR-RA cohort is enriched for high baseline activity and does not include early arthritis patients. Analysis of the BSRBR-RA data show that while EULAR recommendations are sound and robustly evidence-based, achieving the target of sustained remission or low disease activity may remain aspirational for the majority of patients who require a Tumour necrosis factor inhibitor (TNFi) in the UK, most of whom have already shown resistance to csDMARDS (Hamman et al)

There is substantial evidence to treat RA at moderate or lower disease levels.

There is now a substantial body of evidence to support the conclusion that patients with RA and a moderate DAS28 score of 3.2 are unlikely to achieve the T2T standard of low disease activity with continued csDMARDs alone. This has been demonstrated in countries where the eligibility criteria to commence bDMARDs are based on DAS28 thresholds which exclude moderate disease.

Nikiphorou et al demonstrated an association between rheumatoid arthritis disease activity, progression of functional limitation and long-term risk of orthopaedic surgery by combining the analysis of two prospective cohorts, ERAS/ERAN. The study showed that as many as 47% of patients in the 2 cohorts who were categorized in the moderate DAS28 range for one to five years post RA diagnosis, were not permitted bDMARDS according to the thresholds set by the National Institute for Health and Care Excellence (NICE). The consequences of a range of disease activity states were studied for the first five years on function and orthopaedic episodes up to 25 years later and showed that far from being benign, the consequences of persistent moderate disease activity were associated with both poor function and long-term orthopedic episodes. This study had the further advantage of a real-life setting, large patient numbers and long follow ups.

Swedish data from Antirheumatic Therapies in Sweden (ARTIS) register demonstrated cost effectiveness of bDMARDS as far back as 2006 (Askling et al). Other studies have also demonstrated the clinical benefits of starting bDMARDS earlier and at lower disease activity levels including moderate DAS28 of 3.1.(Hyrich, KI et al , Smolen et al).

The concept of “the earlier the better” in terms of diagnosis, prompt treatment initiation and early achievement of remission are early predictors of long-term clinical, functional and radiographic

outcomes and it is acknowledged that treatment within a" window of opportunity" during the first 12 weeks of disease onset, offers sustained and long term benefits. A shorter time to remission has been a consistent and strong determinant of sustained remission so that disease duration is among the most relevant factors affecting the likelihood of patients' response to treatment, even when bDMARDS are prescribed. Additionally, early treatments and tight inflammation control conferred other benefits such as cardiovascular risk reduction and a 30% fall in the risk of all- cause mortality (Monti et al).

It has also been shown that the moderate RA population represent a substantial proportion of clinical practice and that although this population is heterogeneous in terms of prognosis, patients will show a significant radiographic progression despite receiving a single csDMARD, Methotrexate (MTX) .High CRP levels and RF positivity at baseline predicts a higher risk of radiographic progression after 2-3 years of MTX treatment (Fautrel et al).

Real- world data from the Dutch Rheumatoid arthritis Monitoring (DREAM) registry suggested that treatment decisions in early phase RA may need to be based on the consideration of disease activity as well as radiographic progression. For patients with radiographic progression, rheumatologists should consider initiating treatment with bDMARDS or targeted synthetic DMARDS (tsDMARDS) even if disease activity alone would not merit such as therapeutic change. In early RA, when patients treated to T2T, radiographic progression appears to be an individually determined disease process, driven by factors other than consistent high disease activity. For individual patients, the intra- patient relation between disease activity and cumulative radiographic damage during the first six months was a good indicator for the progression of the disease in later years (Klooster et al).

There is now sufficient evidence regarding the use of bDMARDS earlier in the RA treatment pathway.

A posthoc analysis of the PREMIER study found that in some patients with active early RA, by month 6, after the initiation of a single csDMARD (MTX), did not respond and were found to have worse clinical, functional and long term outcomes. This suggested a revision at month three as a more appropriate period to assess clinical response. In contrast, patients who had initially received a combination of adalimumab (ADA) +MTX typically demonstrated comparable long term outcomes at one and two years of therapy and the combination was not associated with the same long term risks of delayed response seen with csDMARD monotherapy (Keystone et al).

A recent systematic network meta-analysis (Donahue et al) identified twenty-two studies during 2012-2017 which compared the effectiveness of combining MTX with a bDMARD or bDMARD monotherapy for early RA and concluded that a combination of a bDMARD and MTX or bDMARD monotherapy improved disease activity and DAS –defined remission within one year of RA diagnosis more than MTX monotherapy alone .

There is now some evidence that Biosimilar DMARDS could be cost effective as an early intervention.

Early initiation of an originator biologic or biosimilar TNFi in patients who have had an inadequate response to MTX was seen to be cost-effective when compared with unsuccessful treatment with MTX alone for 12 months. Use of a Markov model and calculation of ICERS/QALY supported initiation of bDMARDS at six months after MTX monotherapy. (Patel et al)

Moderate disease activity in Rheumatoid Arthritis will lead to high disease activity and the potential for increased human, societal and financial costs. There is also growing evidence that treatment of patients with moderate disease is cost effective at a threshold of £30,000/QALY (Nikiphorou, Fautrel, ACR 2015).

Over the past 5 years a number of biosimilars of adalimumab, etanercept and infliximab have been launched in the UK and resulted in discounts of, on average, between [redacted] from the list price of the originator reference products (Sandoz Data on File). Sandoz believe that current biosimilarprices, when modelled to account for earlier initiation in patients with moderate disease activity (with DAS28 score ≥3.2- 5.1) will lower the calculated ICER for moderate disease patients to below the £30,000 per QALY threshold. The greater utilisation of biosimilars in England has saved the NHS hundreds of millions of pounds per annum in recent years (NHS news, August 2019)). Whilst Sandoz realises that only a proportion of this can be attributed to RA treatment, we believe these savings would potentially off-set any medicine acquisition if bDMARDS are used earlier in the moderate disease treatment paradigm.

References:

1. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis; Singh, Jasvinder A; Saag, Kenneth G; Bridges, S Louis; Akl, Elie A; Bannuru, Raveendhara R; Sullivan, Matthew C; Vaysbrot, Elizaveta; McNaughton, Christine; Osani, Mikala; Shmerling, Robert H; Curtis, Jeffrey R; Furst, Daniel E; Parks, Deborah; Kavanaugh, Arthur; O'Dell, James; King, Charles; Leong, Amye; Matteson, Eric L; Schousboe, John T; Drevlow, Barbara; ISSN: 2326-5191 , 2326-5205; DOI: 10.1002/art.39480, Arthritis and rheumatology , 2016, Vol.68(1),p1-26

2. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update Annals of the rheumatic diseases, June 2020, Vol.79(6), pp.685-699 Smolen, Josef S ; Landewé, Robert B M ; Bijlsma, Johannes W J ; Burmester, Gerd R ; Dougados, Maxime ; et al.

3. Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis: Kerschbaumer A, Sepriano A, Smolen JS,et al. Ann Rheum Dis 2020;**79**:744–759

4. Early response to anti-TNF predicts long-term outcomes including sustained remission: an analysis of the BSRBR-RA Philip D. H. Hamann, John D. Pauling, Neil McHugh,Kimme Hyrich and Gavin Shaddick; and the BSRBR-RA Contributors Group ; Rheumatology 2019; 0:1–6doi:10.1093/rheumatology/kez518

5. Association between rheumatoid arthritis disease activity, progression of functional limitation andlong-term risk of orthopaedic surgery: combined analysis of two prospective cohorts supports EULAR treat to target DAS thresholds: Nikiphorou E,Norton S, Young A, et al.Ann Rheum Dis2016;75:2080–2086

6. Swedish registers to examine drug safety and clinical issues in RA: J Askling, C M Fored, P Geborek, L T H Jacobsson, R van Vollenhoven,N Feltelius, S Lindblad, L KlareskogAnn Rheum Dis 2006;65:707–712. doi: 10.1136/ard.2005.045872

7. Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity; Hyrich, Kl; Deighton, C; Watson, K D; Symmons, D P M; Lunt, M;, ISSN: 1462-0324 , 1462-0332; DOI: 10.1093/rheumatology/kep242, Rheumatology , 2009, Vol.48(10), p.1323-1327

8. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial; Smolen, Js; Smolen, Josef S; Nash, Peter; Durez, Patrick; Hall, Stephen; Ilivanova, Elena; Irazoque-Palazuelos, Fedra; Miranda, Pedro; Park, Min-Chan; Pavelka, Karel; Pedersen, Ronald; Szumski, Annette; Hammond, Constance; Koenig, Andrew S; Vlahos, Bonnie; ISSN: 0140-6736 , 1474547X; DOI: 10.1016/S0140-6736(12)61811-X,, The Lancet. , 2013, Vol.381(9870), p.918-

9. Rheumatoid arthritis treatment: the earlier the better to prevent joint damage. Monti S, Montecucco C, Bugatti S,et al. RMD Open 2015;1:e000057. doi:10.1136/rmdopen-2015-000057

10. Identifying patients with rheumatoid arthritis with moderate disease activity at risk of significant radiographic progression despite methotrexate treatment. Fautrel B, Nab HW, Brault Y, et al. RMD Open 2015; 1:e000018. doi:10.1136/rmdopen-2014-000018

11. Radiographic progression can still occur in individual patients with low or moderate disease activity in the current treat-to-target paradigm: real-world data from theDutch Rheumatoid Arthritis Monitoring (DREAM) registry. Peter M. Klooster, Letty G. A. Versteeg, Martijn A. H. Oude Voshaar, Inmaculada de la Torre, Francesco De Leonardis, Walid Fakhouri, Liliana Zaremba-Pechmann and Mart van de Laar. Arthritis Research & Therapy (2019) 21:237https://doi.org/10.1186/s13075-019-2030-8

12. Clinical, Functional, and Radiographic Implications of Time to Treatment Response in Patients With Early Rheumatoid Arthritis: a Posthoc Analysis of the PREMIER Study: Edward C. Keystone, Boulos Haraoui, Benoît Guérette, Neelufar Mozaffarian, Shufang Liu,and Arthur Kavanaugh. The Journal of Rheumatology 2014; 41:2; doi:10.3899/jrheum.121468

13. Comparative Effectiveness of Combining MTX with Biologic Drug Therapy Versus Either MTX or Biologics Alone for Early Rheumatoid Arthritis in Adults: a Systematic Review and Network Meta-analysis. Katrina E. Donahue, M.D., M.P.H., Elizabeth R. Schulman, M.D.,Gerald Gartlehner, M.D., M.P.H., Beth L. Jonas, M.D., F.A.C.R.,Emmanuel Coker-Schwimmer, M.P.H., Sheila V. Patel, B.S.P.H.,Rachel Palmieri Weber, Ph.D., Carla M. Bann, Ph.D., and Meera Viswanathan, Ph.D. J Gen Intern Med 34(10):2232–45 DOI: 10.1007/s11606-019-05230-0

14. Cost-Effectiveness of Early Treatment with Originator Biologics or Their Biosimilars After MethotrexateFailure in Patients with Established Rheumatoid Arthritis; Dipen Patel. Ahmed Shelbaya. Raymond Cheung. Jyoti Aggarwal .Sang Hee Park. Javier Coindreau. Adv Ther (2019) 36:2086–2095 https://doi.org/10.1007/s12325-019-00986-7

15. NHS cuts medicines costs by three quarters of a billion pounds. (Aug 2019) https://www.england.nhs.uk/2019/08/nhs-cuts-medicines-costs-by-three-quarters-of-a-billion-pounds/

6. Are there any potential equality issues that should be taken into account when considering these treatments?

In line with NICE'S Equality and Objectives and Equality programme 2016-2020, Sandoz do not foresee any equity issues when considering these treatments.

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Targeted submission

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Your name	[redacted]
Organisation name	National Rheumatoid Arthritis Society
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

1. It is proposed that this partial review is based on the original economic model developed by the Assessment Group in TA375. See here for the Assessment Group report. The assessment Group will update the model to address a limitation which means that currently, on progression from moderate to severe disease, patients are only modelled as having conventional DMARDs not biological DMARDs as in clinical practice. **Please comment on the proposal to use the Assessment Group model from TA375 amended as above.**
We agree that the amended model from TA375 is appropriate.

2. In order to amend the model to address the above issue the Assessment Group will need to source information on the relationship between the change in Health Assessment Questionnaire (HAQ) score and the change in disease activity (DAS28) score.

Are you aware of any data on this relationship?

We agree with the papers listed by the BSR in their submission, as follows:

Boyd TA et al *Open Rheumatol J.* 2013; 7: 58–63. 1.143 patients followed over 24 months found a significant correlation between DAS28 and HAQ all time points.

Nikiphorou E et al *Ann Rheum Dis* 2016;75:2080–2086. Evaluated the association between DAS28 *categories* and HAQ from the ERAS and ERAN databases.

Twigg S et al *J Rheumatol.* 2017 Sep; 44: 1331–1340. Correlates between DAS28 and HAQ in 1415 patients in the YEAR study.

3. In TA375 the committee identified uncertainties relating to long-term disease progression for people having conventional DMARDs and the mapping from HAQ scores to EQ-5D (health-related quality of life) utility values. It based decisions on:

- Early Rheumatoid Arthritis Study data to model disease progression with conventional DMARDs rather than assume a linear progression
- Hernandez et al (2013) to calculate EQ-5D utility values

The review paper did not find any new evidence to address these uncertainties, so it is proposed that the Assessment Group analyses also use these assumptions.

Are you aware of any new evidence in these areas?

Again, we agree with the papers put forward by the BSR in their submission as follows:

- Wolfe F et al Scale Characteristics and Mapping Accuracy of the US EQ-5D, UK EQ-5D, and SF-6D in Patients with Rheumatoid Arthritis *J Rheumatol* 2010; 37: 1615-1625

- Carreno A et al. Using HAQ-DI to estimate HUI-3 and EQ-5D utility values for patients with RA in Spain. *Outcomes Assessment* 2011;14:192-200

- Alava MH et al The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis: further validation and development of the limited dependent variable, mixture model approach. *Rheumatology* 2013;52:944-950 (*referred to above incorrectly as Hernandez*)

Since 2013:

- Pennington B Mapping from the Health Assessment Questionnaire to the EQ-5D: The Impact of Different Algorithms on Cost-Effectiveness Results *Value in Health* 2014; 17:762-771

- Nair SC et al Does disease activity add to functional disability in estimation of utility for rheumatoid arthritis patients on biologic treatment? *Rheumatology* 2016;55:94-102

- Kim H-L and Lee E-K Mapping health assessment questionnaire disability index (HAQ-DI) score, pain visual analog scale (VAS), and disease activity score in 28 joints (DAS28) onto the EuroQol-5D (EQ-5D) utility score with the KORean Observational study Network for Arthritis (KORONA) registry data *Rheumatology International* 2016;36:505–513

- Patton T et al. Mapping between HAQ-DI and EQ-5D-5L in a Chinese patient population. *Qual Life Res* 2018; 27: 2815–2822

- Dakin, H et al. Review and critical appraisal of studies mapping from quality of life or clinical measures to EQ-5D: an online database and application of the MAPS statement. *Health Qual Life Outcomes* 2018;16: 31

4. If you are the manufacturer of one of the interventions, please provide details of your product(s) including price and any confidential discounts.

Not Applicable

5. Please provide any other comments on the potential for a change in the recommendations for moderate active disease.

Our views coincide with what the BSR has written in regard to Q5 in their submission and we supported this data when it was first sent to NICE last year during our joint discussions with NICE/NHSE.

In addition, we would like to submit new data on people currently not on a biologic or other advanced therapy. In 2019, NRAS conducted a survey of people (>600) who were currently not on a biologic/advanced therapy. The paper, (main authors Dr. Patrick Kiely and Dr. Elena Nikiphorou) has been submitted for peer review. Here is the abstract: (full paper attached to this submission)

Abstract

Objectives

To reveal the everyday impact of living with RA in people not treated with advanced therapies; biologic or targeted synthetic disease modifying anti-rheumatic drugs.

Methods

People with RA, disease duration more than 2 years, not currently treated with advanced therapies, completed an on-line survey promoted by the National Rheumatoid Arthritis Society. Items covered demographics, current treatment, RA flare frequency, the Rheumatoid Arthritis Impact of Disease (RAID) tool and questions reflecting work status and ability. Descriptive and multivariable regression analyses were performed.

Results

There were 612 responses, mean age 59 years, 88% female, disease duration 2- 5 years 37.7%, 5 – 10 years 27.9%. In the last year 90% reported an RA flare, >6 flares in 23%. A RAID 'patient acceptable state' was recorded in 12.4%. Each of the seven domains were scored in the high range by >50% respondents. 74.3% scored sleep problems and 72% fatigue in the high range. A need to change working hours was reported by 70%. Multivariable analyses revealed increasing difficulties with daily physical activities, reduced emotional and physical wellbeing in the past week were all significantly associated with pain, number of flares and ability to cope ($p<0.005$). The RAID score was significantly predictive of the number of flares.

Conclusions

Patients not currently treated with advanced therapies experience profound difficulties in everyday living with RA, across a broad range of measures. We advocate that patient reported measures be used to facilitate holistic care, addressing inflammation and other consequences of RA on everyday life.

The data from this survey show all too clearly the hugely debilitating impact of RA on patients denied access to advanced therapies. By not being able to progress onto more effective therapies at an earlier stage than they might normally be able to in the course of their disease, there is a continuing, unacceptable for some, burden of disease which impacts not only on the individuals but on the resources of the NHS as indicated in the number of flares reported. In the BSR data in their submission, increasing disability in this group has been shown from observations in several studies.

We lag behind Europe in our use of advanced, targeted therapies. NG100 states quite clearly that we should treat active RA in adults with the aim of achieving a target of remission or low disease activity if remission cannot be achieved (treat-to-target). [2018] 1.2.2 *Consider making the target remission rather than low disease activity for people with an increased risk of radiological progression (presence of anti-CCP antibodies or erosions on X-ray at baseline assessment).* [2018]. This has created an anomaly between the goals of the guideline and interpretation of the individual drug guidance and pathway which derives from HTAs.

May we highlight to you the evidence base which underpins the new EULAR 2019 recommendations for the management of RA published this year (*Ann Rheum Dis*. 2020;79(6):685-699). Specifically, these latest and bang up to date recommendations include the addition of a fifth overarching principle (iv below) to the previous 4 in the 2016 recommendations:

i. Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist
ii. Treatment decisions are based on disease activity and other patient factors such as progression of structural damage, comorbidities and safety issues
iii. Rheumatologists are the specialists who should primarily care for patients with RA
iv. Patients may need multiple courses of treatment with different MOAs –no limit to number of switches
v. RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist

Given the above and with the massive change to the pricing landscape with the advent of biosimilars and subsequent drop in pricing of the anti TNF originator products and other advanced therapies, now ***must surely*** be the time to bring our treatment of people with RA in the UK up to the level of care available across most of the rest of Europe in regard to accessing the right treatment for the right patient at the right time.

6. Are there any potential equality issues that should be taken into account when considering these treatments?

Across England and Wales, just 49% of those who are disabled or have a health condition are in work. For everyone else this figure is 80% —a 31 percentage point gap. The government has set out an ambitious aim to halve this disability employment gap, supporting over a million disabled people to move into or maintain work.

We therefore agree with the BSR in their submission that many people living with RA in 'moderate' disease activity would fulfil the criteria for disability as defined in the Equality Act 2010. Some of these individuals are unable to work but with access to more appropriate treatment, a proportion would be more able to return to work. It could be argued that denying treatment to any disabled people that would enable them to work, is discriminatory.

RA disease impact in patients not treated with advanced therapies; survey findings from the National Rheumatoid Arthritis Society

Supplementary Tables

Supplementary Table 1. Sociodemographic characteristics of individuals participating in the survey.

Characteristic	**n (%) or mean, S.D.**	Missing n (%)
Age	Mean = 59, SD = 11.84 Range: 69 (Min. = 19, Max. = 88)	N/A
Gender	**Female** N=540 (88.2%) **Male** N=68 (11.1%)	4 (0.7%)
Length of time since diagnosis	**2-5 years** N=231 (37.7%) **5-10 years** N=171 (27.9%) **10+ years** N=209 (34.2%)	1 (0.2%)
Ethnicity		
White	603 (98.5%)	N/A
Mixed*	3 (0.5%)	
Black^	1 (0.2%)	
Asian[$]		
Education		
University education/ professional/vocational equivalents	262 (42.8%)	N/A
A Levels or equivalent	60 (9.8%)	
GCSE/ O level grade or equivalent	108 (17.6%)	
Vocational, NVQ, BTEC or equivalent	91 (14.9%)	
No qualifications	57 (9.3%)	
Other/Prefer not to say	34 (5.6%)	
Work		
Employed 1-39 hours per week	188 (30.7%)	N/A
Employed 40+ hours	58 (9.5%)	
Not Employed nor seeking work	49 (8.0%)	
Job seeking	10 (1.6%)	
Disabled and not able to work	79 (12.9%	
Retired	228 (37.3%)	
Geographical spread		
Southern England *(London SHA, Sough Central SHA, South East Coast SHA, South West SHA)*	228 (37.3%)	1 (0.2)
Northern England *(includes Yorkshire & the Humber)*	42 (6.9%)	
East of England SHA	71 (11.6%)	
Midlands *(includes East & West Midlands)*	84 (13.7%)	
Wales	26 (4.2%)	
Northern Ireland	10 (1.6%)	
Scotland	60 (9.8%)	

*Includes mixed: White and Asian; and any other mixed background.

^ Includes Black/Black British-Caribbean.

[$]Includes Asian/ Asian-British, Asian/ Asian British-Pakistani, Any other Asian background.

Supplementary Table 2. Participant reporting of key RA symptoms experienced in the past week.

Pain in the last week (Range 1 – 10, with 10 being indicative of extreme levels of pain)			Difficulties doing daily physical activities in the last week (Range 1 – 10, with 10 being indicative of extreme difficulties in doing daily physical activities)		
	Frequency	Valid Percent		Frequency	Valid percent
0 – No pain	30	4.9	0 – No difficulties	50	8.2
1	40	6.5	1	44	7.2
2	49	8.0	2	53	8.7
3	67	10.9	3	54	8.8
4	65	10.6	4	48	7.8
5	71	11.6	5	75	12.3
6	95	15.5	6	81	13.2
7	94	15.4	7	79	12.9
8	61	10.0	8	69	11.3
9	17	2.8	9	25	4.1
10 - Extreme pain	23	3.8	10 - Extreme difficulties	34	5.6
Missing	-	-	Missing	-	-
Total	612	100.0	Total	612	100.0
$Score < 5$	251	40.9	$Score < 5$	249	40.7
$Score \geq 5$	361	59.1	$Score \geq 5$	363	59.3
Fatigue in the last week (Range 1 – 10, with 10 being indicative of being totally exhausted)			Sleep difficulties in the last week (Range 1 – 10, with 10 being indicative of extreme difficulties sleeping in the last week)		
	Frequency	Valid Percent		Frequency	Valid percent
0 – No fatigue	26	4.2	0 – No difficulty	0	0.0
1	24	3.9	1	34	5.6
2	39	6.4	2	35	5.7
3	35	5.7	3	34	5.6
4	48	7.8	4	54	8.8
5	56	9.2	5	55	9.0
6	51	8.3	6	59	9.6
7	96	15.7	7	91	14.9
8	108	17.6	8	89	14.5
9	66	10.8	9	53	8.7
10 – Totally exhausted	63	10.3	10 - Extreme difficulties	108	17.6
Missing	-	-	Missing	-	-
Total	612	100.0	Total	612	100.0
$Score < 5$	172	28.0	$Score < 5$	157	25.7
$Score \geq 5$	440	72.0	$Score \geq 5$	455	74.3
Physical wellbeing in the last week (Range 1 – 10, with 10 being indicative of being very bad)			Emotional wellbeing in the last week (Range 1 – 10, with 10 being indicative of very bad)		
	Frequency	Valid Percent (N = 611)		Frequency	Valid percent (N = 586)
0 – Very good	32	5.2	0 – Very good	49	8.4
1	34	5.6	1	40	6.8

2	43	7.0	2	52	8.9
3	58	9.5	3	66	11.3
4	56	9.2	4	55	9.4
5	116	19.0	5	72	12.3
6	74	12.1	6	54	9.2
7	95	15.5	7	76	13.0
8	69	11.3	8	70	11.9
9	15	2.5	9	23	3.9
10 – Very bad	19	3.1	10 – Very bad	29	4.9
Missing	1	-	Missing	26	-
Total	612	100.0	Total	612	100.00
$Score < 5$	223	36.5	$Score < 5$	262	44.8
$Score \geq 5$	388	63.5	$Score \geq 5$	324	55.2

Ability to cope with their RA in the last week
(Range 1 – 10, with 10 being indicative of people feeling their ability to cope is not good)

	Frequency	Valid percent (N = 611)
0 – Very well	69	11.3
1	51	8.3
2	57	9.3
3	62	10.1
4	60	9.8
5	99	16.2
6	78	12.8
7	58	9.5
8	48	7.9
9	13	2.1
10 – Very poorly	16	2.6
Missing	1	-
Total	612	100.0
$Score < 5$	299	48.8
$Score \geq 5$	312	51.2

RA disease impact in patients not treated with advanced therapies; survey findings from the National Rheumatoid Arthritis Society

Elena Nikiphorou[1,2], Hannah Jacklin[3], Ailsa Bosworth[3], Clare Jacklin[3]*, Patrick Kiely[4,5]*

[1]Centre for Rheumatic Diseases, Department of Inflammation Biology, School of Immunology and Microbial Sciences, Faculty of Life Sciences & Medicine, King's College London

[2]Department of Rheumatology, King's College Hospital, London, UK

[3]National Rheumatoid Arthritis Society, Maidenhead, UK

[4]Rheumatology, St George's University Hospitals NHS Foundation Trust, London

[5]Institute of Medical and Biomedical Education, St George's University of London, London, UK

*Joint senior authors

Corresponding author:

Elena Nikiphorou MBBS/BSc, MD(Res), PGCME, FRCP, FHEA

King's College London,

Centre for Rheumatic Diseases,

Weston Education Centre,

SE5 9RJ,

London,

UK.

Email: enikiphorou@gmail.com

Abstract

Objectives

To reveal the everyday impact of living with RA in people not treated with advanced therapies; biologic or targeted synthetic disease modifying anti-rheumatic drugs.

Methods

People with RA, disease duration more than 2 years, not currently treated with advanced therapies, completed an on-line survey promoted by the National Rheumatoid Arthritis Society. Items covered demographics, current treatment, RA flare frequency, the Rheumatoid Arthritis Impact of Disease (RAID) tool and questions reflecting work status and ability. Descriptive and multivariable regression analyses were performed.

Results

There were 612 responses, mean age 59 years, 88% female, disease duration 2- 5 years 37.7%, 5 – 10 years 27.9%. In the last year 90% reported an RA flare, >6 flares in 23%. A RAID 'patient acceptable state' was recorded in 12.4%. Each of the seven domains were scored in the high range by >50% respondents. 74.3% scored sleep problems and 72% fatigue in the high range. A need to change working hours was reported by 70%. Multivariable analyses revealed increasing difficulties with daily physical activities, reduced emotional and physical wellbeing in the past week were all significantly associated with pain, number of flares and ability to cope ($p<0.005$). The RAID score was significantly predictive of the number of flares.

Conclusions

Patients not currently treated with advanced therapies experience profound difficulties in everyday living with RA, across a broad range of measures. We advocate that patient reported measures be used to facilitate holistic care, addressing inflammation and other consequences of RA on everyday life.

Keywords

Rheumatoid arthritis

RAID

Patient reported outcomes

Key messages:

- In established RA patients not on advanced therapies, PROMs indicate high levels of suffering.
- The rheumatoid arthritis impact of disease (RAID) acceptable state is very uncommon.
- High levels of pain, physical disability, sleep difficulties and fatigue are prominent symptoms.

INTRODUCTION

It is widely established that prompt and effective treatment in Rheumatoid Arthritis (RA) using treat-to-target (T2T) strategies(1) improves disease outcomes. A range of therapies are available, including conventional synthetic, targeted synthetic and biologic Disease Modifying Anti-Rheumatic Drugs (cs/ts/bDMARDs). The principles of T2T incorporate treatment escalation, utilising all available therapies, to achieve and maintain a chosen target, usually remission or a low disease activity state. A variety of disease activity scores are used, capturing specific objective measures of inflammation and broad patient reported subjective measures of disease impact.

The 28-joint count disease activity score (DAS28) is used in the UK to determine eligibility for advanced therapies (ts/bDMARDs). However, there is a discrepancy between the least stringent T2T outcome, a low DAS28 score (≤3.2, LDAS), and the minimum threshold of a high DAS28 score (≥5.1, HDAS) required in some guidelines to permit the use of ts/bDMARDs(2). This means that people with moderate disease activity, between these thresholds (DAS28 >3.2 and <5.1, mDAS), are not eligible for advanced therapies. Eligibility is also restricted by the NICE biologics pathway in England and Wales as it limits the maximum number of advanced therapies a patient may ever receive, denying a trial of all possible options(2). Reflecting restrictions such as these, huge variations are reported in DMARD use globally(3).

Patients with RA who have not achieved remission or at least LDAS, have poor outcomes from the consequences of unsuppressed inflammation on their joints, including function and requirement for orthopaedic surgery, and the cardiovascular consequences of accelerated atherogenesis(4–6). Yet when patients in the mDAS category receive advanced therapies they respond as well as those in HDAS and better than those remaining on csDMARDs(7,8), in terms of T2T goals of remission or LDAS and functional outcomes. This confirms that substantial benefits may be gained by treating patients in mDAS with advanced therapies.

Patient and rheumatologist perceptions of what constitutes a successful treatment outcome can differ (9), with patients using a broader definition than that provided by DAS28, leading to discordance in the understandings of disease severity between patients and physicians(9). In this large Korean survey, more than half of patients with RA thought their disease more severe than their physicians, with pain, fatigue and sleep disturbance being some of the factors associated with discordance. The widely used composite outcome scores DAS28 and the Simple Disease Activity Index (SDAI) are derived from observer, patient and laboratory assessments. Patient assessments in these scores are limited to a tender joint count and a subjective global assessment of disease. A variety of composite patient reported outcome measures (PROMs) assess the impact of RA on a

broader range of aspects of living with RA, such as the Rheumatoid Arthritis Impact of Disease (RAID), the Rheumatoid Arthritis Disease Activity Index (RADAI) and the Routine Assessment of Patient Index Data-3 (RAPID3). The RAID score is a patient derived differentially weighted seven item validated and reliable tool, sensitive to change and EULAR adopted.(10) It correlates well with RADAI, patient global measures, short form-36 (SF-36) physical and mental subscales, EQ-5D and the DAS28 score(10,11). On an individual patient level a score below 2 is deemed a patient acceptable state(12,13) and both absolute and relative minimally clinical important improvements are also defined(13).

This study focusses on the everyday impact of RA in patients not receiving advanced therapies with ts/bDMARDs. It aims to assess in detail a wide range of aspects of quality of life and everyday living using the RAID score and other measures of the impact RA. The work has been instigated by National Rheumatoid Arthritis Society (NRAS, https://www.nras.org.uk/), the UK RA patient organisation.

METHODS

Survey design and dissemination

Patients with RA were invited by NRAS to complete a survey (available from NRAS on request). This was hosted using the NRAS Health-Unlocked online peer support forum and shared more widely through NRAS social media channels including Facebook, Instagram, LinkedIn and Twitter. A landing page explained the rationale behind the survey, emphasizing the aim to understand patients' experiences of living with RA. This was followed by screening questions to identify the target population based on current therapies.

Target population

The target population was people with RA, over the age of 16, with a disease duration of 2 years or more and living in the UK. Included patients were allowed to be on analgesics, NSAIDs, corticosteroids and csDMARDs but not on advanced therapies defined as bDMARDs and tsDMARDs.

Survey components

Items recorded socio-demographic information including age, gender, ethnicity, highest educational achievement and employment status. RA specific information included; disease duration, current therapies and access to advanced therapies.

The frequency of RA flares in the last year was recorded, based on the definition: "an episode of increased RA disease activity accompanied by worsening symptoms, functional impacts, and clinical

indicators of sufficient magnitude and duration to place individuals at greater risk of joint damage and poorer outcomes when left untreated".

The impact of RA on quality of life in the last week was assessed by completion of the RAID patient reported outcome score covering seven domains: pain, functional disability, fatigue, sleep, coping/self-efficacy, physical and emotional well-being. Each of the 7 domains is scored on an eleven-integer numerical rating scale (NRS), with 0 representing a good low activity score and 10 a high severe activity score. A patient acceptable state is defined as a RAID score of <2. In the absence of guidance, we arbitrarily classified the NRS scores for each individual domain into the following ranges (low range 0 – <5, high range ≥5, mild 0-2, severe 8-10) to gain an idea which domains scored particularly poorly or well.

Difficulties at work were measured using a selection of questions extracted from the Work Productivity and Activity Impairment (WPAI) questionnaire (http://oml.eular.org/sysModules/obxOML/docs/id_98/WPAI-GH_English_US_V2.pdf).

Statistical analysis

The SPSS statistical package 26 was used for all analyses including calculation of the total RAID score. A combination of descriptive statistics alongside univariable and multivariable regression analyses, were undertaken to explore associations between key independent variable outcomes. Outcome variables were examined in separate models and included; pain in the last week, ability to cope with their RA in the last week and the number of RA flares experienced in the past 12 months.

A stepwise backwards regression was run for each including all possible 'predictor' variables, which were selected for their potential to influence each of the outcome variables. Predictor variables were then examined for evidence of collinearity, before being scrutinised for individual contribution and significance. Age and gender were maintained in the models as an a priori decision.

RESULTS

612 patients completed the survey. The mean age was 59 years, 88% were female and 98.5% were of white ethnicity. RA disease duration was 2- 5 years in 37.7%, 5 – 10 years in 27.9% and over 10 years in 34.2%. Full sociodemographic characteristics are shown in Supplementary Table 1.

RA treatment

529 patients (86.4%) were taking at least 1 csDMARD and 15.4% were on corticosteroids. csDMARDs were used as monotherapy in 262 patients (42.8%) and as combination therapy in 267 patients (43.6%). The majority of patients were on methotrexate (61%) followed by hydroxychloroquine

(37%). Other medication included sulphasalzine (30%), leflunomide (9%) and azathioprine (0.5%). The most frequent combination csDMARD therapy regime was methotrexate with hydroxychloroquine (n= 151, 25%) followed by methotrexate and sulfasalazine (n=95, 16%).

76% of respondents indicated that advanced therapies had not been offered or discussed with them. Of these, 8% reported not being eligible for these therapies. 3% reported that they'd experienced side effects implying previous use of at least one advanced therapy, and only 0.3% reported that they were not on advanced therapies because they were in remission.

RA flares

In the last 12 months 140 (23%) respondents indicated having experienced six or more flares, 111 (18%) reported three flares while 60 (10%) indicated that they'd had no flares. Of those who'd experienced flares, 215 (39%) indicated that on average a flare lasted 3-7 days and 73 (13%) indicated that it lasted for more than 5 weeks.

Impact of disease in the last week

Responses to all seven RAID domains were completed in the majority of cases (N=587) with one domain missing in 24 additional cases. The missing domain was 'emotional well-being' in all 24 cases, and was substituted with the mean of the submitted responses to the other six domains. A total RAID score was therefore calculated for 611 respondents. The mean was 4.79 (SD 2.04, range 0.24-9.10). A RAID score below 2, deemed a patient acceptable state(12,13), was recorded in 12.4% of participants.

Table 1 shows for each domain the proportion of respondents scoring low range (<5), high range (≥5), mild (0-2) and severe (8-10) scores. In each of the seven RAID domains over 50% of respondents recorded a score in the high range in the last week. Sleep and fatigue were the domains with the highest proportion of respondent scores in the high range and severe categories, with 74.3%/40.8% and 72%/38.7% of respondents scoring in these categories respectively. Ability to cope was the lowest scoring domain, with least disability amongst respondents, however even here 51.2% scored in the high range and only 28.9% in the mild range.

The full spread of scores in each domain is shown in Supplementary Table 2.

Impact on occupation

A total of 371 respondents answered questions on current employment. 57 of these (15%) reported 7 days or more off work in the last 6 months. However, 427 individuals responded to a question assessing whether they'd had to change their working hours due to their condition, indicating a

larger number of participants had been employed at some point since RA diagnosis. Of these, 298 (70%) indicated that their RA had caused them to change their working hours.

Stepwise Backwards regression analyses

In multivariable analyses (Table 2), for every unit increase in the scores on daily physical activities and on emotional well-being in the past week, there was a significant increase in pain experienced in the past week and worsening in the ability to cope ($p<0.005$). Increasing difficulties with daily physical activities, reduced emotional and physical wellbeing in the past week were all significantly associated with all three outcomes of pain, number of flares (in the last 12 months) and ability to cope ($p<0.005$). The RAID score was significantly predictive of the number of flares in age and gender adjusted models, whereby for every unit increase in the score, there was an increase in the number of flares by 0.5 units (b 0.52;95%CI 0.45-0.58).

DISCUSSION

This survey, led by NRAS, has focussed on the impact of disease in patients with established RA currently not receiving advanced therapies. It shows that RA flares are extremely common with 90% experiencing at least one flare and nearly a quarter reporting 6 or more flares in the last year. Only 12.4% of respondents were currently in a patient acceptable state, as defined by a total RAID score <2. The high impact of RA on everyday life is further emphasised by the finding that in all seven domains >50% respondents recorded scores in the high range, indicating a significant burden in the last one week. This is supported by impact on work data from the survey, with 70% of respondents reporting a change in working hours due to their RA. Difficulties with daily physical activities and worsened physical and emotional well-being were significantly associated with higher pain, greater number of flares and worsened ability to cope. Thus, across all assessed PROMs, RA patients currently not taking advanced therapies experience an inter-related burden of adverse outcomes from their disease.

These findings question the use of DAS28 or SDAI as the only measures to direct treatment escalation decisions in T2T models of care. The patient global component does not reveal the breadth and severity of impact of RA on patients' everyday lives that measures such as RAID and composite PROM tools assess. In a holistic model of care these important measures of quality of life should be recorded and addressed, as advocated by the National Institute for Health and Care Excellence (NICE)(14). In support of our study, recent data from the Rheumatoid Arthritis Medication Study (RAMS) demonstrate that despite a 'satisfactory' rating of their condition, early RA patients with high PROM scores are less likely to respond to therapy, calling for high vigilance to optimize care and outcomes(15).

Although this survey specifically targeted patients not on advanced ts/bDMARDs, it was not possible to determine the current DAS28 score or the treatment history for each patient. The minimum disease duration of 2 years means that it is likely that those with HDAS (i.e. DAS28 >5.1) up to that time point would have already been treated with advanced therapies and therefore excluded from the survey. Some may have been in the HDAS range and not on advanced therapies because they were about to start or were in transition to a second or third b/tsDMARD. However only 3% indicated previous adverse events to bDMARDs, suggesting very few might have been in a transition state between advanced therapies. We conclude that it is likely that the majority of respondents had never received these therapies, and in UK practice this means they would have had a DAS <5.1. regardless of current DAS28 score, mDAS or better, these findings indicate a very high impact of RA on everyday quality of life. The dominance of fatigue and sleep domains recording the greatest disability is also supported by previous studies, including patients who were in remission or LDAS(16–19).

The strengths of this survey are its size with 612 respondents, with age and gender as expected for an established RA population, and its ecological validity with broad geographical reach across the UK, making findings largely generalisable. Similarly, the frequency of csDMARD use is reflective of common treatment approaches in the UK. Limitations of this study include the survey-based nature of data collection at a single time point, and the ethnicity being primarily white, limiting generalizability of findings to other ethnic groups.

In conclusion, this study highlights the extensive impact RA exerts on everyday quality of life in patients not treated with advanced therapies, extending previous work demonstrating the poor long-term function and orthopaedic outcomes in similar patients. PROMs represent a valuable source of information to facilitate holistic care, combining suppression of inflammation with minimisation of the impact of disease on important aspects of daily life, including fatigue, sleep, and well-being. We advocate routine collection of PROMs in daily practice, to provide insights into disease severity and impact otherwise not captured in composite scores such as DAS28.

Funding

NRAS

Acknowledgements

We are indebted to all patients who took part in this survey.

Contributors

EN: Data analysis overview, data interpretation, manuscript drafting and revision

HJ: Data analysis and interpretation, manuscript revision

AB, CJ: Conception of work, data interpretation, manuscript revision

PK: Data interpretation, manuscript drafting and revision

Competing interests

None declared

Ethics Approval

None required

Twitter

@pkiely500

@ElenaNikiUk

@AilsaBosworth1

@NRAS_UK

@Clare_NRAS

REFERENCES:

1. Smolen JS. Treat-to-target as an approach in inflammatory arthritis. Curr Opin Rheumatol [Internet]. 2016 May [cited 2017 Dec 7];28(3):297–302. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27027815

2. NICE TA375. No Title [Internet]. Available from: https://www.nice.org.uk/guidance/ta375

3. Nikiphorou E, Galloway J, Riel P van, Yazici Y, Haugeberg G, Ostor A, et al. The spectrum of early rheumatoid arthritis practice across the globe: Results from a multinational cross sectional survey. Clin Exp Rheumatol [Internet]. 2017 May 1 [cited 2020 Sep 6];35(3):0477–83. Available from: https://pubmed.ncbi.nlm.nih.gov/28134086/

4. Nikiphorou E, Norton S, Young A, Carpenter L, Dixey J, Walsh DA, et al. Association between rheumatoid arthritis disease activity, progression of functional limitation and long term risk of orthopaedic surgery: Combined analysis of two prospective cohorts support EULAR Treat to Target (T2T) DAS thresholds. Ann Rheum Dis. 2016 Mar 15;75(12).

5. Conaghan PG, Hensor EMA, Keenan AM, Morgan AW, Emery P. Persistently moderate DAS-28 is not benign: Loss of function occurs in early RA despite step-up DMARD therapy. Rheumatology [Internet]. 2010 Jun 11 [cited 2020 Sep 7];49(10):1894–9. Available from: https://pubmed.ncbi.nlm.nih.gov/20542894/

6. Kiely P, Walsh D, Williams R, Young A. Outcome in rheumatoid arthritis patients with continued conventional therapy for moderate disease activity--the early RA network (ERAN). Rheumatology (Oxford) [Internet]. 2011 May [cited 2015 Aug 16];50(5):926–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21169343

7. Hyrich KL, Deighton C, Watson KD, Symmons DPM, Lunt M. Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity. Rheumatology (Oxford) [Internet]. 2009 Oct 1 [cited 2015 Dec 22];48(10):1323–7. Available from: http://rheumatology.oxfordjournals.org/content/48/10/1323.abstract?ijkey=af1791448abee27282ab49da8d7883f0001f930e&keytype2=tf_ipsecsha

8. Kotak S, Mardekian J, Horowicz-Mehler N, Shah A, Burgess A, Kim J, et al. Impact of Etanercept Therapy on Disease Activity and Health-Related Quality of Life in Moderate Rheumatoid Arthritis Patients Population from a National British Observational Cohort. Value Heal [Internet]. 2015 Sep 1 [cited 2020 Sep 15];18(6):817–23. Available from: https://pubmed.ncbi.nlm.nih.gov/26409609/

9. Soo-Kyung Cho, Yoon-Kyoung Sung, Chan-Bum Choi, So-Young Bang, Hoon-Suk Cha, Jung-Yoon Choe, et al. What factors affect discordance between physicians and patients in the global assessment of disease activity in rheumatoid arthritis? Mod Rheumatol [Internet]. 2017;27(1):35–41. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emex&NEWS=N&AN=610260447

10. Gossec L, Paternotte S, Aanerud GJ, Balanescu A, Boumpas DT, Carmona L, et al. Finalisation and validation of the rheumatoid arthritis impact of disease score, a patient-derived composite measure of impact of rheumatoid arthritis: a EULAR initiative. Ann Rheum Dis [Internet]. 2011 Jun [cited 2017 May 4];70(6):935–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21540201

11. Salaffi F, Di Carlo M, Vojinovic J, Tincani A, Sulli A, Soldano S, et al. Validity of the rheumatoid arthritis impact of disease (RAID) score and definition of cut-off points for disease activity states in a population-based European cohort of patients with rheumatoid arthritis. Jt Bone

Spine [Internet]. 2018 May 1 [cited 2020 Sep 7];85(3):317–22. Available from: https://pubmed.ncbi.nlm.nih.gov/28549945/

12. Dougados M, Brault Y, Logeart I, van der Heijde D, Gossec L, Kvien T. Defining cut-off values for disease activity states and improvement scores for patient-reported outcomes: The example of the Rheumatoid Arthritis Impact of Disease (RAID). Arthritis Res Ther [Internet]. 2012 May 30 [cited 2020 Sep 7];14(3). Available from: https://pubmed.ncbi.nlm.nih.gov/22647431/

13. Salaffi F, Carotti M, Gutierrez M, Di Carlo M, De Angelis R. Patient Acceptable Symptom State in Self-Report Questionnaires and Composite Clinical Disease Index for Assessing Rheumatoid Arthritis Activity: Identification of Cut-Off Points for Routine Care. Biomed Res Int [Internet]. 2015 [cited 2020 Sep 7];2015. Available from: https://pubmed.ncbi.nlm.nih.gov/26167506/

14. NICE Annual Review [Internet]. Available from: https://www.nice.org.uk/sharedlearning/developing-an-annual-review-clinic-for-people-with-rheumatoid-arthritis

15. Gwinnutt JM, Hyrich KL, Lunt M, Barton A, Verstappen SMM. Long-term outcomes of patients who rate symptoms of rheumatoid arthritis as “satisfactory.” Rheumatology (Oxford) [Internet]. 2020 Aug 1 [cited 2020 Sep 7];59(8):1853–61. Available from: https://pubmed.ncbi.nlm.nih.gov/31729526/

16. Carpenter L, Barnett R, Mahendran P, Nikiphorou E, Gwinnutt J, Verstappen S, et al. Secular changes in functional disability, pain, fatigue and mental well-being in early rheumatoid arthritis. A longitudinal meta-analysis [Internet]. Vol. 50, Seminars in Arthritis and Rheumatism. W.B. Saunders; 2020 [cited 2020 Sep 7]. p. 209–19. Available from: https://pubmed.ncbi.nlm.nih.gov/31521376/

17. Zhang L, Shen B, Liu S. Rheumatoid arthritis is associated with negatively variable impacts on domains of sleep disturbances: evidence from a systematic review and meta-analysis. Psychol Heal Med [Internet]. 2020 [cited 2020 Sep 7]; Available from: https://pubmed.ncbi.nlm.nih.gov/32420757/

18. Van Steenbergen HW, Tsonaka R, Huizinga TWJ, Boonen A, Van Der Helm-Van Mil AHM. Fatigue in rheumatoid arthritis; A persistent problem: A large longitudinal study. RMD Open [Internet]. 2015 Jan 1 [cited 2020 Sep 7];1(1). Available from: https://pubmed.ncbi.nlm.nih.gov/26509063/

19. Mistry J, Sharif M, Prideaux A, Smith C, Sumbwanyambe M, Sibley M, et al. Use of rheumatoid arthritis impact of disease (RAID) in routine care; identification of DAS28 remission and unmet patient reported outcomes. Rheumatol Adv Pract [Internet]. 2020 Apr 27 [cited 2020 Sep 7];4(2). Available from: https://pubmed.ncbi.nlm.nih.gov/32685911/

Table 1

Summary scores across seven patient reported outcomes in the past week

Domain	Score <5 (%) Low range	Score ≥5 (%) High range	Score 0 – 2 (%) Mild	Score 8-10 (%) Severe
RAID total score	**50.2**	**49.8**	**12.4**	**4.6**
Pain	**40.9**	**59.1**	**19.4**	**16.6**
Functional disability	**40.7**	**59.3**	**24.1**	**21.0**
Fatigue	**28.0**	**72.0**	**14.5**	**38.7**
Sleep	**25.7**	**74.3**	**11.3**	**40.8**
Physical well-being	**36.5**	**63.5**	**17.8**	**16.9**
Emotional well-being	**44.8**	**55.2**	**24.1**	**20.7**
Coping	**48.8**	**51.2**	**28.9**	**12.6**

*% respondents with RAID total score 0 - <2, defined as a patient acceptable state

Table 2. Multivariable models with pain, number of RA flares and ability to cope as dependent outcomes.

	MODEL 1: **Pain in the last week**	**MODEL 2:** **Number of RA flares experienced in the last 12 months**	**MODEL 3:** **Ability to cope with their RA in the last week**
	Coefficients (95% CI)	Coefficients (95% CI)	Coefficients (95% CI)
	N = 584	N = 607	N = 393
Predictor variables			
Gender	-.120 (-.445, .206)	.040 (-.372, .452)	.039 (-.397, .476)
Age	-.009 (-.018, .000)	-.009 (-.020, .002)	.020*** (.008, .031)
Number of RA flares experienced in the last 12 months	.167*** (.103, .230)	-	-
DMARDs: Take Leflunomide	-	.499** (.053, .945)	-
Pain in the last week	-	.302*** (.222, .381)	-
Difficulties with daily physical activities in the last week	.474*** (.403, .545)	-	.323*** (.234, .412)
Physical wellbeing in the last week	.188*** (.104, .272)	.154*** (.072, .237)	.206*** (.098, .314)
Emotional wellbeing in the last week	-.068** (-.129, -.006)	-	.336*** (.258, .414)
Ability to cope with their RA in the last week	.130*** (.056, .204)	-	-
Model information			
Model fit	0.000***	0.000***	0.000***
R	.876	.574	.861
R^2	.767	.329	.741

*** p<0.005; ** p<0.05 Other variables adjusted for in the models, included difficulties with working with the hands, DMARD use and feeling that RA is controlled enough to allow daily life. The R value represents the simple correlation. The R^2 value indicates how much of the total variation in the dependent variables, can be explained by the independent variable(s).

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Targeted submission

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Your name	[redacted]
Organisation name	British Society for Rheumatology
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

1. It is proposed that this partial review is based on the original economic model developed by the Assessment Group in TA375. See here for the Assessment Group report. The assessment Group will update the model to address a limitation which means that currently, on progression from moderate to severe disease, patients are only modelled as having conventional DMARDs not biological DMARDs as in clinical practice.

Please comment on the proposal to use the Assessment Group model from TA375 amended as above.

We agree that the amended model from TA375 is appropriate.

2. In order to amend the model to address the above issue the Assessment Group will need to source information on the relationship between the change in Health Assessment Questionnaire (HAQ) score and the change in disease activity (DAS28) score.

Are you aware of any data on this relationship?

Boyd TA et al *Open Rheumatol J.* 2013; 7: 58–63. 1.143 patients followed over 24 months found a significant correlation between DAS28 and HAQ all time points.

Nikiphorou E et al *Ann Rheum Dis* 2016;75:2080–2086. Evaluated the association between DAS28 *categories* and HAQ from the ERAS and ERAN databases.

Twigg S et al *J Rheumatol.* 2017 Sep; 44: 1331–1340. Correlates between DAS28 and HAQ in 1415 patients in the YEAR study.

3. In TA375 the committee identified uncertainties relating to long-term disease progression for people having conventional DMARDs and the mapping from HAQ scores to EQ-5D (health-related quality of life) utility values. It based decisions on:

- Early Rheumatoid Arthritis Study data to model disease progression with conventional DMARDs rather than assume a linear progression
- Hernandez et al (2013) to calculate EQ-5D utility values

The review paper did not find any new evidence to address these uncertainties, so it is proposed that the Assessment Group analyses also use these assumptions.

Are you aware of any new evidence in these areas?

We are aware of the following:

- Wolfe F et al Scale Characteristics and Mapping Accuracy of the US EQ-5D, UK EQ-5D, and SF-6D in Patients with Rheumatoid Arthritis *J Rheumatol* 2010; 37: 1615-1625

- Carreno A et al. Using HAQ-DI to estimate HUI-3 and EQ-5D utility values for patients with RA in Spain. *Outcomes Assessment* 2011;14:192-200

- Alava MH et al The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis: further validation and development of the limited dependent variable, mixture model approach. *Rheumatology* 2013;52:944-950 (*referred to above incorrectly as Hernandez*)

Since 2013:

- Pennington B Mapping from the Health Assessment Questionnaire to the EQ-5D: The Impact of Different Algorithms on Cost-Effectiveness Results *Value in Health* 2014; 17:762-771

- Nair SC et al Does disease activity add to functional disability in estimation of utility for rheumatoid arthritis patients on biologic treatment? *Rheumatology* 2016;55:94-102

- Kim H-L and Lee E-K Mapping health assessment questionnaire disability index (HAQ-DI) score, pain visual analog scale (VAS), and disease activity score in 28 joints (DAS28) onto the EuroQol-5D (EQ-5D) utility score with the KORean Observational study Network for Arthritis (KORONA) registry data *Rheumatology International* 2016; 36:505-513

- Patton T et al. Mapping between HAQ-DI and EQ-5D-5L in a Chinese patient population. *Qual Life Res* 2018; 27: 2815–2822

- Dakin, H et al. Review and critical appraisal of studies mapping from quality of life or clinical measures to EQ-5D: an online database and application of the MAPS statement. *Health Qual Life Outcomes* 2018;16: 31

We consider the choice of methodology chosen by the Assessment group to be critical as emphasised by Pennington et al in 2014.

4. If you are the manufacturer of one of the interventions, please provide details of your product(s) including price and any confidential discounts.

N/A

5. Please provide any other comments on the potential for a change in the recommendations for moderate active disease.

NICE Guideline NG 100 recommends that patients with rheumatoid arthritis (RA) should be treated to a target of remission or low disease activity in all patients. In those who fail conventional synthetic disease modifying anti-rheumatoid drugs (csDMARDs) and have a disease activity score (DAS28) >5.1 TA375 recommends biologic DMARDs (bDMARDs). In those with persistent moderate disease with a DAS28 >3.2 and ≤ 5.1, TA375 did not approve bDMARDs. However, patients with persistent moderate disease have increasing disability from observations in several studies:

- Conaghan and colleagues[1] found that even over a 6 month period, up to 25% of those with moderate disease had progressive disability.
- The Early Rheumatoid Arthritis Study[2] (ERAS) is a multicentre inception cohort which recruited 1,465 patients with early RA (<2 years disease duration, no prior csDMARD) between 1986 and 1999 from nine hospitals in England, followed yearly for up to 25 years (median follow-up 10 years). The dataset recorded HAQ values of patients at baseline, 6 months, and yearly from year 1 to year 15. We commissioned a detailed analysis of the database. We analysed patients who would be eligible for a biologic drug from TA375 compared with those with persistently moderate disease (patients who had failed methotrexate or at least two non-methotrexate DMARDs or at least one combination DMARD). For those patients who received a TNF inhibitor during the study, only data up to the year prior to the prescription of the TNFi was included in the analysis. There were 868 patients who had a mean DAS28 in the moderate range (119 patients of these patients had a DAS28 that was never >5.1 - 13% of those not in low disease state or remission). In the whole ERAS dataset, 602 patients had high HAQ progression, defined as an annual progression rate ≥0.06. Of these 602 patients, 319 (53%) had moderate RA with a mean DAS28 ≥3.2 and ≤5.1. Therefore approximately a third (36.8%) of all moderate patients had high HAQ progression.
- In the Early Rheumatoid Arthritis Network (ERAN) study, Kiely and colleagues[3] found that only 52% of 170 patients with moderate disease achieved a Health Assessment Questionnaire score (HAQ) < 1.25 after 2 years despite csDMARDs, compared with 79% of 161 patients who had low disease activity or remission.
- In a further analysis of the ERAS and ERAN database, Nikiphorou and colleagues[4] found significant progression over time of HAQ independent of whether the DAS score was at the higher or lower part of the moderate range. However, those in the higher range required more orthopaedic surgery.
- A recent meta-analysis of 'moderate' RA by Edwards and colleagues[5] concluded that certain factors predicted a worse radiographic, DAS or

functional outcome including a DAS towards the upper moderate range and CCP positivity.

Patients with moderate disease have a similar response to treatment with TNFi compared with patients with severe disease.

- In a review of the BSR biologics register Hyrich and colleagues[6] evaluated the response to a TNF inhibitor (TNFi) in 224 patients with moderate disease compared with 4,687 with severe disease and found the magnitude of improvement in HAQ was similar. They concluded that improvement in HAQ score 12 months after start of anti-TNF therapy was not dependent on baseline DAS28 scores suggesting that substantial benefits may also be gained by treating those with moderately active disease despite standard DMARD therapy.
- A more recent study evaluated a total of 1,754 patients with moderate RA in the BSR biologics register[7]: 211 of those who had received etanercept were compared with 1,543 who had only received csDMARDs. Those treated with etanercept at baseline had more work disability and tended toward a higher DAS28 score but treatment led to a greater reduction in DAS28, HAQ and Health Related Quality of Life (derived from HAQ and SF36 scores); disease remission occurred more often with less progression with the TNFi confirming the benefit of treating those with moderate disease.

These data demonstrate that without access to advanced therapies such as TNFi, many patients with moderate disease will have progressive disease with increasing morbidity.

In their paper discussing the health economics of TA375, Stevenson and colleagues[8] stated: "Exploratory analyses indicate that if the price of bDMARD (excluding Rituximab) were reduced by 50%, the mean ICER would decline to £24,500 for patients with severe RA and £31,500 for patients with moderate to severe RA" i.e. just above the upper limit of the NICE threshold for innovative technologies. With the reduction in price of TNF inhibitors following the introduction of biosimilar compounds, the ICERs for moderate disease will now fall under the £30,000/QALY threshold.

References

1. Conaghan PG et al *Rheumatology* 2010;49:1894–1899
2. Jayakumar K et al *Rheumatology* 2012;51:169-75
3. Kiely P et al *Rheumatology* 2011;50:926–31
4. Nikiphorou E et al *Ann Rheum Dis* 2016;75:2080–2086
5. Edwards CJ et al *Rheumatol Adv Pract.* 2019;3:rkz002
6. Hyrich KL et al *Rheumatology* 2009;48:1323–1327
7. Kotak S et al. *Value in Health* 2015;18:817-23

8. Stevenson M et al *J Rheumatol* 2017;44:973-980

6. Are there any potential equality issues that should be taken into account when considering these treatments?

All those with 'moderate' RA who would benefit from biologic therapies would fulfil the criteria for disability as defined in the Equality Act 2010. Most of these individuals are unable to work but with treatment the majority would be able to return to work. It could be argued that denying treatment to the disabled that would enable them to work is discriminatory.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Frank McKenna

Name of your organisation BSR

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **YES**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **Nominated Expert by BSR**
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
Nil

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

I wrote the BSR response submitted recently for this process. I do not have any other additional comments.
Regards
Frank McKenna

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Peter Taylor

Name of your organisation University of Oxford and Oxford University Hospitals NHS Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? I am an honorary consultant rheumatologist for Oxford University Hospitals NHS Trust
-
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Rheumatoid arthritis is treated initially with conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) (for example, methotrexate, sulphasalazine, hydroxychloroquine and leflunomide) either as monotherapy or in combination. Methotrexate is generally one of the first csDMARDs used unless there are contraindications or intolerance/toxicity. If the patient fails to attain an adequate response, namely to reach a remission or low disease activity state by a composite score of disease activity, they should advance under **the supervision of a specialist in a secondary care setting** to an approved targeted therapy which could be a biologic or a JAK inhibitor. However, for two decades, NICE have denied access to such advanced therapies for our patients unless they are assessed to be in high disease activity by a composite score such as DAS28 $\geq$5.1. The technologies under consideration are all thoroughly validated and highly efficacious therapeutics in clinical trials and in abundant "real-world" evidence. But clinical efficacy across populations of people living with rheumatoid arthritis is highly heterogeneous. In acknowledgement of this, the most contemporary and thoroughly evidenced based management recommendations are those of the European League Against Rheumatism (EULAR) which introduced a new overarching principle in their most recent update which states that "Patients may need multiple courses of treatment with different MOAs –no limit to number of switches" (*Ann Rheum Dis*.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

2020;79(6):685-699). The current and many previous iterations of fully evidence based **EULAR recommendations have also stressed that a patient with a DAS28 > 3.2, ie in moderate disease activity and with poor prognostic features, should have access to an advanced therapy**. Therefore, the current NICE recommendations for management of RA and TA375 been out of step with European (and North American) recommendations for very many years. The EULAR recommendations are exemplary and underpinned by a number of systematic literature reviews which fully explore the available and pertinent evidence base.

There is a variation in use of the current technology under appraisal across the UK because separate CCGs choose to interpret current NICE TA375 recommendations differently. And in the worst scenario, such as in my hospital trust CCG, the interpretation is that after failing to respond to three different advanced therapies that no further advanced therapies will be reimbursed. This effectively condemns the patient to a life of chronic pain and varying degrees of disability and very often to the comorbidities associated with long term steroid and opiate use.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The technology under appraisal has been extensively tested over more than a decade in both clinical trials and in clinical practice with unequivocal evidence of beneficial (and often transformative) outcomes in terms of clinical symptoms and

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

signs, mental health (Kekow J, et al. Rheumatology (Oxford) 2011;50:401–9), inhibition of structural damage and preservation or improvement in function, reduced mortality (Ziadé N, *et al. J Rheumatol* 2008;35:1950–7), improved employment (both presenteeism and absenteeism; Radner H, et al. Arthritis Res Ther 2014;16:R56; Linde L, et al. J Rheum 2010;37:285–90; Kim D, et al. J Rheum 2017;44:1112–17;Hallert E, *et al. Rheumatology* 2012;51:338–46), reduced orthopaedic surgery over time (Nikiphorou E, et al. Ann Rheum Dis 2016;75:2080–6), and overall improvement in quality of life as well as reducing the overall costs of treating rheumatoid arthritis (Curtis JR, et al. Pharmacoepidemiol Drug Saf 2017;26:310–19). The technology used in clinical care has all the advantages that have been demonstrated in clinical trials and is used in the same patient phenotypes that have been tested in trials (methotrexate inadequate responders; other csDMARD inadequate responders and biologic inadequate responders) with the exception that access is restricted to high disease activity under current NICE recommendations.

All the therapies under consideration have potential adverse effects although the overall benefit:risk ratio is highly favourable. Non-serious infectious complications are among the most common and serious infections occur within the range of 4-6/100 patient years of exposure. Rheumatologists are very familiar with management strategies to mitigate risks and intervene rapidly if they arise. Overall, the biologic DMARDs have proven to be remarkably safe and greatly enhance the quality of life of people living with rheumatoid arthritis when these agents can be used optimally over a lifetime of the evolution of the disease.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

The current NICE guidance which the present MTA seeks to update has undoubtedly had an adverse impact on people with disabilities related to moderate rheumatoid arthritis over the last two decades. Such adverse impacts range from premature mortality through preventable work disability, joint destruction and need for arthroplasty through a variety of impacts on quality of life. If the current appraisal permits access of these advanced therapies to people with moderately active rheumatoid arthritis it will help redress the inequity of the last generation and could not, in my view, disadvantage a group of people protected by the equality legislation.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Published data in UK patients with a DAS28 of 3.2–5.1 (the moderate disease activity range of relevance to the current MTA) indicate that after 1 year of treatment, the likelihood of achieving a target low DAS28 <3.2, or a low HAQ, at Years 2 or 3 is poor in a routine care setting by adding or switching between csDMARDs (Kiely P, et al. Rheumatology (Oxford) 2011;50:926–31). This has important and highly detrimental implications for people living with rheumatoid arthritis whose current access to advanced therapies is disallowed by NICE recommendations that have preceded the current MTA review.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

In my view, existing infrastructure would be sufficient to implement possible guidance on this technology with the result that over the medium to long term it will reduce the burden of care for patients with rheumatoid arthritis who will enjoy a greatly improved overall health, require few orthopaedic interventions, and have better employment opportunity and quality of life.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

Patient expert statement

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Thank you for agreeing to give us your views on these technologies and their possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

NICE National Institute for Health and Care Excellence

1.Your name Ailsa Bosworth	
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	National Rheumatoid Arthritis Society

4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your	☐ I have personal experience of the condition ☐ I have personal experience of the technologies being appraised ☐ I have other relevant personal experience. Please specify what other experience:

statement? (please tick all that apply)	☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I've lived with severe, refractory inflammatory polyarthritis, originally diagnosed as RA, for 40 years. If someone had told me when I was diagnosed what I would be experiencing during the next 40 years and beyond, I would have been absolutely terrified and probably become quite depressed in spite of the fact that I am a positive and glass half full person. I have had 20 operations, so far including bi-lateral ankle replacements, bi-lateral knee replacements, bi-laterial hip replacements, bi-lateral elbow replacements, neck fusion, bi-lateral wrist fusion and have lost the useful sight in my right eye due to having uveitis as a consequence of the RA. I experience regular levels of pain which would cause most people to take to their beds. Fatigue and insomnia are regular symptoms in addition to the pain. I have to use a wheelchair for distances longer than about 1000 yards. I have significant disability and mobility issues and am very dependent on my husband for daily activity assistance, although I can get up, shower and dress without assistance (thank God). This disease is heterogenous but for most people pain and fatigue are the most difficult symptoms to live with. Despite the above I have worked all my life and continue to work. I wouldn't wish RA on my worse enemy, it is a truly horrible disease. Carers have to do a lot generally, my husband does all the physical stuff around the house including the cooking, although I love cooking but can no longer do that as the consequences on my feet and ankles are too great.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Without the advent of biologics (I'm on my 9th advanced therapy switch – I've gone back onto the only TNF which seems to be able to best control my joints) which I've been on for the last 20 years, my life has literally been saved. Without my TNF I would be unable to work and would probably be permanently wheelchair bound. Actually I can't bear to think how awful life would be without effective medication. I've had long periods in the last 20 years when I've switched treatments to try and get better control of joints or eyes and the drug just hasn't worked which generally means I have to resort to 30 mg. day of oral steroids just to try and get sufficient pain relief to get out of bed. I have to admit to experiencing many occasions when all I feel is despair but when these happen, I work hard to get myself out of it – as I said I am always

	hopeful and always optimistic in spite of the RA!
10. Is there an unmet need for patients with this condition?	Oh my goodness yes. We need people to be able to access effective medication at an earlier stage than is currently enabled by NICE guidance and we need more and better treatments for the 7-8 % of people with refractory disease like me. Also many drugs lose efficacy over time and you need to have something to be able to move onto, especially if you are diagnosed young as I was. Whilst we certainly have a vastly improved armamentarium of treatments since the advent of biologics in 1999, and you could be forgiven if you are not involved in rheumatology for thinking that RA was sorted, it isn't.
Advantages of the technologies	
11. What do patients or carers think are the advantages of the technologies?	When it comes to impact on individual's lives, the advantages are simply vast and extensive. These technologies have literally given people their lives back when csDMARDs are not fully effective at controlling disease activity. We know also from the BSRBR work that TNFs reduce risk of cvd which is considerably elevated in RA, their impact can pull people out of depression and anxiety due to the pain relief. They enable people to keep working and keep financially independent instead of having to rely on state benefits. All of these individual benefits also benefit the NHS because they mean people stay well for longer and are not using precious NHS resources to the same extent. We've been able to get rid of rheumatology inpatient beds and rheumatology wards and surgery has reduced. Hopefully we won't see patients like me in future years because when DMARDs fail, hopefully people will be able to move onto advanced technologies sooner, thus preventing joint destruction, surgery and greater levels of disability.
Disadvantages of the technologies	
12. What do patients or carers think are the disadvantages of the technologies?	To be honest I can't really think of any – sadly as with me, they don't always work and you risk further joint damage in the wait to find a drug that works – hopefully the research into personalised medicine will help with this problem in due course.

Patient population	
13. Are there any groups of patients who might benefit more or less from the technologies than others? If so, please describe them and explain why.	Any patient who is not doing well on cs DMARDs has the potential to benefit from these technologies. However, there are patients who may have had cancer in recent years for whom the technologies may not be suitable as a result but I believe the guidance around this issue has changed or is changing as a consequence of years of using these drugs. There may be other medcal reasons why some patients may not benefit or be allowed to have these drugs.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technologies?	I think COVID has revealed that some BAME communities have clearly not had access to equal care, opportunity and treatment but that is perhaps a wider issue than just in relation to this MTA review.
Other issues	
15. Are there any other issues that you would like the committee to consider?	I think that the paper submitted with the NRAS organisation submission revealing new real world data on people currently not on a biologic or other advanced therapy from the survey conducted by NRAS in 2019 shows all too clearly that people who don't currently meet the eligibility criteria of a DAS of >5.1 do worse in the long term than people who meet the criteria and progress successfully to a biologic treatment.

Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • RA is a dreadful disease and has a massive impact on the lives of those and their families who live with it • RA is a very heterogenous disease and even with the great drugs we now have, there remains unmet need • The NRAS survey shows all too clearly the burden of those whose disease activity remains under the 5.1 threshold • The landscape is now right to give access to those with moderate disease access to these technologies • Even so called moderate disease has a massive, negative impact on quality of life	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

Patient expert statement

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Thank you for agreeing to give us your views on these technologies and their possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

NICE National Institute for Health and Care Excellence

1.Your name	**Teresa Shakespeare-Smith**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	National Rheumatoid Arthritis Society (NRAS)

4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't ☒ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your	☒ I have personal experience of the condition ☒ I have personal experience of the technologies being appraised ☐ I have other relevant personal experience. Please specify what other experience:

statement? (please tick all that apply)	☒ I am drawing on others' experiences. Please specify how this information was gathered: as a co-ordinator of the Hertfordshire NRAS group and as a community pharmacist I have had the privilege of hearing other patients' accounts of their Rheumatoid Arthritis (RA) journeys and the difference that being prescribed advanced therapies has had made to their health and lives in general. I am a member of some Facebook groups for people living with RA and have read patients' testimonies here too.
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Being diagnosed with an incurable, painful disease like RA can be extremely distressing as it is lifechanging and as you can be diagnosed at any age post 16, it can have a major impact on your future life plans, dreams and aspirations, although being diagnosed today has significantly better potential outcomes than 25+ years ago when treatments and the way the disease was treated were quite different. RA impacts on every area of life and impacts both physical and emotional wellbeing. Health beliefs, how you come to diagnosis (how long it takes to be diagnosed), the network of support you have and how aggressive the disease is will all impact on how you come to terms with your diagnosis and cope day to day. It can be very distressing for a partner of someone with RA to witness their loved-one in severe pain and suffering the debilitating effects of fatigue and so this disease does very much impact on the whole family. Seeing the rapid deterioration of the health of a parent with early RA can be very frightening for children of all ages. It can have a massive effect on family dynamic, children perceiving a role reversal feeling the need to look after a parent and that parent fearing becoming a burden. As ¾ of people are diagnosed when of working age, anxiety over job-loss due to their disease is significant. This is particularly the case at time of diagnosis when they may have already had quite a lot of time off work in the process of finding out what is wrong and may already be at risk of losing their job. Stress is a recognised trigger for RA flares, so worrying about the possibility of losing your job or having to take more time off due to the condition can exacerbate the problem. For young people who are not yet in a permanent relationship, it can be very hard to come to terms with the fact that they have a long term condition, making them feel less desirable, much less confident and worried that they will not find a partner. Young adults may fear reduced fertility or the effects of the disease/medication on a pregnancy or relapse and inability to cope after giving birth. Diagnosed in mid-years with young children to care for can also be incredibly challenging. Imagine not being able to pick up your baby and change its nappy. For

	older people diagnosed as they approach retirement for example, dreams of being able to travel and look after grandchildren can suddenly seem unachievable. There remains a lot of pain and distress at all stages of this disease and when you have been labelled with “moderate disease”, struggling on conventional DMARDs and pain-killers, you do find yourself hoping that your condition becomes much worse and joint destruction visible in order to be considered for advanced therapies. I certainly felt I had to become much more ill before there was any hope of me receiving advanced therapies, achieving remission and being able to get my life back on track. For many, moderate disease = limbo.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	One of the key issues associated with current care is the variability of access to best, evidence-based care and access to all the relevant members of a consultant-led multi-disciplinary team. This has been demonstrated in the past by the Kings Fund and National Audit Office reports into services for people with RA and most recently by the second National Early Inflammatory Arthritis Audit into early RA run by the BSR. People do experience different levels of care and not all, by any means, have access to research studies for example. In the early stages of their disease, people don’t know what good looks like or what they should be able to ask for or expect and they are also vulnerable at that time as a consequence. This is where NRAS comes in – their goal is to be there at the start of everyone’s journey and whenever they need them along the way. NRAS tries to emphasise the importance of supported self-management early on as the more you know about the disease and the more you can do to help yourself in a positive way, the better your outcomes are likely to be. Unfortunately, whilst there is a lot of rhetoric about self-management for people with LTCs, we still live with a very ‘medical management’ model where investment in patient education, support and self-management by commissioners is far too low. That’s one of the reasons it is essential that health professionals sign-post patients to organisations who can help and support like NRAS. There is no doubt that the increase in access to advanced therapies in the last 20 years has revolutionised the ability to treat more effectively than the era prior to the introduction of Anti-TNF. Access to treatment where there are specific eligibility criteria – ref the biologics and biosimilars – is better than pre-NICE, however, with the introduction of biosimilars, the market has changed and there is a lot of confusion at the moment with local procurement deals ensuring that what is available in one area, may not be the same as the next. Even with all the new treatments available, the heterogeneity of this disease syndrome means that there remains unmet need. Even with cheaper drugs available and many people thinking that therefore more people will be able to get the treatment they need, this is not the

	case unless NICE change the eligibility criteria which currently apply. Many patients accept that their condition has to deteriorate considerably before they qualify for advanced therapies and after some time struggling to cope see this deterioration as a necessary step in their RA journey! Meanwhile they may have already had to access services several times, such as GP appointments and flare clinics or be squeezed into already full Rheumatology clinics for help in the form of steroid tablet courses or steroid injections or referral to another healthcare professional.
10. Is there an unmet need for patients with this condition?	Yes, we are not yet at a stage where stratifying treatment as is done in the field of cancer care, is possible except to a crude degree in RA. Much research is being conducted into being able to identify biomarkers (blood and tissue) so that we can move more to a place when a doctor will be able to match a patient to a specific drug and we also need to be able to treat patients with bDMARDS and other advanced therapies earlier in the pathway. Approximately 6-8% of patients are resistant to treatment (refractory) and many have to move over time from one therapy to another to maintain disease control. Despite a considerably enlarged arsenal of drugs by comparison to over 20 years ago, there remains unquestionable unmet need. I believe there is unmet need in patients living with moderate disease for a long time, particularly sero-negative cases where when they feel their disease is very active and they are struggling to function, their blood test results do not reflect this. As someone who is living with visible joint destruction, I feel that I would have benefitted from being able to start on biologic therapy much sooner. While RA was able to cause irreversible damage to my joints, there is also the worry that it may have caused, so far unseen, damage to internal organs too.
Advantages of the technologies	
11. What do patients or carers think are the advantages of the technologies?	The advantage of advance therapies is that they can be life-changing, enabling many patients to achieve remission and to lead more normal lives. Giving patients advanced therapies before they reach severe disease status could reduce pain and disability for the patient and reduce stress for patient, family and carers. It might enable patients to get back to work and be self-sufficient instead of relying on benefits, which would contribute to better mental health. Earlier advanced therapies could reduce joint destruction and the need for many extra appointments in flare clinics and further down the line reduce the need for costly joint replacement operations. Being put onto advanced therapies is likely to reduce the need for

	regular strong pain killers or steroids and also enable a patient to become more active and therefore adopt a more healthy lifestyle to maintain a “normal” state of health.
Disadvantages of the technologies	
12. What do patients or carers think are the disadvantages of the technologies?	I am unaware of any disadvantages for patients or carers.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technologies than others? If so, please describe them and explain why.	Patients who have been muddling through for years with moderate disease and experiencing slow deterioration of joints and constant fatigue would benefit from changes to the treatment pathways. When you have lived with a condition like RA for any time, you become so used to living “half a life” with joint pain and stiffness, disability and fatigue that you are grateful for very small improvements and forget what “normal” used to feel like. When I was put onto my first biologic I thought “now I remember what I used to feel like” – it truly gave me my like back.
Equality	
14. Are there any potential equality issues that should be taken into account when	I am unaware of any equality issues.

considering this condition and the technologies?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	No.
Key messages	

16. In up to 5 bullet points, please summarise the key messages of your statement:

- Advanced therapies change lives – indeed give people their lives back
- Being able to start advanced therapies before developing severe disease could reduce joint destruction and disability and enable patients to lead more normal lives.
- Giving advanced therapies earlier might reduce the demand for flare clinics and extra appointment time in rheumatology clinics reducing pressure on over-stretched rheumatology teams.
- Giving advanced therapies earlier would reduce the continued use of strong pain killers and steroids which themselves can have long-term health implications.
- Giving advanced therapies earlier might reduce the need for joint replacement operations and minimise damage to other organs (lungs, liver, heart, kidneys, eyes etc) caused by long-term uncontrolled disease reducing cost to the NHS and reduce the physical, emotional and financial cost to patients, families and carers.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

Confidential until published

Adalimumab, etanercept, infliximab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Produced by	The School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
	Emma Simpson, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
	Gill Rooney, Programme Manager, ScHARR, University of Sheffield, Sheffield, UK
	Ruth Wong, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK
	Christopher J Edwards, Consultant Rheumatologist, NIHR Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, SO16 6YD
Correspondence Author	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
Date completed	Date completed (04/01/2021)

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 14/66/01.

Declared competing interests of the authors

Chris Edwards declares that he has received honoraria, provided consultancy or been part of a speaker's bureau for AbbVie, Pfizer, BMS, Celltrion, Fresenius Kabi, Biogen and Janssen in relation to rheumatoid arthritis interventions. None of the remaining authors have any conflicts of interest to declare.

Acknowledgements

We would like to thank Andrew Metry, for help in discussing the project.

Rider on responsibility for report

'This report was commissioned by the NIHR Evidence Synthesis Programme. The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Stevenson M, Simpson E, Rooney G, Wong R, Edwards CJ. Adalimumab, etanercept, infliximab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Contributions of authors

Emma Simpson and Gill Rooney undertook the systematic review. Emma Simpson, Gill Rooney and Matt Stevenson evaluated the clinical evidence related to the relationship between changes in HAQ score and DAS28 score. Matt Stevenson amended the health economic model and generated the results. Ruth Wong generated the search strategy used. Chris Edwards provided clinical advice. All authors were involved in drafting and commenting on the final report.

Table of Contents

List of Tables

List of Figures

1 LIST OF ABBREVIATIONS

ABA	Abatacept
ADA	Adalimumab
bDMARD	Biologic disease-modifying antirheumatic drug
BeST	Behandel Strategieen; in English, treatment strategies
CATCH	Canadian Early Arthritis Cohort
csDMARD	Conventional Synthetic Disease-Modifying Antirheumatic Drug
DAS	Disease Activity Score
DAS28	Disease Activity Score 28 joints
DAS28-CRP	Disease Activity Score 28 joints - C-Reactive Protein
DAS28-ESR	Disease Activity Score 28 joints - Erythrocyte Sedimentation Rate
DAS44	Disease Activity Score 44 joints
DCP	Data from daily clinical practice
DMARD	Disease-Modifying Antirheumatic Drug
EQ-5D	European Quality of Life 5-Dimensions
ERAS	Early Rheumatoid Arthritis Study
ETN	Etanercept
EULAR	European League Against Rheumatism
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire Disability Index
IFX	Infliximab
IQR	Interquartile Range
IV	Intravenously
J-HAQ	Japanese version of the Health Assessment Questionnaire
MTX	Methotrexate
NOAR	Norfolk Arthritis Register
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
PAS	Patient Access Scheme
QALY	Quality-adjusted life years
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trial
RTX	Rituximab
TA	Technology Appraisal
T2T	Treat to Target

TCZ	Tocilizumab
TNFi	Tumour Necrosis Factor inhibitor
UK	United Kingdom
USA	United States of America

2. EXECUTIVE SUMMARY

This work has been undertaken to partially update NICE technology appraisal 375 (TA375) to consider the cost-effectiveness of biologic disease-modifying antirheumatic drugs (bDMARDs) in patients with moderate-to-severe rheumatoid arthritis (RA). Moderate-to-severe RA is defined as a Disease Activity Score (28 joints) (DAS28) score between 3.2 and 5.1. The manufacturers of four bDMARDs (abatacept, adalimumab, etanercept and infliximab) paid to be considered within the partial update of NICE TA375.

In addition to updating the prices of bDMARDs due to the emergence of biosimilars, the model used for TA375 was updated to account for the fact that patients with moderate-to-severe RA would receive bDMARDs when their RA was deemed severe, with a DAS28 score greater than 5.1. To action this change, the relationship between changes in Health Assessment Questionnaire (HAQ) score and changes in DAS28 scores was required. A systematic search of literature was conducted to source information on this parameter, focussing primarily on people with moderate-to-severe RA. One database was searched: Ovid MEDLINE 1946 to the 1st of October 2020. The systematic review was supplemented by company submissions and papers identified by clinical experts.

Nine studies were identified meeting the inclusion criteria, with data reserved for consideration in sensitivity analyses provided in ten other studies, in subgroups of two of the nine included studies, and from one company submission. Estimates in the change in DAS28 score per 0.125 change in HAQ score was estimated using graphical software where necessary.

There was a wide range in the estimated change in DAS28 score associated with a 0.125 change in HAQ score which ranged from -6.50 to 0.90[1]. The Assessment Group believed that the best estimate was a value of 0.48 which was taken from a study with the intention of estimating the relationship between changes in DAS28 scores and HAQ scores and provided a value near the middle of other estimates. Sensitivity analyses were conducted using a lower value of [redacted] to an upper value of 0.90.

Cost-effectiveness results cannot be provided in this document due to the commercial-in-confidence nature of the prices of biosimilars and due to confidential patient access schemes. These results are contained in a confidential addendum.

3 BACKGROUND

3.1 Description of health problem

Rheumatoid arthritis (RA) is a chronic inflammatory disease which is characterised by progressive and irreversible joint damage, impaired joint function, pain and tenderness caused by swelling of the synovial lining of joints.[2] RA is manifested with increasing disability and reduced quality of life.

3.2 Current service provision

NICE Technology Appraisal (TA375)[3] recommended adalimumab (ADA), etanercept (ETN), infliximab (IFX), certolizumab pegol, golimumab, tocilizumab (TCZ), and abatacept (ABA) in combination with methotrexate (MTX) is recommended for treating patients with RA only if: 1) RA is severe, that is a Disease Activity Score 28 joints (DAS28) score greater than 5.1; 2) the diseases has not responded to intensive therapy with a combination of conventional synthetic disease-modifying antirheumatic drug (csDMARDs); and 3) that the agreed patient access schemes (PAS) for ABA, certolizumab pegol, golimumab and TCZ are provided. ADA, ETN, certolizumab pegol or TCZ can be used as monotherapy for people who cannot take MTX because it is contraindicated or because of intolerance. NICE also stated that treatment should be started with the least expensive drug.

At the time of writing, no biologic disease-modifying antirheumatic drugs (bDMARDs) are recommended by NICE for the treatment of moderate-to-severe RA, which is defined as those patients with a DAS28 score between 3.2 and 5.1. The focus of this partial update is on estimating the cost-effectiveness of bDMARDs for patients with moderate-to-severe RA. Due to the emergence of biosimilars, and the resulting falls in acquisition price for a number of the technologies, it is anticipated that bDMARDs will now be more cost-effective than at the time of TA375.

3.3 Description of technologies under assessment

Whilst NICE TA375 provided recommendations on seven interventions, the update only focuses on four: ABA, ADA, ETN, and IFX, as the manufacturers of the omitted interventions did not pay the fee required by NICE for the intervention to be appraised.

ABA 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. It is provided in two formulations, intravenously (iv)

and subcutaneously (sc). The dose regimen for ABA iv is 500 mg below 60 kg, 750 mg between 60 kg and 100 kg, 1000 mg above 100 kg; 0, 2 and 4 weeks, then every 4 weeks thereafter. For ABA sc the dose regimen is 125 mg weekly following a loading dose of 500mg below 60 kg, 750mg between 60 kg and 100 kg, 1000 mg above 100 kg.

ADA, ETN and IFX, all inhibit the activity of tumour necrosis factor alpha, a pro-inflammatory mediator that is partly responsible for damage to the joints in RA. ADA and ETN are provided sc, whereas IFX is an iv administration. ADA is provided at doses of 40mg every other week, ETN at doses of 50mg every week, and IFX is provided at 3mg/kg at weeks 0, 2 and 6 and then every 8 weeks.

All four drugs being appraised are subject to PAS or pricing for biosimilars that are deemed commercial in confidence. As such, the prices cannot be reported in this document, but are contained in a confidential addendum.

4 DEFINITION OF THE DECISION PROBLEM

The decision problem is to assess the cost-effectiveness of ABA, ADA, ETN, and IFX when used to treat patients with moderate-to-severe RA compared with the current treatment paradigm. NICE has requested that all parameters values preferred by the NICE Appraisal Committee when it produced guidance for TA375 should be maintained with the exception of two elements which are discussed below.

1) Updating of the prices, where applicable, of ABA, ADA, ETN, IFX, rituximab (RTX) and TCZ.

This has been undertaken to ensure that any price reductions that have occurred since the introduction of biosimilars into the market, or through any changes in PAS are considered. Due to the sequence of interventions modelled, RTX and TCZ are also incorporated as these treatments would be used following discontinuation of the first bDMARD.

2) Amending the mathematical model to ensure that patients with moderate-to-severe RA who do not receive bDMARDs, will receive bDMARDs when their RA becomes severe.

In the model constructed for TA375, patients with moderate-to-severe RA were modelled as having two potential treatment pathways. 1) receive bDMARDs immediately and then progress through a sequence that comprised of RTX, TCZ and then csDMARDs or 2) to forever stay on csDMARDs. This omitted the option for the patient to remain on csDMARDs until their RA became severe, at which point in accordance with NICE recommendations, bDMARDs could be provided. In order to action this change, the model needed to estimate the relationship between changes in Health Assessment Questionnaire (HAQ) score, which was the key metric used in the modelling, and changes in DAS28 score, which is the metric used to determine the severity of RA. The relationship between changes in the parameters were deemed more pertinent for the work than relationships between absolute HAQ and DAS28 scores, as the model explicitly monitors changes in HAQ, which is a scale from zero to 3.0 with steps of 0.125.

Once a relationship between changes in HAQ and changes in DAS28 has been assumed, the amended model monitors the DAS28 score of the patient. If the patient is on the csDMARD-first strategy they will be provided with a bDMARD once the patient reaches a DAS28 score greater than 5.1. Further details of the mechanics of this change are provided in Section 6.

5 ASSESSMENT OF CLINICAL EFFECTIVENESS

This chapter details the methods used to identify evidence related to the relationship between changes in HAQ and changes in DAS28, and also presents the results found.

5.1 Methods for reviewing effectiveness

A systematic search of literature was conducted to source information on the relationship between the change in HAQ score and the change in DAS28 score.

Searches

One database was searched: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to the 1st of October, 2020.

The MEDLINE search strategy is shown in Table 1:

Table 1 MEDLINE search strategy: Search conducted October 01 2020

#	Searches	Results
1	exp Arthritis, Rheumatoid/	113387
2	((rheumatoid or early) adj arthritis).tw.	107028
3	1 or 2	149310
4	(("disease activity score" or das*) adj5 ("health assessment questionnaire" or haq*)).tw.	738
5	(relationship or associat* or corrolat*).tw.	5263889
6	3 and 4 and 5	332
7	limit 6 to english language	328

Additionally, references provided within company submissions were checked and papers known to our clinical expert added. The reference lists of relevant studies were checked. All identified citations from the electronic searches and other resources were imported into, and managed using, Endnote X9 software (Clarivate analytics 2020 TM).

Study selection

All titles and abstracts were independently examined for inclusion by two reviewers. Any citations that clearly did not meet the inclusion criteria were excluded. Full text articles were sourced and independently checked by two reviewers. Disagreements were resolved by

discussion, with involvement of a third member of the team. Study selection was based on the following inclusion and exclusion criteria.

Inclusion criteria

Population

Adults (aged 18 years and over) with active RA. If data allow, there is a preference for studies reporting on patients with moderate-to-severe RA (DAS28 3.2-5.1). If there are insufficient data, then any severity of RA would be considered.

Outcome

Change in HAQ/ Health Assessment Questionnaire Disability Index (HAQ-DI) and the associated change in DAS28 (DAS28-erythrocyte sedimentation rate (DAS28-ESR) or DAS28-c-reactive protein (DAS28-CRP).

Study design

Studies were required to provide relevant data, and were not required to be designed solely to address the question of relative changes in HAQ and DAS28.

Exclusion criteria

Population

Children. Studies of several types of arthritis where data not available separately for RA.

Outcomes

Data that cannot be used to calculate change in HAQ and the associated change in DAS28, over the same time period, and in the same group of RA patients. No DAS28 data reported (disease activity score 44 joints (DAS44) is excluded). No HAQ / HAQ-DI data reported (The Japanese version of the Health Assessment Questionnaire (J-HAQ) is excluded as overall disability index higher in the J-HAQ than in the original HAQ[4]).

Study design

Animal models; preclinical and biological studies; narrative reviews, editorials, opinions; and non-English-language papers. Publication type: articles published as abstracts only where insufficient information is available on outcomes or methods.

Where data meeting inclusion criteria are lacking, some allowance may be given (in severity of RA or prior treatment with biologics) for studies to be used in sensitivity analyses.

Data extraction and synthesis

Data relevant to the decision problem were extracted by one reviewer, and checked by another. Data were extracted without blinding to authors or journal. Graphical data of change in HAQ or DAS28 were estimated using Engauge software [version 12.1; Mark Mitchell, Los Angeles, CA, USA (2011)]. Data of change in HAQ and DAS28 over the same time period, in the same population of patients, were used to calculate an estimated change in DAS28 for a change in HAQ of 0.125 points.

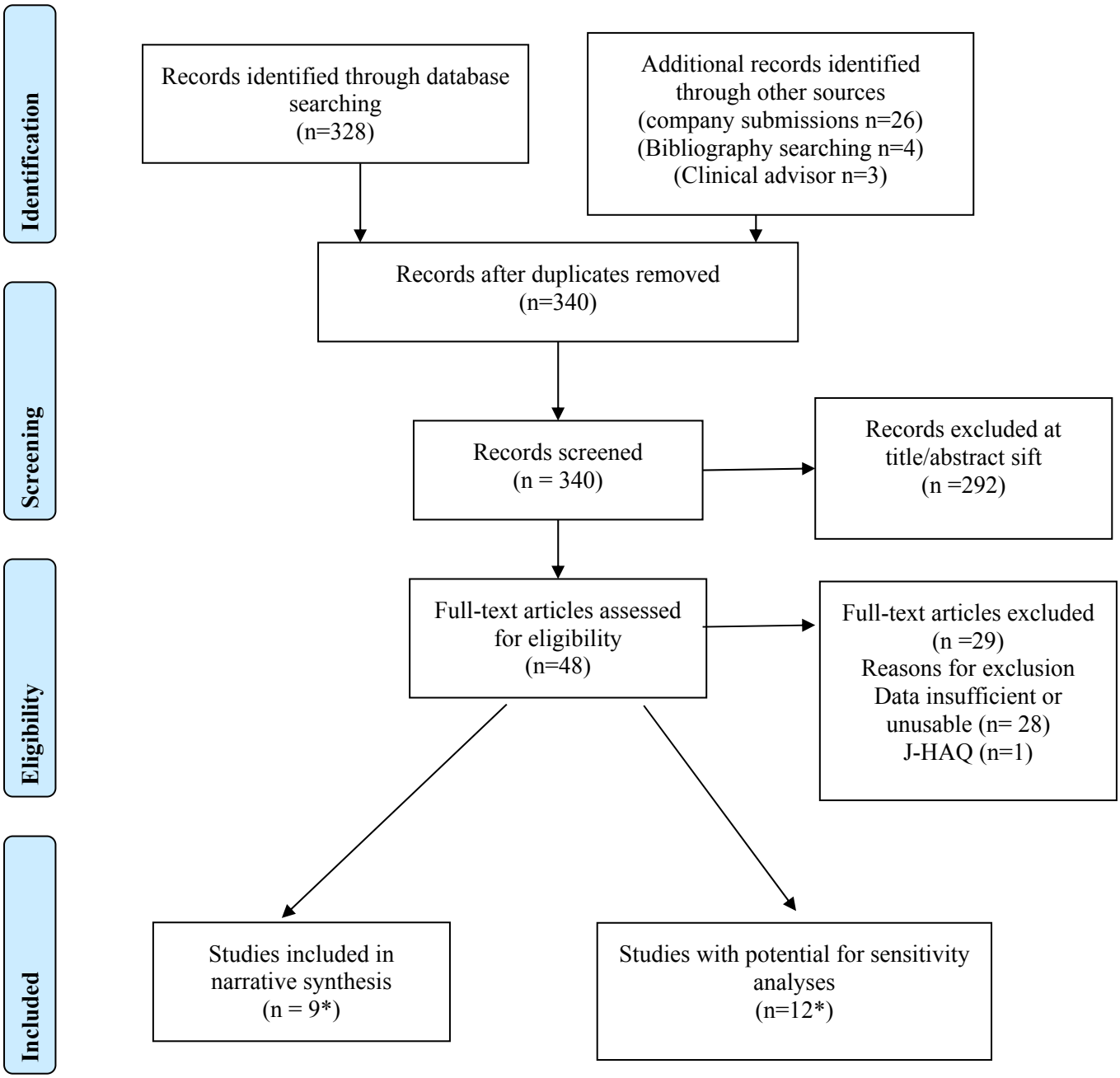
5.2 Results

The MEDLINE search was conducted on the 1st of October 2020. It identified 328 records (without removing duplicates). Twenty-six articles were referenced by company submissions, three articles were recommended by our clinical advisor. The bibliography search yielded four additional articles. The search total, following removal of duplicates was 340 (Figure 1).

Following title/abstract sift, 48 full-text articles were checked. The 29 studies excluded at the full-text stage are listed (with rationale for exclusion) in Appendix 1, leaving 19 studies containing relevant information. Of these nineteen, which nine met the inclusion criteria, and eleven provided data that would be considered for sensitivity analyses if the included studies could not provide sufficient data – two studies provided information for both categories. Results from the studies which met the inclusion criteria are provided in the main text, whereas data for studies which provide data considered for sensitivity analyses are shown in Appendix 2. The reasons for exclusion were having patients with an average baseline DAS28 score > 5.1 (n=8), using DAS44 rather than DAS28, (n=2) and having patients with an average baseline DAS28 score <3.2 (n=1). Additionally, AbbVie provided potentially useful data, although having examined the studies referred to, it appeared probable that these were for patients with an average baseline DAS28 score > 5.1. Data from the AbbVie submission are summarised at a high-level in Appendix 2.

Characteristics of included studies are shown in Table 2. Only one paper (Boyd et al 2013[5]) had a primary outcome to investigate the relationship between function and disease activity over time, and this was a sub-study of the Canadian Early Arthritis Cohort (CATCH). In all nine studies, HAQ and DAS28 were assessed by qualified clinicians (rheumatologists or rheumatology nurses), as part of ongoing patient care, and are unlikely to be subject to biases. As validated, widely used measures, HAQ and DAS28 were not subject to change throughout the follow-up periods of studies.

Figure 1 Flow diagram of study selection (based on PRISMA guidelines http://prisma-statement.org/)



*Two studies provided data for both categories.

Unpublished data provided by company submissions could also be included. This resulted in one additional data set with the potential for use in sensitivity analyses

Table 2 Included study characteristics

Reference	Study type	Study objective	Sample size	Follow-up (months)
Ariza-Ariza et al 2006[6]	Prospective multicentre study	To compare the utility values and quality-adjusted life years (QALYs) obtained by the Time Trade-Off instrument (TTO) and the European Quality of Life -5 Dimensions (EQ-5D)	300	12
Augustsson et al 2010[1]	Database study	Investigating Tumour Necrosis Factor inhibitor (TNFi) and workforce participation	594	60
Boyd et al 2013[5]	Data from Canadian Early Arthritis Cohort (CATCH)	Sub-study investigating function and disease activity in early arthritis	1,143	24
de Andrade et al 2017[7]	Single centre prospective cohort study	Investigating disease activity and physical function after treat-to-target strategy	229	108
Fioravanti et al 2019 [8]	Prospective cohort from two centres in Italy	Investigating TCZ therapy	44	6
Gwinnutt et al 2020[9]	the Rheumatoid Arthritis Medication Study, a UK multicentre cohort study	Investigating clusters of symptoms associated with poor outcomes in early RA	1,127	12
Ling et al 2016[10]	data from two cohorts: the Norfolk Arthritis Register (NOAR); and the Early Rheumatoid Arthritis Study (ERAS)	Investigating effect of HLA-DRB1 on disease activity	NOAR n=2,158 ERAS n=329	60
Nair et al 2014[11]	data from clinical practice from the observational Nijmegen Early Rheumatoid Arthritis inception cohort	Investigating whether treatment effects of pragmatic clinical trials are generalisable to data from daily clinical practice (DCP),	DCP n=198	6
Twigg et al 2017[12]	Data from Yorkshire Early Arthritis Register (YEAR)	To assess patient-reported variables as predictors of change in disease activity and disability	1,415	12

TNFi=tumour necrosis factor inhibitor; TCZ=tocilizumab; DCP=Data from daily clinical practice; NOAR= Norfolk Arthritis Register; ERAS = Early Rheumatoid Arthritis Study

Baseline variables of included trials are shown in Table 3. Mean/median DAS28 scores were between 3.2 and 5.1 (that is, moderate-to-severe) in all nine studies although, this was only for one of the two cohorts in Nair et al 2014[11]).

Baseline ages were similar across studies, with the lowest mean age 40 years,[1] and highest age median 60 years.[9] All six studies had a majority of female patients, as is to be expected from prevalence of RA. Baseline disease duration ranged from six months[10 5] to 10.6 years.[7] This is considered by our clinical advisor to be generalisable to the RA population seeking treatment in England.

The estimated change in DAS28 associated with a 0.125 change in HAQ are provided in Table 4. In all studies apart from Ariza-Ariza *et al*.[6] and cluster 6 of Gwinnutt *et al*. [9] HAQ and DAS28 scores decreased indicating an improvement, on average, in the condition of the patients. As such, the assessment group has had to assume that the relationship between decreases in HAQ score and in decreases in DAS28 are generalisable to when there are increases in the HAQ score.

A wide range was observed in the estimated relationship between the change in DAS28 score when HAQ changes. Ariza-Ariza *et al*.[6] reported a large, negative correlation whilst a positively correlated estimate of 0.90 was derived from Twigg *et al*.[12] The ERG believes that the most appropriate estimate (0.48) would be provided by Boyd *et al*.[5] which has the advantage of the relationship being the primary outcome of the study, having a reasonable long follow-up of 24 months, having no bDMARD use, and with an estimate that was not too removed from the remaining studies.

Acknowledging the uncertainty in the parameter the ERG ran two sensitivity analyses using a higher value and a lower value. The higher value (0.90) was estimated from Twigg *et al.*[12] which was a fairly recent, large, study of reasonable length without the use of bDMARDs. For the lower value, the ERG preferred to use data reserved for sensitivity analyses and use the values estimated by AbbVie which regressed change in DAS28 on HAQ based on individual patient data from four RCTs of upadacitinib. The reason for choosing this source is that the estimated value ([redacted]) is amongst the lowest observed, that individual patient data had been used, and importantly that this was the only source where both HAQ and DAS score was assumed to increase.

Table 3 Baseline characteristics of included studies

Reference	Study Sample size	Baseline DAS28*	Baseline HAQ	Prior Treatment	Treatment during study	Baseline age (years)	Gender (% female)	Baseline disease duration
Ariza-Ariza *et al.* 2006[6]	300	DAS28-ESR Mean 4.5 SD1.5	HAQ Mean 1.2 SD0.9	csDMARDs, or bDMARDs at physician discretion	csDMARDs, or bDMARDs at physician discretion	Mean 59.6 SD 13.3	82	Years Mean 10.3 SD 8.7
Augustsson *et al.* 2010[1]	594	DAS28 Mean 4.7 SD 1.4 N=521	HAQ Mean 1.0 SD 0.6 N=528	No prior bDMARD	First treatment with TNFi IFX (52.9%) ETN (34.5%) ADA (12.6%)	Mean 40.0 SD 9.3	66	Years Mean 9.4 SD 8.5
Boyd *et al.* 2013[5]	1,143	DAS28 mean 4.53 SD 1.99	HAQ Mean 0.94 SD 0.72	csDMARDs with or without prednisone (physician discretion) or csDMARD naive	csDMARDs with or without prednisone (physician discretion)	Mean 52.2 SD 15.8	71.2	Months Mean 6.3 SD 3.7
de Andrade *et al.* 2017[7]	229	DAS28 Mean 4.6 SD 1.5	HAQ-DI Mean 1.4 SD 0.05	csDMARD	T2T strategy, two courses of csDMARDs followed by bDMARD (TNFi, with physician discretion for ABA, TCZ, RTX)	Mean 55 SD 11	83.8	Years Mean 10.6 SD 7.4
Fioravanti *et al.* 2019[8]	44	DAS28-ESR Median 4.630 IQR 4.23-5.25	HAQ Median 1.68 IQR 1.04-2.38	At least two csDMARDs	TCZ (n=20); TCZ+MTX (n=24)	Median 58.50 IQR 48-69.75	86.4	Years Median 8 IQR 5-15
Gwinnutt *et al.* 2020[9]	1,127	DAS28-CRP median 4.1 IQR 3.2, 5.2	HAQ Median 1.00 IQR 0.38, 1.63	MTX naive	Starting MTX	Median 60 IQR 50, 69	63.4	Median 6 months, IQR 4, 10
Ling *et al.* 2016[10]	2,158 NOAR cohort;	DAS28-ESR NOAR Median 3.76 IQR 2.79, 4.78	HAQ NOAR Median 0.875	csDMARDs, and/or corticosteroids	csDMARDs, and/or corticosteroids	Age at symptom onset NOAR Median 55	NOAR 65 ERAS 67	Months NOAR Median 6 IQR 3, 12

Reference	Study Sample size	Baseline DAS28*	Baseline HAQ	Prior Treatment	Treatment during study	Baseline age (years)	Gender (% female)	Baseline disease duration
	329 ERAS cohort	ERAS Median 5.06 IQR 4.19, 5.84	IQR 0.25, 1.5 ERAS Median 1 IQR 0.625, 1.6875			IQR 43–67 ERAS Median 54 IQR 44–62		ERAS Median 6 IQR 3, 11
Nair *et al.* 2014[11]	198 Data from DCP	DAS28 DCP Mean 5.0 SD 1.3	HAQ DCP Mean 0.8 SD 0.7	csDMARD naive, no prior corticosteroids	csDMARDs, NSAIDS and/or corticosteroids, and/or biologics	DCP Mean 54.7 SD 15.2	DCP 61.3	<1 year
Twigg *et al.* 2017[12]	1,415	DAS28-CRP Mean 5.01 SD 1.33	HAQ-DI Mean 1.22 SD0.57	csDMARDs	csDMARDs, and/or corticosteroids	Mean 57.7 SD 14.2	66	Months Mean 7.1 SD 4.3

*unless otherwise stated, unclear if calculated with ESR or CRP

DAS28=Disease Activity Score 28 joints; ESR= erythrocyte sedimentation rate; CRP= C-reactive protein; HAQ = Health Assessment Questionnaire; HAQDI = Health Assessment Questionnaire Disease Index; csDMARD=conventional synthetic disease-modifying antirheumatic drug; NOAR= Norfolk Arthritis Register; ERAS = Early Rheumatoid Arthritis Study; DCP=Data from daily clinical practice;

TNFi=tumour necrosis factor inhibitor; MTX=methotrexate; ABA=abatacept; TCZ=tocilizumab; RTX=rituximab; IQR=interquartile range; IFX=infliximab; ADA=adalimumab; ETN=etanercept; NSAIDS=non-steroidal anti-inflammatories; T2T=treat-to-target

Table 4 Step changes estimated

Reference	Sample size [providing data]	Baseline DAS	Baseline HAQ	Treatment during study	Follow-up (Months)	Change in DAS associated with 0.125-point change in HAQ
Ariza-Ariza *et al.* 2006[6]	163	DAS28-ESR Mean 4.5 SD1.5	HAQ Mean 1.2 SD0.9	csDMARDs, or bDMARDs at physician discretion	12	-6.5 DAS28 decrease HAQ increase
Augustsson *et al.*2010[1]	528	Mean 4.7 SD 1.4 N=521	Mean 1.0 SD 0.6 N=528	First treatment with TNFi IFX (52.9%) ETN (34.5%) ADA (12.6%)	60	0.59* HAQ and DAS28 score decrease
Boyd *et al.* 2013[5]	214	mean 4.53 SD 1.99	Mean 0.94 SD 0.72	DMARDs with or without prednisone (physician discretion)	24	0.48* HAQ and DAS28 score decrease
de Andrade *et al.* 2017[7]	229 [156 at year 9]	Mean 4.6 SD 1.5	Mean 1.4 SD 0.05	T2T strategy, two courses of csDMARDs followed by biologic (TNFi, with physician discretion for ABA, TCZ, RTX)	108	0.39* HAQ and DAS28 score decrease
Fioravanti *et al.* 2019[8]	44	Median 4.630 IQR 4.23-5.25	Median 1.68 IQR 1.04-2.38	TCZ (n=20); TCZ+MTX (n=24)	6	0.34 HAQ and DAS28 score decrease
Gwinnutt *et al.* 2020[9]	Cluster 5 71 Cluster 6 46	DAS28-CRP Cluster 5 Median 3.4 Cluster 6 Median 3.8 [at month 6 of study – baseline of calculation]	Cluster 5 HAQ Median 1.5 Cluster 6 HAQ Median 1.25 [at month 6 of study – baseline of calculation]	Starting MTX	6 [change from months 6 to 12 of the study]	Cluster 5 0.56 HAQ and DAS28 score decrease Cluster 6 Not calculable No change in HAQ, DAS28

Reference	**Sample size [providing data]**	**Baseline DAS**	**Baseline HAQ**	**Treatment during study**	**Follow-up (Months)**	**Change in DAS associated with 0.125-point change in HAQ**
						score decrease
Ling *et al.* 2016[10]	NOAR 2,158 ERAS 329	NOAR Median 3.76 IQR 2.79, 4.78 ERAS Median 5.06 IQR 4.19, 5.84	NOAR Median 0.875 IQR 0.25, 1.5 ERAS Median 1 IQR 0.625, 1.6875	csDMARDs, and/or corticosteroids	60	NOAR = 0.13 ERAS = 0.11 HAQ and DAS28 score decrease
Nair *et al.* 2014[11]	198 (DCP)	Mean 5.0 SD 1.3	HAQ Mean 0.8 SD 0.7	csDMARDs, NSAIDS and/or corticosteroids, and/or biologics	6	0.33 HAQ and DAS28 score decrease
Twigg *et al.* 2017[12]	1,415	5.01	1.22	csDMARDs, and/or corticosteroids	12	0.90 HAQ and DAS28 score decrease

*estimated from graph

DCP=Data from daily clinical practice; TNFi=tumour necrosis factor inhibitor; NOAR= Norfolk Arthritis Register; ERAS = Early Rheumatoid Arthritis Study;

6 INDEPENDENT ECONOMIC ASSESSMENT

6.1 Methods

As stated, NICE requested that that all parameters values preferred by the NICE Appraisal Committee when it produced guidance for TA375 should be maintained bar updating the prices of interventions and allowing patients to receive bDMARDs when their DAS28 score was greater than 5.1. Comprehensive details of the modelling approach are provided in Stevenson *et al.*[13] In TA375, the sequence after the first bDMARD was accepted, to be the use of RTX and then TCZ, providing TCZ was not used earlier in the treatment sequence then csDMARDs.

The following first line bDMARDs were evaluated: ABA iv, ABA sc, ADA, ETN, and IFX. Each was followed by RTX and then TCZ reverting to csDMARDs following the failure of TCZ. The comparator arm was csDMARDs until a patient reached a DAS score of greater than 5.1 where on the advice of our clinical expert a sequence of ADA, RTX and TCZ was used. For all analyses it was assumed that MTX was used in combination with the bDMARD, and that following TA375 guidance, the results for combination therapy would also be used to generalise to the bDMARDs being used in monotherapy.

The model operationalises the change to bDMARD when the patient has severe RA by calculating the number of HAQ increases, in steps of 0.125, that would be required for the DAS28 score of the patient to be greater than 5.1. Once these net number of HAQ step increases have been reached the patient is assumed to receive ADA.

The model structure has the capacity to run 10 cohorts of patients. Having evaluated early results, the Assessment Group decided that 2 cohorts would be used for the csDMARD strategy, 2 for each of the ADA, ETN, and IFX strategies and 1 each for ABA iv and ABA sc. This was because more precision may be needed for the interventions with biosimilars available as the uncertainty associated with the simulated experience of identical patients (often referred to as first-order uncertainty) would be reduced by apportioning two cohorts.

50,000 patients per cohort were simulated, at that point the Monte Carlo sampling error was low, as for both QALYs and costs, the range between the highest and lowest value from the runs for each bDMARD-first strategy being less than 0.5% of the average value. These variations in costs and QALYs were correlated as younger patients would, on average, accrue both greater QALYs and costs.

Only deterministic results were run as there were shown to be little difference between probabilistic and deterministic results in TA375. Each simulation took in the order of 9 hours to complete.

6.2 The assumed efficacy of the interventions.

The assumed efficacy of each intervention used in the model is provided in Table 5. A good European League Against Rheumatism (EULAR) response is better than a moderate EULAR response, which is better than no response. In line with TA375, both ABA sc and RTX was assumed to have the same efficacy of ABA iv.

Table 5: Assumed efficacy associated with each treatment, all bDMARDs with MTX

EULAR response	ABA iv	ADA	csDMARDs	ETA	IFX	TCZ
Good	26.3%	28.1%	9.7%	53.0%	25.6%	57.2%
Moderate	41.4%	40.5%	35.5%	32.4%	42.8%	33.0%
No response	32.3%	31.4%	54.8%	14.6%	31.6%	9.8%

Further details on the consequences of each EULAR response is provided in Stevenson *et al.*[13] If there is no EULAR response to a bDMARD after 6 months the next treatment in the strategy is used.

6.3 Model results

As there are biosimilars for RTX, and TCZ has a commercial-in-confidence PAS, full results are not provided here but are supplied to the NICE Appraisal Committee in a confidential addendum. However, to provide some transparency, the QALYs gained by each strategy are provided in Figure 2. For csDMARDs there are three values, each associated with a different relationship between changes in HAQ and change in DAS score. As the results for bDMARDs should not be affected by this parameter, and differences are just Monte-Carlo sampling error, the value for each bDMARD is the average of the three runs. It is seen that when the DAS score of patients with moderate-to-severe RA increases more rapidly, more QALYs are gained due to the earlier use of bDMARDs. However, this would also be associated with additional intervention costs.

Figure 2: QALYs gained by each strategy

As stated, the cost-effectiveness results cannot be presented in this document due to commercial-in-confidence pricing. However, the results were not overly sensitive to the choice of parameter value for the relationship between HAQ score changes and DAS28 changes.

7 CONCLUSIONS

There appears to be considerable uncertainty in the relationship between changes in HAQ scores and changes in DAS28 scores. A limitation within the published literature is that HAQ score was increasing in only one study; as such the Assessment Group had to assume that the relationship associated with decreasing HAQ scores would also apply when HAQ scores increased.

Our best estimate (0.48) is that reported by Boyd *et al.*[5] which was a study designed for the purpose of establishing such a relationship and provided a value near the middle of other estimates. Sensitivity values were provided for higher (0.90) and lower values ([redacted]) for this relationship.

Cost-effectiveness results cannot be provided in this document, but the incremental cost-effectiveness results were not overly sensitive to the assumed relationship between change in HAQ score and change in DAS28 score.

8 REFERENCES

1. Augustsson J, Neovius M, Cullinane-Carli C, Eksborg S, van Vollenhoven RF. Patients with rheumatoid arthritis treated with tumour necrosis factor antagonists increase their participation in the workforce: potential for significant long-term indirect cost gains (data from a population-based registry). *Annals of the Rheumatic Diseases* 2010;69:126-31.
2. Scott DL, Steer S. The course of established rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2007;21:943-67.
3. National Institiute for Health and Care Excellence. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. 2016. https://www.nice.org.uk/guidance/ta375 (Accessed 23/12/2020).
4. Matsuda Y, Singh G, Yamanaka H, Tanaka E, Urano W, Taniguchi A, *et al.* Validation of a Japanese version of the Stanford Health Assessment Questionnaire in 3,763 patients with rheumatoid arthritis. *Arthritis Rheum* 2003;49:784-8.
5. Boyd TA, Bonner A, Thorne C, Boire G, Hitchon C, Haraoui BP, *et al.* The Relationship Between Function and Disease Activity as Measured by the HAQ and DAS28 Varies Over Time and by Rheumatoid Factor Status in Early Inflammatory Arthritis (EIA). Results from the CATCH Cohort. *The open rheumatology journal* 2013;7:58-63.
6. Ariza-Ariza R, Hernandez-Cruz B, Carmona L, Dolores Ruiz-Montesinos M, Ballina J, Navarro-Sarabia F, *et al.* Assessing utility values in rheumatoid arthritis: a comparison between time trade-off and the EuroQol. *Arthritis & Rheumatism* 2006;55:751-6.
7. de Andrade NPB, da Silva Chakr RM, Xavier RM, Viecceli D, Correa RHB, de Oliveira Filho CM, *et al.* Long-term outcomes of treat-to-target strategy in established rheumatoid arthritis: a daily practice prospective cohort study. *Rheumatology International* 2017;37:993-7.
8. Fioravanti A, Tenti S, Bacarelli MR, Damiani A, Li Gobbi F, Bandinelli F, *et al.* Tocilizumab modulates serum levels of adiponectin and chemerin in patients with rheumatoid arthritis: potential cardiovascular protective role of IL-6 inhibition. *Clinical & Experimental Rheumatology* 2019;37:293-300.
9. Gwinnutt JM, Hyrich KL, Lunt M, Co-Investigators R, Barton A, Verstappen SMM. Long-term outcomes of patients who rate symptoms of rheumatoid arthritis as 'satisfactory'. *Rheumatology* 2020;59:1853-61.
10. Ling SF, Viatte S, Lunt M, Van Sijl AM, Silva-Fernandez L, Symmons DP, *et al.* HLA-DRB1 Amino Acid Positions 11/13, 71, and 74 Are Associated With Inflammation Level, Disease Activity, and the Health Assessment Questionnaire Score in Patients With Inflammatory Polyarthritis. *Arthritis & Rheumatology* 2016;68:2618-28.

11. Nair SC, Kievit W, Janse RW, Bijlsma JW, Fransen J, Lafeber FP, *et al.* Generalization and extrapolation of treatment effects from clinical studies in rheumatoid arthritis. *Arthritis care & research* 2014;66:998-1007.

12. Twigg S, Hensor EMA, Emery P, Tennant A, Morgan AW, Yorkshire Early Arthritis Register C. Patient-reported Outcomes as Predictors of Change in Disease Activity and Disability in Early Rheumatoid Arthritis: Results from the Yorkshire Early Arthritis Register. *Journal of Rheumatology* 2017;44:1331-40.

13. Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J, *et al.* Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. *Health Technol Assess* 2016;20:1-610.

14. Adams R, Walsh C, Veale D, Bresnihan B, FitzGerald O, Barry M. Understanding the relationship between the EQ-5D, SF-6D, HAQ and disease activity in inflammatory arthritis. *Pharmacoeconomics* 2010;28:477-87.

15. Baganz L, Richter A, Albrecht K, Schneider M, Burmester GR, Zink A, *et al.* Are prognostic factors adequately selected to guide treatment decisions in patients with rheumatoid arthritis? A collaborative analysis from three observational cohorts. *Seminars in Arthritis & Rheumatism* 2019;48:976-82.

16. Bechman K, Tweehuysen L, Garrood T, Scott DL, Cope AP, Galloway JB, *et al.* Flares in Rheumatoid Arthritis Patients with Low Disease Activity: Predictability and Association with Worse Clinical Outcomes. *Journal of Rheumatology* 2018;45:1515-21.

17. Bergstra SA, Couto MC, Govind N, Chopra A, Salomon Escoto K, Murphy E, *et al.* Impact of the combined presence of erosions and ACPA on rheumatoid arthritis disease activity over time: results from the METEOR registry. *RMD Open* 2019;5:e000969.

18. Boers M, Buttgereit F, Saag K, Alten R, Grahn A, Storey D, *et al.* What Is the Relationship Between Morning Symptoms and Measures of Disease Activity in Patients With Rheumatoid Arthritis? *Arthritis care & research* 2015;67:1202-9.

19. Bremander A, Forslind K, Eberhardt K, Andersson MLE. Importance of Measuring Hand and Foot Function Over the Disease Course in Rheumatoid Arthritis: An Eight-Year Follow-Up Study. *Arthritis care & research* 2019;71:166-72.

20. Campbell RC, Batley M, Hammond A, Ibrahim F, Kingsley G, Scott DL. The impact of disease activity, pain, disability and treatments on fatigue in established rheumatoid arthritis. *Clinical Rheumatology* 2012;31:717-22.

21. Carvalho PD, Ferreira RJO, Landewe R, Vega-Morales D, Salomon-Escoto K, Veale DJ, *et al.* Association of 17 Definitions of Remission with Functional Status in a Large Clinical Practice Cohort of Patients with Rheumatoid Arthritis. *Journal of Rheumatology* 2020;47:20-7.

22. Drossaers-Bakker KW, de Buck M, van Zeben D, Zwinderman AH, Breedveld FC, Hazes JM. Long-term course and outcome of functional capacity in

rheumatoid arthritis: the effect of disease activity and radiologic damage over time. *Arthritis Rheum* 1999;42:1854-60.

23. Fatima S, Schieir O, Valois MF, Bartlett SJ, Bessette L, Boire G, *et al.* Health Assessment Questionnaire at One Year Predicts All-Cause Mortality in Patients with Early Rheumatoid Arthritis. *Arthritis & Rheumatology* 2020;06:06.

24. Heinimann K, von Kempis J, Sauter R, Schiff M, Sokka-Isler T, Schulze-Koops H, *et al.* Long-Term Increase of Radiographic Damage and Disability in Patients with RA in Relation to Disease Duration in the Era of Biologics. Results from the SCQM Cohort. *Journal of Clinical Medicine* 2018;7:13.

25. Lee KE, Choi SE, Xu H, Kang JH, Park DJ, Lee SS. HAQ score is an independent predictor of sustained remission in patients with rheumatoid arthritis. *Rheumatology International* 2017;37:2027-34.

26. Linde L, Sorensen J, Ostergaard M, Horslev-Petersen K, Rasmussen C, Jensen DV, *et al.* What factors influence the health status of patients with rheumatoid arthritis measured by the SF-12v2 Health Survey and the Health Assessment Questionnaire? *Journal of Rheumatology* 2009;36:2183-9.

27. Michaud K, Wallenstein G, Wolfe F. Treatment and nontreatment predictors of health assessment questionnaire disability progression in rheumatoid arthritis: a longitudinal study of 18,485 patients. *Arthritis care & research* 2011;63:366-72.

28. Nikiphorou E, Norton S, Young A, Carpenter L, Dixey J, Walsh DA, *et al.* Association between rheumatoid arthritis disease activity, progression of functional limitation and long-term risk of orthopaedic surgery: combined analysis of two prospective cohorts supports EULAR treat to target DAS thresholds. *Annals of the Rheumatic Diseases* 2016;75:2080-6.

29. Norton S, Sacker A, Dixey J, Done J, Williams P, Young A, *et al.* Trajectories of functional limitation in early rheumatoid arthritis and their association with mortality. *Rheumatology* 2013;52:2016-24.

30. Norton S, Fu B, Scott DL, Deighton C, Symmons DPM, Wailoo AJ, *et al.* Health Assessment Questionnaire disability progression in early rheumatoid arthritis: systematic review and analysis of two inception cohorts. *Seminars in arthritis and rheumatism* 2014;44:131-44.

31. Pan Y, Norton S, Gwinnutt JM, Kearsley-Fleet L, Symmons DPM, Lunt M, *et al.* Not all moderate disease is the same - Identification of disability trajectories among patients with rheumatoid arthritis and moderate disease activity. *PLoS ONE [Electronic Resource]* 2019;14:e0215999.

32. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44-8.

33. Rydell E, Forslind K, Nilsson JA, Jacobsson LTH, Turesson C. Smoking, body mass index, disease activity, and the risk of rapid radiographic progression in patients with early rheumatoid arthritis. *Arthritis Research & Therapy* 2018;20:82.

34. Scott DL, Pugner K, Kaarela K, Doyle DV, Woolf A, Holmes J*, et al.* The links between joint damage and disability in rheumatoid arthritis. *Rheumatology (Oxford)* 2000;39:122-32.

35. Shadick NA, Gerlanc NM, Frits ML, Stolshek BS, Brady BL, Iannaccone C*, et al.* The longitudinal effect of biologic use on patient outcomes (disease activity, function, and disease severity) within a rheumatoid arthritis registry. *Clinical Rheumatology* 2019;38:3081-92.

36. Sokka T, Kankainen A, Hannonen P. Scores for functional disability in patients with rheumatoid arthritis are correlated at higher levels with pain scores than with radiographic scores. *Arthritis Rheum* 2000;43:386-9.

37. Tanaka E, Mannalithara A, Inoue E, Hara M, Tomatsu T, Kamatani N*, et al.* Efficient management of rheumatoid arthritis significantly reduces long-term functional disability. *Annals of the Rheumatic Diseases* 2008;67:1153-8.

38. Ten Klooster PM, Oude Voshaar MAH, Fakhouri W, de la Torre I, Nicolay C, van de Laar M. Long-term clinical, functional, and cost outcomes for early rheumatoid arthritis patients who did or did not achieve early remission in a real-world treat-to-target strategy. *Clinical Rheumatology* 2019;38:2727-36.

39. van der Heijde D, Klareskog L, Singh A, Tornero J, Melo-Gomes J, Codreanu C*, et al.* Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. *Ann Rheum Dis* 2006;65:328-34.

40. Ward MM, Guthrie LC, Alba MI. Measures of arthritis activity associated with patient-reported improvement in rheumatoid arthritis when assessed prospectively versus retrospectively. *Arthritis care & research* 2015;67:776-81.

41. Welsing PM, van Gestel AM, Swinkels HL, Kiemeney LA, van Riel PL. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. *Arthritis & Rheumatism* 2001;44:2009-17.

42. Tanaka E, Mannalithara A, Inoue E, Iikuni N, Taniguchi A, Momohara S*, et al.* Effects of long-term corticosteroid usage on functional disability in patients with early rheumatoid arthritis, regardless of controlled disease activity. *Rheumatology International* 2012;32:749-57.

43. Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L*, et al.* Baricitinib in Patients with Refractory Rheumatoid Arthritis. *New England Journal of Medicine* 2016;374:1243-52.

44. Wendler J, Burmester GR, Sorensen H, Krause A, Richter C, Tony HP*, et al.* Rituximab in patients with rheumatoid arthritis in routine practice (GERINIS): six-year results from a prospective, multicentre, non-interventional study in 2,484 patients. *Arthritis Research & Therapy* 2014;16:R80.

45. Koizumi R, Koyama K, Wako M, Ohba T, Takayama Y, Haro H. Clinical conditions needed to acquire sustained functional remission in rheumatoid arthritis patients. *Clinical Rheumatology* 2020; 10.1007/s10067-020-05451-3.

46. Baker JF, Conaghan PG, Emery P, Baker DG, Ostergaard M. Relationship of patient-reported outcomes with MRI measures in rheumatoid arthritis. *Annals of the Rheumatic Diseases* 2017;76:486.

47. van der Kooi E, Klarenbeek NB, Guler-Yuksel M, Kerstens PJ, van der Lubbe PA, Westedt ML*, et al.* A decrease in disease activity score (DAS) level is associated with a decrease in health assessment questionnaire (HAQ) score, independent of follow-up duration, during 5 years of tightly controlled treatment: results from the BeSt study. *Annals of the Rheumatic Diseases* 2011;70:168-71.

48. Andersson MLE, Forslind K, Hafstrom I, Group BS. Patients with Early Rheumatoid Arthritis in the 2000s Have Equal Disability and Pain Despite Less Disease Activity Compared with the 1990s: Data from the BARFOT Study over 8 Years. *Journal of Rheumatology* 2017;44:723-31.

49. Behrens F, Koehm M, Schwaneck EC, Schmalzing M, Gnann H, Greger G*, et al.* Use of a "critical difference" statistical criterion improves the predictive utility of the Health Assessment Questionnaire-Disability Index score in patients with rheumatoid arthritis. *BMC Rheumatology* 2019;3:51.

50. Nair SC, Bijlsma JW, van der Werf JH, van der Veen MJ, Linn-Rasker SP, Vreugdenhil S*, et al.* Do radiographic joint damage and disease activity influence functional disability through different mechanisms? Direct and indirect effects of disease activity in established rheumatoid arthritis. *Journal of Rheumatology* 2013;40:1505-12.

51. Radner H, Alasti F, Smolen JS, Aletaha D. Physical function continues to improve when clinical remission is sustained in rheumatoid arthritis patients. *Arthritis Research & Therapy* 2015;17:203.

9 APPENDICES

Appendix 1: Excluded studies with rationale for exclusion

Full-text articles excluded (n =29)

Reasons for exclusion

Data insufficient or unusable *(n= 28)*
Adams *et al*. 2010[14]
Baganz *et al*. 2019[15]
Bechman *et al*. 2018[16]
Bergstra *et al*. 2019[17]
Boers *et al*. 2015[18]
Bremander *et al*. 2019[19]
Campbell *et al*. 2012[20]
Carvalho *et al*. 2020[21]
Drossaers-Bakker *et al*. 1999[22]
Fatima *et al*. 2020[23]
Heinimann *et al*. 2018[24]
Lee *et al*. 2017[25]
Linde *et al*. 2009[26]
Michaud *et al*. 2011[27]
Nikiophorou *et al*. 2016[28]
Norton *et al*. 2013[29]
Norton *et al*. 2014[30]
Pan *et al*. 2019[31]
Prevoo *et al*. 1995[32]
Rydell *et al*. 2018[33]
Scott *et al*. 2000[34]
Shadick *et al*. 2019[35]
Sokka *et al*. 2000[36]
Tanaka *et al*. 2008[37]
Ten Klooster *et al*. 2019[38]
van der Heijde *et al*. 2006[39]
Ward *et al*. 2015[40]
Welsing *et al*. 2001[41]

J-HAQ *(n=1)*
Tanaka *et al*. 2012[42]

Appendix 2 Potential sensitivity analyses

Studies with potential for inclusion in sensitivity analyses

Eleven published studies were considered for sensitivity analyses if the included studies could not provide sufficient data. Data from a cohort presented in one of the included studies, Nair et al 2014 [11] had baseline DAS over 5.1 and is presented in this appendix. Details are provided in Table 6.

Most of the studies had a population with no prior biologic treatment, however three studies included patients with prior biologics at baseline (Genovese et al 2016[43] Wendler et al 2014.[44] Koizumi et al 2020[45]).

In all eleven studies, HAQ and DAS were assessed by physicians. Blinding of outcome assessors was explicit in two studies[46] [43] and a third study had DAS calculations by a blinded research nurse.[47]

Furthermore, unpublished data presented by AbbVie in its submission to NICE has been included in Table 6.

Table 6 Study characteristics of studies providing data, but excluded

Reference	Study	Sample size	Follow-up	Reason not meeting inclusion criteria
Abbvie unpublished data	"*upadacitinib trials' data*"	>1000	≥ 3 months	Baseline DAS28 score > 5.1
Andersson *et al*. 2017[48]	Comparing outcomes of two cohorts of RA patients, data from the BARFOT study	Cohort 1 n=928 Cohort 2 n=1010	8 years	Baseline DAS28 score > 5.1
Baker *et al*. 2017[46]	MRI sub-study of GOBEFORE, RCT of golimumab among methotrexate-naïve patients	291	12 months	Baseline DAS28 score > 5.1
Behrens *et al*. 2019[49]	Data from multicentre observational trial, full	2740	6 months	Baseline DAS28 score > 5.1 (for

Reference	Study	Sample size	Follow-up	Reason not meeting inclusion criteria
	cohort and restricted cohort data, to determine a statistically defined critical difference for HAQ-DI			cohort providing data)
Genovese *et al*. 2016[43]	Investigating baricitinib treatment, RA-BEACON RCT	527	24 weeks	Baseline DAS28 score > 5.1
Gwinnutt *et al*. 2020[9] Clusters 1-4	Investigating clusters of symptoms associated with poor outcomes in early RA in the Rheumatoid Arthritis Medication Study, a UK multicentre cohort study	455	12 months 6 months of HAQ and DAS28 score changes	Baseline DAS28 score > 5.1
Koizumi *et al*. 2020[45]	Investigating factors for maintaining long-term functional remission, data from database of patient records	205 (of whom Remission n=154; No remission n=51)	1 year	Baseline DAS28 score < 3.2. Data from Japanese treatment, and so probably J-HAQ (not HAQ)
Nair *et al*. 2013[50]	Investigating disease activity and functional disability in T2T of RA, data from three cohorts, Netherlands	1, 034 (of whom Pyramid cohort n=551; CAMERA I n=299; CAMERA II n=236)	120 months	Baseline DAS28 score > 5.1
Nair *et al*. 2014[11]	Investigating whether treatment effects of pragmatic clinical trials are generalisable to clinical practice, data from pragmatic clinical trials of the Utrecht Rheumatoid Arthritis Cohort	Data from RCTs n=398;	6 months	Baseline DAS28 score > 5.1
Norton *et al*. 2013[29]	to identify subgroups with distinct	1460	10 years	DAS44 used (not DAS28)

Reference	Study	Sample size	Follow-up	Reason not meeting inclusion criteria
	trajectories of functional (HAQ) progression, Consecutive patients diagnosed with RA with symptoms <2 years (median 6 months) and prior to disease-modifying treatment were recruited into the Early RA Study (ERAS)			
Radner *et al.* 2015[51]	investigating the course of physical function in patients with sustained (24 weeks) DAS28 remission (DAS28CRP≤2.6), Information from clinical trials in RA patients and newly introduced TNFi or csDMARDs	610	24 weeks	Baseline DAS28 score > 5.1
van der Kooi *et al.* 2011[47]	Investigating DAS and functional ability during DAS-steered treatment, data from BeST RCT	508	5years	DAS44 used (not DAS28)
Wendler *et al.* 2014[44]	Investigating RTX in RA, prospective observational study (GERINIS study)	1658	8 months	Baseline DAS28 score > 5.1

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results

calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

January 2021

Issue 1 AbbVie data for relationship between DAS28 and HAQ score and choice of base case analysis source

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The data provided by AbbVie in the evidence submission for this MTA review, as well as in the company submission for upadacitinib (TA665 and ID3878), was ruled out for the base case analysis by the AG, because baseline DAS28 score was said to be >5.1 (Section 5.2, page 10 and Appendix 2, Page 28, Table 6) therefore this data was considered to refer to severe patients. This is incorrect.	We would like to clarify that only patients with moderately active rheumatoid arthritis (defined based on DAS28 [3.2, 5.1] at baseline) from the SELECT-COMPARE, SELECT-MONO, SELECT-BEYOND and SELECT-NEXT trials were included in the analysis supplied. These patients had a mean (sd) baseline DAS28 (CRP) score of [redacted] ([redacted]; SELECT-COMPARE), [redacted] ([redacted]; SELECT-MONO), [redacted] ([redacted]; SELECT-BEYOND) and [redacted] ([redacted]; SELECT-NEXT). Please revise the relevant sections to clarify that the data supplied by Abbvie only considers patients with moderately active rheumatoid arthritis.	ICERs would be as per the scenario analysis using the lower bound estimate DAS28 score change associated with a 0.125 HAQ change. We believe this to have only marginal impact on final ICER values but consider the Abbvie data to be less prone to uncertainty.
The selection between the Boyd et al and the data supplied by Abbvie from the SELECT trials has been based upon incorrect assumptions (see issue above). There are limitations to the Boyd et al analysis which may make it less suitable.	In the publication used to inform the relationship between DAS28 and HAQ (Boyd et al, 2013), the median time since diagnosis was only 6 months, and patients were mostly DMARD naïve. Additionally, the study was set up to analyse an incident cohort with less joint damage than the prevalent population, as reported by the authors. The baseline characteristics of the patients included in the AbbVie analysis are much more in line with the population of interest for the current decision problem. As shown in the table below, comparing baseline characteristics between Boyd et al and the moderate subgroups of the SELECT trials, the duration of disease is much longer in the SELECT trials, and the number of damaged joints is also higher. Additionally, 99.9% of moderate patients in the SELECT trials had received at least one prior cDMARD. We therefore suggest using this source to inform the relationship between DAS28 and HAQ score in the base case analysis.	

Characteristic	Boyd et al 2013 (CATCH study) (n=1144)	SELECT-COMPARE* (n=350)	SELECT-MONO* (n=221)	SELECT-BEYOND* (n=114)	SELECT-MONO* (n=183)
Age (years), mean ± SD	52.2 ± 15.8	[redacted]	[redacted]	[redacted]	[redacted]
Female sex, %	71.2	[redacted]	[redacted]	[redacted]	[redacted]
Duration of symptoms (months) ± SD (range)	6.3 ± 3.7	[redacted]	[redacted]	[redacted]	[redacted]
HAQ score, mean ± SD	0.94 ± 0.72	[redacted]	[redacted]	[redacted]	[redacted]
DAS28 score, mean ± SD	4.53 ± 1.99	[redacted]	[redacted]	[redacted]	[redacted]
Tender joint count (TJC28) ± SD	8.19 ± 6.82	[redacted]	[redacted]	[redacted]	[redacted]
Swollen joint count (SJC28) ± SD	7.42 ± 6.28	[redacted]	[redacted]	[redacted]	[redacted]

*Moderate subgroups only of the SELECT trials

Issue 2 Source of inputs from Twigg et al. (2017), Gwinnutt et al (2020), and Ling et al. (2016).

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
We have reviewed the reference for Twigg et al (2017) which is used as the upper bound in the sensitivity analyses, we were unable to find the reported values for the relationship between HAQ and DAS28 score from this paper. We were also unable to replicate the results presented based on the Gwinnutt et al (2020) and Ling et al (2016) publications.	We propose that the AG describes in its report how the values reported are derived from the referenced sources. It may be that the upper bound requires revision.	Unclear

Issue 3 Pricing

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The pricing structure used for biosimilars is not clear. The model that was received upon request did not include biosimilar prices at all, but instead used the same prices as for the original MTA.	Clarify and ensure that prices being used are nationally available to ensure a fair comparison can be made. Whilst the pricing structure for etanercept, infliximab and rituximab biosimilars is reasonably clear and nationally available, it is less clear for the adalimumab biosimilar. The only discounted price appropriate for use by NICE in assessing the cost-effectiveness of adalimumab is that offered by AbbVie under the Adalimumab Framework for 2020-2022. According to the current Methods Guide (Section 5.5.2), the default position is to use a technology's list price and to deviate from that only if there are reduced prices that meet certain	Unclear

	specific criteria, i.e. they are transparent and consistently available nationally across the NHS for a guaranteed period of time. Importantly, all adalimumab biosimilar products are subject to regional allocation, therefore cannot be considered consistently available across the NHS at a nationally available price. The Methods Guide also requires selecting and evaluating evidence (including with respect to costs) that avoids selection bias (e.g., at Section 3.3.11). This principle would be at risk if the adalimumab price selected for the purpose of the MTA was not national, transparent, and consistently available across the NHS.	

Issue 4 "Haqadjust" vba function

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The AG report describes on page 18 the use of two cohorts in the model for some of the sequences, because of uncertainty associated with the simulated experience of identical patients, which would be reduced by appointing two cohorts. This is referred to as 'first-order' uncertainty. However, first-order uncertainty is why the model is run for a high number of patients, to test the cost-effectiveness in a number of different patients within the cohort, keeping all parameters constant. Therefore, a patient with the same	We have reviewed the model, and found that the function 'haqadjust()' within Module 'sim_haqadjust' and Sub 'haqprog()' within Module 'sim_haqprog' use random numbers within the code. This means that for each sequence a different random number is applied, and therefore the HAQ change associated with response is not constant if the same patient has the same response within the same sequence, or HAQ progression is not constant for the same patient. We therefore suggest that a fixed random number (one per treatment line) is included in the Excel spreadsheet, and the VBA code refers to that instead of generating the random number within the VBA code.	This is expected to reduce the uncertainty around the model results.

characteristics, should always yield the same results when the same sequence is applied.		

Baseline Characteristics in the Moderate Disease Severity Population

Characteristic	SELECT-COMPARE	SELECT-MONO	SELECT-BEYOND	SELECT-NEXT
Age (years), mean ± SD				
Female sex, %				
Duration of RA disease (months), mean ± SD				
Duration of RA symptoms (months), mean ± SD				
HAQ score, mean ± SD				
DAS28-CRP score, mean ± SD				
28-Joint count, mean ± SD				
Tender joint count 28				
Swollen joint count 28				
66/68 Joint count, mean ± SD				
Tender joint count 68				
Swollen joint count 66				
Prior treatments, %				
Prior Biologic DMARD (At least one)				
Prior Anti-TNF Biologics (At least one)				
Prior csDMARD (At Least One)				
One Prior csDMARD				
Two Prior csDMARDs				
Three or More Prior csDMARDs				
Treatment during study, %				
ABT-494				
ABT-494 15mg QD				
ABT-494 30mg QD				
Placebo				
Methotrexate				
Adalimumab				

NOTES

[1] SELECT trial patients were included in each subpopulation based on 1) moderate RA disease severity at baseline based on NICE definition (DAS28-CRP score >3.2 and ≤5.1) ; 2) whether the patient was enrolled in a trial conducted in a csDMARD-IR RA population (SELECT NEXT, SELECT COMPARE, and SELECT MONO) or bDMARD-IR RA population (SELECT BEYOND). Patients with missing DAS28-CRP at baseline or disease severity not in range were not included in the analysis.

[2] Data from baseline visits were used for analyses (Week 0). Only observed data were used.

Comments on Assessment Report

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Amgen Limited

04 Feb 2021

Contains no confidential information

Comments on Assessment Report

We welcome the opportunity to respond to the Assessment Report (AR) for the multiple technology appraisal (MTA) of adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis (RA) after conventional disease-modifying antirheumatic drugs (DMARDs) only have failed. We have outlined the key points of our response below.

Adalimumab biosimilars address a pressing unmet need in moderate RA and present an opportunity to optimise RA disease management

There is a clear and pressing unmet need for access to biologic DMARDs (bDMARDs) such as adalimumab to improve disease control and quality of life (QoL) among patients with persistently moderate RA (defined as a Disease Activity Score-28 [DAS28] score of 3.2 to 5.1) in spite of standard of care conventional DMARD (cDMARD) treatment. Despite being substantially more clinically effective compared to cDMARD treatment, adalimumab for the treatment of moderate RA was not recommended in NICE TA375 due to cost-effectiveness challenges.[1] Consequently, the existing treatment pathway in England limits treatment options for patients with moderate RA to cDMARDs and denies access to bDMARDs,[2, 3] leaving moderate RA patients exposed to the significant risks of disease progression, irreversible joint damage, and associated consequences.

Since NICE TA375 was issued, Amgevita and other biosimilar versions of adalimumab have become available, creating the potential to realise significant cost savings to the NHS in the treatment of RA. This provides an opportunity to enable earlier patient access to adalimumab, optimising clinical management of moderate RA. Furthermore, this is consistent with the NICE TA375 Review Proposal paper, which suggests that biosimilar entry could be sufficient to recommend use of adalimumab in moderate RA.[4]

Adalimumab has already been appraised for moderate RA in TA375, and Amgen supports taking a pragmatic approach to evaluating the impact of Amgevita and other biosimilars on existing NICE Guidance

In instances where NICE Guidance already exists for the originator, a significant undertaking has already occurred to fully understand the cost-effectiveness implications to the treatment pathway. In circumstances where an additional HTA is deemed absolutely necessary to evaluate the cost-effectiveness of biosimilars in a specific indication – for example because the originator was not cost-effective – abbreviated processes should be adopted to enable accelerated appraisal timelines that fast-track patient access to efficacious treatments. As an increasing number of biosimilars are expected to be launched in the UK, a pragmatic approach will enable NICE to provide timely Guidance to optimise clinical practice.

Amgevita and other adalimumab biosimilars provide a clear value proposition in moderate RA to patients and the NHS, and NICE should endeavour to remove unnecessary barriers or delays to establishing cost-effectiveness in this patient population. Amgen fully supports NICE's pragmatic approach to this appraisal, which acknowledges the value biosimilars offer and substantially accelerates standard MTA timelines.[4]

Amgevita is highly likely to be a cost-effective use of NHS resources for the treatment of moderate RA

In line with the pragmatic approach to the appraisal, Amgen supports the Assessment Group's (AG) decision to take a simplified approach to the economic evaluation of adalimumab use at an earlier stage of disease. As such the TA375 model update has focused on reflecting the two key changes to the treatment pathway that could materially impact the model results: 1) biosimilar prices for interventions, and 2) the appropriate comparator, which is bDMARD treatment upon progression to severe RA.

In the updated model, it is clear that the quality-adjusted life year (QALY) gains achieved by adalimumab are substantially higher than the comparator across the range of scenarios presented. By comparing the QALY gains achieved by adalimumab versus the comparator, this updated model suggests that adalimumab biosimilars are highly likely to be cost-effective in moderate RA.

However, the overall cost-effectiveness results are difficult to interpret, as incremental cost-effectiveness ratios (ICERs) were not presented in the report due to commercial-in-confidence pricing. Amgen recognises that confidentiality creates challenges in reporting ICERs, but advocates that NICE should endeavour to provide some results (for example, ICER ranges) to allow interpretation of analysis conclusions without breaching confidentiality.

In conclusion, adalimumab is an important, efficacious and cost-effective treatment option for moderate RA that should be approved by NICE in this indication

Based on clinical evidence that Tumour Necrosis Factor alpha (TNFα) inhibitors demonstrate consistent efficacy across both moderate and severe RA,[5, 6] the British Society for Rheumatology and the European League Against Rheumatism have both long since recommended the early use of TNFα inhibitors in patients with moderate activity disease.[7, 8] Patients with moderate RA in European countries have benefited from access for many years.[9] Collectively, these data suggest that initiating TNFα inhibitors such as adalimumab before patients progress to severe RA increases the likelihood of achieving NICE-recommended treatment goals for RA and realising the consequent benefits. Allowing RA patients to receive adalimumab treatment at an earlier stage of disease will improve disease management of RA as a whole by 1) improving patient QoL and reducing the cost-of-illness in moderate RA due to improved disease control and 2) reducing the number of patients progressing to severe RA, further improving patient QoL and reducing the costs associated with severe RA.

Although these benefits were recognised in TA375, adalimumab was not recommended in moderate RA due to cost-effectiveness challenges. This barrier to accessing the moderate population has now been addressed by the entry of biosimilars, such as Amgevita, into the market. We therefore propose that NICE recommends adalimumab for the treatment of moderate RA.

References

1. NICE 2016. TA375: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. Available at [accessed 26 August 2020]: https://www.nice.org.uk/guidance/ta375.
2. NICE 2020. NICE Pathways: Drug treatment for rheumatoid arthritis. Available at [accessed 26 August 2020]: https://pathways.nice.org.uk/pathways/rheumatoid-arthritis.
3. NICE 2018. NG100: Rheumatoid arthritis in adults: management. Available at [accessed 26 August 2020]: https://www.nice.org.uk/guidance/ng100.
4. NICE 2019. Review of TA375; Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. Available at [accessed 26 August 2020]: https://www.nice.org.uk/guidance/ta375/evidence/review-proposal-paper-pdf-6904907822.
5. Hyrich KL, Deighton C, Watson KD, Symmons DP, Lunt M. Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity. Rheumatology (Oxford, England). 2009;48(10):1323-7.
6. Kavanaugh A, Keystone E, Greenberg JD, Reed GW, Griffith JM, Friedman AW, et al. Benefit of biologics initiation in moderate versus severe rheumatoid arthritis: evidence from a United States registry. Rheumatology (Oxford, England). 2017;56(7):1095-101.
7. Deighton C, Hyrich K, Ding T, Ledingham J, Lunt M, Luqmani R, et al. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. Rheumatology. 2010;49(6):1197-9.
8. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Annals of the rheumatic diseases. 2020;79(6):685-99.
9. Kiely P, Walsh D, Williams R, Young A. Outcome in rheumatoid arthritis patients with continued conventional therapy for moderate disease activity--the early RA network (ERAN). Rheumatology (Oxford, England). 2011;50(5):926-31.

Technology appraisal

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Biogen Idec Ltd response to Technology Assessment Group report

February 2021

Abbreviations

ACR	American College of Rheumatology
AG	Assessment Group
bDMARDs	Biologic disease-modifying anti-rheumatic drugs
cDMARDs	Conventional disease-modifying anti-rheumatic drugs
CEM	Cost-effectiveness model
DAS28	Disease Activity Score using 28 joints
DMARDs	Disease-modifying anti-rheumatic drugs
EULAR	European Alliance of Associations for Rheumatology
HAQ	Health Assessment Questionnaire
HCP	Health care professional
ICER	Incremental cost-effectiveness ratio
IL	Interleukin
JAK	Janus kinase
MoA	Mechanism of action
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
QOL	Quality of life
QALY	Quality-adjusted life-year
RA	Rheumatoid arthritis
RMOC	Regional Medicines Optimisation Committee
SLR	Systematic literature review
TNF	Tumour necrosis factor
UK	United Kingdom

Executive summary

The Company welcomes the partial review of TA375 to consider the cost-effectiveness of biologic disease-modifying anti-rheumatic drugs (bDMARDs) in moderate rheumatoid arthritis (RA) and the opportunity to comment on the associated Assessment Group (AG) report. In our response, we highlight important areas that the AG should consider within the economic model and their report; as well as those issues relevant to the Committee for decision-making.

Data from clinical trials and registries demonstrates that a good clinical response or remission from disease can be achieved with cycling.[1–5] Cycling refers to treatment with another anti-tumour necrosis factor (TNF) for patients who cannot tolerate, or whose disease has not responded to, or whose disease has stopped responding after an initial response to treatment with a first. Cycling provides the opportunity to optimise clinical outcomes and significantly improve cost-effectiveness by ensuring multiple treatment options within the anti-TNF class are used before switching to a treatment with a different mechanism of action (MoA) (Section 1). Therefore, a NICE recommendation supporting cycling with anti-TNFs concurrently available would align with United Kingdom (UK) clinical practice and international RA guidelines.[6,7] This would afford patients and clinicians the flexibility to tailor patient care, taking into consideration the route of administration, tolerability and treatment efficacy.

Clarity around the proposed positioning of anti-TNF treatments in moderate RA is requested, as this is not indicated in the AG report. The Company proposes that adalimumab, etanercept and infliximab are recommended for the treatment of moderate RA after the failure of one monotherapy conventional(c)-DMARD treatment, and prior to the use of treatments with an alternative MoA, such as janus kinase (JAK) inhibitors or interleukin (IL)-6 inhibitors (Section 2).

Additional factors relevant to decision-making have not been considered in the AG report. The Committee noted in TA375 that the innovative status of bDMARDs, reduction in surgery and hospitalisation rates and extensive benefits to patients and their carers were important factors to consider.[8] Known uncertainty of the cost-effectiveness of bDMARDs in moderate RA, such as uncertainty of HAQ progression and quality of life identified in TA375, have also not been explored (Section 3). Utilising these plausible alternative assumptions in the economic model significantly improves the cost-effectiveness of anti-TNFs in moderate RA.[9] The Company requests that uncertainty is fully assessed by the AG and considered by the Committee.

Finally, the lack of published incremental cost-effectiveness ratios (ICERs) in the AG report hinders the transparency of decision making and is inconsistent with other appraisals. NICE guidance stipulates that data fundamental to decision making should not be withheld in confidentiality and the Company urges that results are made available (Section 4).[10]

In conclusion, we believe that adalimumab, etanercept and infliximab are cost-effective treatments in moderate RA. Our response provides further insight into the benefits that these treatments elicit for the Committee's consideration. As such, we believe that the cost-effectiveness of these treatments is underestimated in the analyses performed by the AG.

Response to the Technology Assessment Group Report

1 Cycling of anti-TNF treatments is widely recommended by clinicians and is a cost-effective treatment strategy

1.1 Cycling of anti-TNFs has been endorsed by clinicians

- Cycling refers to treatment with another anti-TNF for patients who cannot tolerate, or whose disease has not responded to, or whose disease has stopped responded after an initial response to treatment with a first.
- NICE guidelines recommend progression to the next line of treatment if response to bDMARDs is not attained within 6 months. Cycling provides the opportunity to optimise clinical outcomes for patients with moderate RA, delaying progression and the time to subsequent treatments which are only recommended for severe disease. A NICE recommendation supporting cycling with anti-TNFs concurrently available aligns with UK clinical practice and UK and international RA guidelines.
- Cycling ensures there is flexibility within the guidance to enable patients and clinicians to tailor patient care that is best suited to their clinical and lifestyle requirements, thereby improving patient outcomes.
- Cycling of anti-TNF treatments before progression to treatments with an alternative mechanism of action is a cost-effective strategy for the National Health Service (NHS).

Cycling refers to treatment with another anti-TNF for patients who cannot tolerate, or whose disease has not responded to, or whose disease has stopped responding after an initial response to treatment with a first. Data from clinical trials and registries, supported by the notion recognised in the European Alliance of Associations for Rheumatology (EULAR) guidelines and the Regional Medicines Optimisation Committee (RMOC) statement, show a significant proportion of patients regain clinical remission or good disease control with the cycling of anti-TNFs following lack of response to the first, compared to patients who remained on the original treatment ($p<0.01$).[1–5] Further data has demonstrated that better improvements in disease control were seen in patients who cycled to treatment with adalimumab or etanercept after infliximab due to inefficacy in the first treatment; the difference was suggested to be due to differences in the MoA.[2] Etanercept competitively inhibits the binding of both TNF and lymphotoxin α to cell surface TNF receptors whereas infliximab and adalimumab bind both cell surface and soluble TNF but not lymphotoxin.[2,11] Alternative hypotheses to why patients may respond to one anti-TNF and not another include differential bioavailability of treatments,

the development of anti-drug antibodies, differences in stability of the drug–TNF complex and finally differences in patient adherence between anti-TNF treatments.[12]

Cycling, where clinically appropriate, could delay the switch to medications with a different MoA. This would delay the time until all treatment classes have been exhausted, since once a patient has moved on from a specific treatment class it is not likely to be reintroduced as it was deemed insufficient or not tolerated. Maintaining a range of treatments available with different MoA across the disease spectrum would reduce the risk of developing refractory disease and delay or prevent disease progression.[13] Therefore, cycling of anti-TNF treatments, where appropriate, can extend the therapeutic window of anti-TNFs and maximise the use of a MoA before moving to another treatment class. For these reasons, cycling of anti-TNF treatments is followed in clinical practice in the UK and endorsed by the guidelines from EULAR and recommendations from other specialist bodies, such as the RMOC.[6,7]

Moreover, there is a preference to exhaust the current treatment class via cycling before switching to a treatment with a different MoA; it is therefore likely that cycling of anti-TNF treatments will be limited if anti-TNFs are not concurrently available. Moreover, the noted differences in the MoA of anti-TNFs highlight the concurrent availability of anti-TNFs to ensure optimised outcomes with cycling. In addition to facilitating cycling, ensuring the concurrent availability of anti-TNFs, without constraining selection, would offer choice and flexibility to patients and healthcare professionals (HCPs). Flexibility enables treatment selection to be determined by discussion between the HCP and patient, giving consideration to the treatment most suited to the patient's requirements and lifestyle to optimise disease management and outcomes. Empowering patients to actively participate in the decision-making process and contribute to the treatment decision is also expected to improve adherence which, in turn, is correlated with better clinical outcomes.[14,15]

However, Section 6.1 of the AG report states that '*the sequence after the first bDMARD was accepted, to be the use of [rituximab] and then [tocilizumab]*'. Therefore, there has been no consideration given to cycling by the AG or the concurrent availability of anti-TNFs. Therefore, the Committee should consider flexibility within the updated guidance to endorse anti-TNF cycling with anti-TNFs concurrently available to optimise patient outcomes, patient choice, and align with UK clinical practice as well as UK and international RA guidelines.

1.2 Cycling of anti-TNFs is a cost-effective treatment strategy

In Section 6.2 of the Assessment Report, the AG state that '*if there is no EULAR response to a bDMARD after 6 months the next treatment in the strategy is used*'. However, the economic model does not consider the cost-effectiveness of cycling anti-TNF treatments as recommended in guidance published by EULAR and ACR.[6,7] As noted in Section 1.1, cycling provides the opportunity to optimise clinical outcomes by ensuring multiple treatment options within the anti-TNF class are used before switching to a treatment with a different MoA. The Company's analyses demonstrate that the ICER for anti-TNFs treatments would reduce significantly, by approximately £10,000-£20,000, when cycling of anti-TNF treatments is implemented in the economic model. Moreover, when a cycling strategy is considered, the ICERs for anti-TNF treatments are cost-effective, lying below NICE's willingness-to-pay threshold.

Therefore, the Company requests that the AG perform analyses to assess the cost-effectiveness of cycling anti-TNF treatments within moderate RA before progression to treatment with another MoA and these analyses are incorporated into the AG Report.

2 Treatment pathways and guidance

- There is a considerable unmet need for patients with moderate RA as, if patients are unresponsive to cDMARDS alone or in combination, there are currently no recommended treatment alternatives available until disease is severe, leaving patients suffering with uncontrolled RA.
- Initiating anti-TNF treatments earlier in the treatment pathway at the moderate RA stage, upon failure of cDMARDs, offers the opportunity to slow or delay disease progression and improve quality of life (QOL) where patients would otherwise remain untreated; earlier initiation of anti-TNFs offers considerable opportunities to minimise the burden of RA to patients, the NHS and wider society.
- The Company proposes that anti-TNF treatment be recommended for the management of moderate RA after the failure of one cDMARD used in monotherapy.

2.1 There is a high unmet need in patients with moderate rheumatoid arthritis unresponsive to cDMARDS

In Section 3.1 of the Assessment Report (Description of health problem), a brief summary of RA is provided. This summary does not identify and recognise the full impact of RA on patients' lives or the unmet need of patients unresponsive to cDMARDs with moderate RA, where there are no recommended treatment options currently available. As a result, this does not convey or assess the true impact of earlier initiation of anti-TNFs to patients' QOL nor to the NHS. The Committee should consider the following points when developing their recommendations for the use of bDMARDs in patients with moderate RA who are unresponsive to cDMARDs.

RA is associated with impaired joint function, pain and tenderness which can lead to systemic complications, affecting the lungs, heart, and eyes. Systemic complications increase risk of other diseases, including a 50%-70% higher risk of heart disease in RA compared to the general population.[16,17] These complications cause increased morbidity and reduced health-related QOL.[18]

RA affects employment, with patients four times more likely to be unemployed than the general population (17.3% vs 4.3%, respectively).[19] Disease severity has been shown to be significantly associated with work impairment, with a 2020 study demonstrating that a unit increase in the Disease Activity Score using 28 joints (DAS28) score led to an increase in work impairment of 4.7% (p= 0.011).[20] Unemployment in patients with RA has decreased since the former survey was conducted in 2007 which is thought to be due to earlier access to effective treatments,[19] demonstrating that the availability of effective treatments can decrease unemployment amongst patients with RA.

cDMARDs, such as oral methotrexate, leflunomide or sulfasalazine, are recommended by NICE as first-line treatment for patients with RA.[21] Subsequent treatments upon the failure of cDMARDs are recommended only in severe RA. Therefore, patients who are unresponsive to cDMARDS, alone or in combination, face a significant unmet need; they must either remain untreated until their RA progresses to severe stage, or continue treatment with ineffective therapies.

The use of anti-TNFs earlier in the treatment pathway offers more time to identify an appropriate treatment by cycling if response or tolerability is not attained with first choice of anti-TNF treatment (please refer to Section 1 for more detail).

2.2 Proposed position of anti-TNF treatment in moderate RA

Whilst the partial review is considering the introduction of bDMARDs in moderate RA, the proposed positioning of the treatments within the treatment pathway has not been clearly communicated. The AG report states in Section 4, definition of the decision problem, that the population considered is '*patients with moderate-to-severe RA*'. However, the economic model gives the option to perform analyses according to multiple historical cDMARD use including the following scenarios: one previous cDMARD monotherapy; two previous cDMARD monotherapies; or one previous cDMARD combination.

The Company believes that all anti-TNF treatments should be recommended for the management of patients with moderate RA after the failure of one cDMARD used in monotherapy, and prior to the use of IL-6 inhibitors or JAK inhibitors. This would align NICE guidance with UK clinical practice with the EULAR and ACR guidelines, which recommend that if the treatment target is not reached after 6 months of initiating methotrexate, a bDMARD or JAK-inhibitor should be considered as alternative treatments.[22,23] Additionally, recommendation of anti-TNF treatments in this position would ensure cycling of anti-TNF treatments, as described in Section 1, is possible before moving on to treatments with a different MoA such as JAK-inhibitors of which the tolerability are less well understood.[24] Anti-TNFs have demonstrated a good tolerability profile based on clinical experience spanning several years;[25] in particular, etanercept has a half-life of 4.3 days, the shortest amongst anti-TNFs, which confers potential advantages.[26]

Therefore, the Company requests that the Committee considers making their recommendation of bDMARDs for the management of moderate RA after the failure of one cDMARD in monotherapy. The cost implications of using anti-TNFs in moderate RA will be partially offset by a reduced uptake of anti-TNF treatment amongst patients with severe disease where they are currently recommended, when compared to current usage.

2.3 Homecare packages offers valuable additional benefits in the treatment choice decision for anti-TNFs

As summarised in Section 3.2 of the Assessment Report (current service provision), the current NICE guidance states that the least expensive recommended treatment should be used first.[27] The guidance additionally stipulates that administration costs, dose needed and product price per dose should be considered. However, any recommendation issued from this guidance review should also consider homecare offerings, such as those available with Imraldi (adalimumab) and Benepali (etanercept). These services have been designed to support the

patient to self-administer their medication while at home, improve concordance, and to ensure flexibility to suit both the patient and the HCP. Evidence suggests that increasing a patient's ability to manage their own long-term health condition may have a positive impact on reducing hospitalisation, increasing medication adherence, and improving health outcomes.[14,15,28] As such, homecare packages are associated with intangible cost savings.

Therefore, the Company requests that the Committee does not restrict recommendations to the cheapest treatment available.

3 Additional factors and uncertainty relevant for the Committee's decision making

- In addition to the cost-effectiveness of treatments, the innovative nature of bDMARDs, wider savings to NHS resource use and QOL benefits to patients and caregivers are relevant for decision-making.
- Known uncertainty of the cost-effectiveness of bDMARDs in RA characterised in TA375 was not reported or explored in the Assessment Group report; as shown previously, these significantly improve the cost-effectiveness of anti-TNFs in moderate RA. The Company requests that uncertainty is fully assessed by the AG and considered by the Committee in their decision making.

3.1 There are additional considerations relevant for the Committee's decision making including the innovative nature of bDMARDs and their extensive benefits

In the original TA375 appraisal, scenario analyses were performed by the AG to quantify the uncertainty of the cost-effectiveness of bDMARDs.[8] In the published appraisal guidance, the uncertainty in the true cost-effectiveness of treatments was quantified and reported to have been considered by the Committee. The Committee concluded that, at the time of the appraisal, the most plausible ICER for bDMARDs used in severe active RA was likely to lie between the AG's base-case ICER and the AG's ICER for the exploratory analysis for the severe group with the fastest Health Assessment Questionnaire (HAQ) progression (that is, between £41,600 and £25,300, respectively, per QALY gained).[8]

The Committee accepted there were additional factors that were required for decision-making – including innovative drugs, reduction in surgery and hospitalisation rates and extensive benefits to patients and their families in terms of physical and mental health – which was as follows:

"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 as 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."

The high unmet need of patients with moderate RA, and the impact on employment and QOL, are discussed in Section 2.1. These additional factors – including the innovative nature of the bDMARDs, reduction in hospitalisation rates and the wider societal implications of providing more effective treatments to patients with moderate RA – as identified previously in TA375, are relevant for the Committee to take into account for decision making. The Company requests that the AG give consideration to these factors in their assessment report.

3.2 Uncertainty associated with the cost-effectiveness analyses are required for decision making

In the original TA375 appraisal, scenario analyses were performed by the AG for moderate active RA previously treated with methotrexate, which identified considerable uncertainty compared to the base case and Committee's preferred analysis. The Committee concluded that the most plausible ICER was £51,100 per QALY gained for the bDMARDs in moderate active RA. However, there was considerable uncertainty associated with this, which included:[29]

- The trajectory of HAQ progression was not certain; in the base case a linear HAQ progression was assumed (Section 4.72 of the technology appraisal guidance [TA375]). A sensitivity analysis was performed to capture patients with a faster HAQ progression; this resulted in lower ICERs for the moderate active group in this sub population, when compared to the base case.
- The utility mapping function was uncertain; the base case used calculated utility using a method based on mixture models from Hernandez Alava et al. (Section 4.72: A scenario with an alternative utility mapping function from Malottiki et al. was used which resulted in a lower ICER of £36,000 for bDMARDS plus methotrexate in patients with moderate RA previously treated with methotrexate.
- HAQ progression after 15 years was not certain; the base case assumed HAQ to plateau after 15 years (Section 4.86). The AG ran an exploratory analysis where it assumed the worsening of HAQ progression after 15 years would continue as the rate of progression seen between years 12-15. This scenario reduced the ICER slightly compared to the base case; for moderate patients with the fastest HAQ progression, the median ICER was £25,700.

The Company notes that the majority of the alternative scenarios explored by the AG resulted in lower ICERs, with their base case at the higher end of plausible estimates.

In addition to the uncertainties accepted by the Committee in TA375, further uncertainties have been identified. The efficacy data used to quantify the clinical effectiveness of treatment is derived from a network meta-analysis based upon randomised controlled trials (RCTs) in a

mixed cohort of patients with varying disease severity; the efficacy data of anti-TNF treatments does not reflect the impact of treatment in moderate RA patients specifically. It is anticipated that greater efficacy would be observed with the use of bDMARDs in moderate RA patients compared to severe RA patients, given that earlier initiation of treatment is associated with better outcomes,[30] which would in turn result in a lower ICER.

Moreover, since patients with RA often require care, the impact to caregiver health-related QOL should be considered within the remit of the NICE reference case. Reducing or delaying caregiver burden would contribute further direct health benefits of these treatments and result in a lower ICER for the treatments under review. Furthermore, the costs and benefits were based only on the perspective of the NHS and personal social services.[8] Given the productivity impacts of RA, it would be important to consider the wider societal perspective which would also reduce the ICER.

Only the relationship between DAS28 and HAQ score have been explored as an area of potential uncertainty in this partial review. Further areas have not been acknowledged of explored in this partial update. Therefore, the likely downward trends of ICERs have not been quantified, inhibiting interpretation of the plausible range that the ICERs for the treatments under review may fall into.

The Company requests that the AG performs and reports results of scenario analyses within moderate RA, including: varying the rate of HAQ progression; the time duration over which HAQ deteriorates; the use of alternative utility mapping functions; direct health effects to carers; and the societal perspective. This will quantify the uncertainty in the cost-effectiveness of bDMARDs in moderate RA. Likewise, the Company requests that the Committee consider the likely range of the ICERs for the treatments currently under review when determining their recommendations.

3.3 Representation of moderate RA in relevant studies identified for the relationship between DAS28 score and HAQ

In Section 5.2 of the Assessment Report, assessment of clinical effectiveness results, the findings of the systematic literature review (SLR) conducted by the AG are reported. The studies identified included a range of mean/median DAS28 scores at baseline. Whilst all studies reported an average DAS28 score within the moderate range of RA, patients were on average closer to the upper end of the threshold, representing the more severe RA patients. As a result, the SLR may reflect a more progressed cohort than typical patients with moderate RA. The DAS28 baseline scores of the included references ranged from a mean of 4.50 to 5.10 and a median from 3.76 to 5.06. Three out of nine studies had a mean/median DAS28 score greater than or equal to 5.00 (falling just below the threshold range of severe RA of greater than 5.1). Five out of nine studies had a mean or median DAS28 score of greater than or equal to 4.50 and only one reference included a cohort with a median less than 4; patients newly classified with moderate RA consequently lack representation.

In particular, it is reported that the most appropriate estimate of the relationship between the change in DAS28 and HAQ score is 0.48, sourced from the publication by Boyd *et al*. (2013).[31] This publication had a mean DAS28 score of 4.53 at baseline with a standard deviation of 1.99. The mean DAS28 score reported in Boyd *et al*. (2013) is far closer to the severe RA threshold than the moderate and is biased towards those with more advanced disease. Indeed, from the

variance in DAS28 scores reported at baseline there is a significant proportion of patients within the cohort categorised as severe at baseline. It is therefore not reflective of the complete moderate RA patient population. It is important that clinical parameters are determined from patients with moderate RA as recognised by the EULAR and ACR guidelines, which aligns with UK clinical practice.[32,33] The parametrisation of clinical effectiveness should be aligned with clinical practice since this will directly influence the cost-effectiveness of the regimes under investigation and, therefore, the recommendations that the Committee will develop.

In addition, an important study was excluded by the AG from the SLR that provides relevant information to derive the relationship between change in DAS28 score and HAQ score. The Linde et al. (2009) study included a large cohort of 2,776 RA patients which contained a moderate cohort.[34] The coefficient of the relationship between HAQ and DAS28 score in patients classified as having moderate is reported as 0.43. This facilitates the derivation of the change in DAS28 score of 0.291 associated with a step-change of 0.125 in HAQ score in patients who have moderate RA.

The Company recommends that the AG retrieve the Linde *et al.* (2009) study and select it in the base case as a more representative reflective of the relationship between DAS28 score and HAQ in patients with moderate RA. This will ensure that the clinical data utilised in the model is reflective of patients with moderate RA.

4 Lack of published incremental cost-effectiveness ratios hinders transparency of decision making

- NICE guidance stipulates that data fundamental to decision making should not be withheld in confidentiality;[33] the omission of cost-effectiveness results inhibits a transparent decision-making process.

In Section 7 of the Assessment Report, conclusions, it is stated that the '*cost-effectiveness results cannot be provided in this document*'. The Guide to the Processes of Technology Appraisal published by NICE explicitly state that '*data that are likely to be fundamental to the appraisal committee's decision-making cannot be marked as confidential*'.[10]

Therefore, for the transparency of decision making in this review process, it is imperative that the AG reports the cost-effectiveness findings of their assessment. At the very least, ICERs for all treatments at their list price should be made publicly available to ensure that the results of the analysis can be verified by stakeholders. Failure to report these data inhibits the transparency of any decisions made by the Committee. In previous appraisals of treatments of bDMARDs, where biosimilars were also included, such as TA375, the ICERs were published as part of final guidance. The approach taken withholding the publication of ICERS in this ongoing appraisal is also inconsistent with other appraisals.

Therefore, the Company urges the AG to report ICERs to ensure that the decision-making process is open and transparent, and a consistent approach is maintained in line with NICE's published processes.

5 Summary table of typographical and factual inaccuracies in the Assessment Report

Table 1: Suggested changes to the Assessment Report

Place in the Assessment Report	Description of problem	Description of proposed amendment
Section 3.2, Current service provision	'Recommended' is repeated in the first sentence of the first paragraph.	Remove repeated word
Section 3.2, Current service provision	The disease is incorrectly reported as plural in the first sentence of the first paragraph "2) the diseases has not responded".	Replace "diseases" with "disease"
Section 5.2, Results - Figure 1	Studies with potential for sensitivity analyses "(n=12*)" does not match the figure 'eleven' as reported in the text and in Appendix 2 for the same category.	Update the value in the figure, to the true number of studies with potential for a sensitivity analysis.
Section 5.2	Grammatical error: "In all studies apart from Ariza-Ariza et al.[6] and cluster 6 of Gwinnutt et al.[9] HAQ and DAS28 scores…"	Please amend for grammatical clarity to: "In all studies apart from Ariza-Ariza et al.[6] and cluster 6 of Gwinnutt et al,[9] HAQ and DAS28 scores…"

References

1. Soliman MM, Ashcroft DM, Watson KD, *et al.* Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2011. 70: 583–589.
2. Chatzidionysiou K, Askling J, Eriksson J, *et al.* Effectiveness of TNF inhibitor switch in RA: results from the national Swedish register. *Ann Rheum Dis* 2015. 74: 890–896.
3. Hyrich KL, Lunt M, Dixon WG, *et al.* Effects of switching between anti-TNF therapies on HAQ response in patients who do not respond to their first anti-TNF drug. *Rheumatology* 2008. 47: 1000–1005.
4. Bombardieri S, Ruiz AA, Fardellone P, *et al.* Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. *Rheumatology (Oxford)* 2007. 46: 1191–1199.
5. Bessette L, Khraishi M, Kivitz AJ, *et al.* Single-Arm Study of Etanercept in Adult Patients with Moderate to Severe Rheumatoid Arthritis Who Failed Adalimumab Treatment. *Rheumatol Ther* 2017. 4: 391–404.
6. Smolen JS, Landewé RBM, Bijlsma JWJ, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Annals of the Rheumatic Diseases* 2020. 79: 685–699.
7. Updated RMOC Advisory statement: Sequential Use of Biologic Medicines. *SPS - Specialist Pharmacy Service* at <https://www.sps.nhs.uk/articles/rmoc-advisory-statement-sequential-use-of-biologic-medicines/>
8. NICE. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed | Guidance | TA375. 2016. at <https://www.nice.org.uk/guidance/TA375>

9. Stevenson M, 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 antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. *Health Technol Assess* 2016. 20: 1–610.
10. NICE. Guide to the processes of technology appraisal. 2014. Available at: https://www.nice.org.uk/process/pmg19/resources/guide-to-the-processes-of-technology-appraisal-pdf-72286663351237
11. Combe B. Update on the use of etanercept across a spectrum of rheumatoid disorders. *Biologics* 2008. 2: 165–173.
12. Hyrich KL, Lunt M, Dixon WG, *et al.* Effects of switching between anti-TNF therapies on HAQ response in patients who do not respond to their first anti-TNF drug. *Rheumatology* 2008. 47: 1000–1005.
13. Kearsley-Fleet L, Davies R, Cock DD, *et al.* Biologic refractory disease in rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Annals of the Rheumatic Diseases* 2018. 77: 1405–1412.
14. NHS England. NHS England » Patient activation and PAM FAQs. at <https://www.england.nhs.uk/personalisedcare/supported-self-management/patient-activation/pa-faqs/#Q15>
15. Hibbard J & Gilburt H. Supporting people to manage their health. 2014. at <https://www.kingsfund.org.uk/publications/supporting-people-manage-their-health>
16. Peters MJL, Symmons DPM, McCarey D, *et al.* EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010. 69: 325–331.
17. Chodara AM, Wattiaux A & Bartels CM. Managing cardiovascular disease risk in rheumatoid arthritis: clinical updates and three strategic approaches. *Curr Rheumatol Rep* 2017. 19: 16.

18. Ceccarelli F, Massafra U, Perricone C, *et al.* Anti-TNF treatment response in rheumatoid arthritis patients with moderate disease activity: a prospective observational multicentre study (MODERATE). *Clin Exp Rheumatol* 2017. 35: 24–32.
19. NRAS - National Rheumatoid Arthritis Society. Work Matters - A UK wide survey of adults with Rheumatoid Arthritis and Juvenile Idiopathic Arthritis on the impact of their disease on work. 2017. at <https://www.nras.org.uk/publications/work-matters>
20. Galloway J, Capron J-P, De Leonardis F, *et al.* The impact of disease severity and duration on cost, early retirement and ability to work in rheumatoid arthritis in Europe: an economic modelling study. *Rheumatol Adv Pract* 2020. 4: rkaa041–rkaa041.
21. NICE. Rheumatoid arthritis in adults: management. NG100. 2018. at <https://www.nice.org.uk/guidance/ng100>
22. Smolen JS, Landewé R, Breedveld FC, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Annals of the Rheumatic Diseases* 2010. 69: 964–975.
23. American College of Rheumatology. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. 2015. at <https://www.rheumatology.org/Portals/0/Files/ACR%202015%20RA%20Guideline.pdf>
24. Harigai M. Growing evidence of the safety of JAK inhibitors in patients with rheumatoid arthritis. *Rheumatology* 2019. 58: i34–i42.
25. Leombruno JP, Einarson TR & Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. *Annals of the Rheumatic Diseases* 2009. 68: 1136–1145.
26. Reddy SP, Shah VV, Lin EJ, *et al.* in *Therapy for Severe Psoriasis* (Elsevier, 2016). (eds. Wu, J. J., Feldman, S. R. & Lebwohl, M. G.) 83–96. doi:10.1016/B978-0-323-44797-3.00008-6
27. NICE. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after

conventional DMARDs only have failed (TA375). at <https://www.nice.org.uk/guidance/ta375/chapter/1-Recommendations>

28. Deeny S, Thorlby R & Steventon A. Reducing emergency admissions: Unlocking the potential of people to better manage their long-term conditions. *The Health Foundation* 2018. at <https://www.health.org.uk/publications/reducing-emergency-admissions-unlocking-the-potential-of-people-to-better-manage-their-long-term-conditions>
29. NICE. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. 2016. at <https://www.nice.org.uk/guidance/ta375/resources/adalimumab-etanercept-infliximab-certolizumab-pegol-golimumab-tocilizumab-and-abatacept-for-rheumatoid-arthritis-not-previously-treated-with-dmards-or-after-conventional-dmards-only-have-failed-pdf-82602790920133>
30. Furst DE, Pangan AL, Harrold LR, *et al.* Greater likelihood of remission in rheumatoid arthritis patients treated earlier in the disease course: Results from the Consortium of Rheumatology Researchers of North America registry. *Arthritis Care & Research* 2011. 63: 856–864.
31. Boyd TA, Bonner A, Thorne C, *et al.* The Relationship Between Function and Disease Activity as Measured by the HAQ and DAS28 Varies Over Time and by Rheumatoid Factor Status in Early Inflammatory Arthritis (EIA). Results from the CATCH Cohort. *Open Rheumatol J* 2013. 7: 58–63.
32. England BR, Tiong BK, Bergman MJ, *et al.* 2019 Update of the American College of Rheumatology Recommended Rheumatoid Arthritis Disease Activity Measures. *Arthritis Care Res (Hoboken)* 2019. 71: 1540–1555.
33. van Gestel A, Haagsma C & van Riel P. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis and rheumatism* 1998. 41: 1845–1850.

34. Linde L, Sørensen J, Østergaard M, *et al.* What Factors Influence the Health Status of Patients with Rheumatoid Arthritis Measured by the SF-12v2 Health Survey and the Health Assessment Questionnaire? *The Journal of Rheumatology* 2009. 36: 2183–2189.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results

calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

January 2021

Company response provided by Biogen Idec Ltd on 04 February 2021.

Issue 1 Out of date data used for mortality

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The data used to inform lifetables in the model is referenced to be from the year 2009-11. The rates of mortality in the general population have reduced in the last 10 years, and as such it would be appropriate to update to the most recently available data.	Update the q_x column input for male and female mortality data in Lifetables!B9:109 and Lifetables!F9:109, respectively, such that it is the latest available, for 2017-2019, from the Office for National Statistics.	Mortality in the general population has been reduced, so the life years gained with treatment are underestimated. It is therefore likely that the incremental QALY gains would be increased.

7th January 2021.

Dear NICE Colleague,

I have reviewed the revision of NICE TA375 and so far have one comment. I may wish to provide further feedback in due course.

Please note that Celltrion produce and market both Remsima (infliximab vials) and Remsima SC (infliximab subcutaneous, available in prefilled devices).

I understand that the review is a comparison between molecules and as such, Remsima SC is not included as a stand-alone product or sub-type of the infliximab molecule.

However, I note that in Section 3.3 of the larger file the following paragraph is written:

ADA, ETN and IFX, all inhibit the activity of tumour necrosis factor alpha, a pro-inflammatory mediator that is partly responsible for damage to the joints in RA. ADA and ETN are provided sc, whereas IFX is an iv administration. ADA is provided at doses of 40mg every other week, ETN at doses of 50mg every week, and IFX is provided at 3mg/kg at weeks 0, 2 and 6 and then every 8 weeks.

I must request that an amendment be considered which reflects that there is a subcutaneous infliximab molecule available, as I believe the above statement could easily mislead readers to believing that infliximab is only available for IV administration.

A simple sentence indicating that there is a subcutaneous version available but it is not specifically reviewed in this document, and informing readers that an Evidence Summary for Remsima SC in RA (ES29) was published in 2020, should suffice.

I would like to discuss this please so very much appreciate your response.

Kind regards,

[redacted]
Celltrion Healthcare UK Limited.
[redacted]

Rheumatoid arthritis (moderate) - adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept (partial review of TA375) [ID2710]

Assessment Report consultation response Pfizer Ltd.

Pfizer welcomes the opportunity to provide feedback on the Assessment Group model, updated for the review of TA375 for moderate RA. In response to the consultation we would like to make the following comments.

1. Technologies included in the guidance

Pfizer would like to reiterate the comment that the targeted review does not take into consideration all available and licensed treatment options in moderate RA. The Assessment Report states that the only technologies considered in the review are abatacept, adalimumab, etanercept and infliximab, because only the manufacturing companies of these products have paid the NICE fee. Whereas the manufacturers of certolizumab pegol, golimumab and tocilizumab decided not to take part in the review. However, besides these 7 technologies, there are several other treatments that have got marketing authorisation in moderate RA. These technologies are baricitinib (TA466), tofacitinib (TA480) and sarilumab TA485), which have all been assessed and recommended by NICE for severe RA, but all have marketing authorization for moderate RA as well. For completeness, besides these, there are 2 other technologies which are currently going through NICE appraisal upadacitinib (TA665 and ID3878) and filgotinib (ID1632). The logical approach would have been to include all available technologies into the review in order to maximize patient access to advanced therapies in moderate RA. And Pfizer believes it is regrettable that not all available treatment options have been included in the review.
As the Appraisal Committee concluded across all RA appraisals; it is important for patients and clinicians to have a range of treatment options in rheumatoid arthritis available, since rheumatoid arthritis is a chronic lifetime condition that can severely reduce quality of life and conventional DMARDs such as methotrexate are inadequate therapy for many people. Therefore, it is contradictory not to include all licensed treatment options in this review, in order to ensure access to advanced therapies for patients with moderate RA. This exclusion will restrict patient and clinician choice and may create a more complex treatment pathway dictated by a restricted NICE review of a much broader pathway instead of conducting a comprehensive multiple technology appraisal, which is inclusive of all licensed treatment options.

[redacted]

2. Modelling approach of treatment sequences

2 advanced biological therapies, 2 JAK inhibitors (upadacitinib and filgotinib) are currently going through NICE appraisal. The positive decision for filgotinib is expected to be published on the 24th February, which recommends filgotinib for moderate to severe RA. The FAD for filgotinib refers to the unpublished guidance of upadacitinib when it discusses modelling approaches, assuming that a

previous appraisal in moderate RA has set the precedent for the modelling approach.
As Pfizer understands the current review of TA375 uses the original Assessment Group model and applies the assumptions that the Appraisal Committee has originally accepted back in 2015. However, we believe that consideration should have been given to the more recent modelling approaches and that their effect on the cost-effectiveness results should have been explored in scenario analyses.
This discrepancy and inconsistency between NICE guidances creates confusion and neglects the methodological changes since the publication of TA375 in 2016. The difference in modelling assumptions can lead to differences in the cost-effectiveness results and therefore should be tested during the appraisal. Otherwise the decision will be based on different inputs and therefore will be inconsistent with previous NICE guidance.
The main area where this discrepancy happens is the modelling of treatment sequences in moderate RA. The current Assessment Group model seems to replicate the same treatment sequence in moderate RA as in severe RA. Therefore, the first line bDMARDs were followed by RTX and then TCZ reverting to csDMARDs following the failure of TCZ. This treatment sequence is significantly longer to the sequence modelled in the filgotinib appraisal and many previous appraisals in moderate RA, where after discontinuation of the first bDMARD patients reverted back to csDMARDs until their disease progressed to severe disease. The shorter sequence was accepted by the NICE committee and was considered as an appropriate representation of the potential treatment pathway after the introduction of the biological treatment in moderate RA.
To measure cost-effectiveness of a technology in RA it is common to measure sequences, which means that the costs and benefits of not only one, but multiple biologics are incurred in any given sequence. The length of sequence has a significant impact on the cost-effectiveness results, therefore using a different method for modelling the treatment sequence across appraisals leads to discrepancy and inconsistency across appraisals.
In terms of the technologies included in the sequence in the review of TA375, the protocol does not state that the manufacturers of RTX or TCZ would have agreed to participate in the review. RTX was not included in the original guidance, therefore the manufacturer was not invited to submit evidence during this review and the manufacturer of TCZ did not chose to participate by paying the NICE fee. Moreover, rituximab is not licensed for moderate RA only for severe disease, therefore it is inappropriate that it appears in the moderate RA sequence as it is unlikely to be used in clinical practice.
Another important point to make is that any recommendation made on the basis of this treatment sequence will imply that RTX and TCZ can be used in moderate RA, which is incorrect. Therefore, we believe this error should be corrected in the model and scenario analyses should be presented to the committee to explore the impact on the cost-effectiveness results. It should also be made clear what modelling approach the committee prefers for future reference, as this will have an implication on any future appraisals in moderate to severe RA.

3. Uncertainty around the efficacy data used in the Assessment Group model

The AG report presents EULAR response rates associated with each treatment in Table 5, however no reference for these response rates is provided in the report. The report goes on to state the consequences of each EULAR response are provided in Stevenson et al 2016, however the response

rates here do no match those in the publication. As such it is unclear for which population these response rates are relevant and we believe this should be made clear for the Appraisal Committee and for consultees and commentators.
During the recent filgotinib appraisal the ERG raised concerns about the assumption that EULAR response rates are the same regardless of the line of treatment or disease severity and stated that bias is likely introduced by using EULAR response rates for all treatments at different points of the treatment pathway. This assumption seems to be applied to the Assessment Group model in the current appraisal, which introduces uncertainty to the results generated by the model.
Similarly, it seems from the model, that the assumptions around the reductions in HAQ-DI associated with each level of EULAR response have not been updated to reflect the values for the moderate RA population, but they are using values that may not be relevant for a purely moderate RA subgroup.
As mentioned in the previous point in order to ensure consistency amongst NICE guidance and future appraisals, it would be important to clarify where the input values came from and what assumptions are relevant and accepted by the NICE committee for modelling moderate to severe RA.

4. Uncertainty around baseline patient characteristics applied in the model

No details are provided about the source of population characteristics used to inform the model, therefore it was not possible for us to check whether they are relevant for a moderate RA subgroup. These details are also not reported in Stevenson et al. 2016[1]. The Assessment Group model suggests a baseline HAQ score of 1.45, which is comparable to the HAQ scores in previous clinical trials, including ORAL STANDARD trial[2] (1.5) for tofacitinib, and FINCH 1 trial[3] (1.6) for filgotinib, however these trials were conducted in more severe populations, which would be expected to have higher HAQ scores at baseline than the moderate RA considered in this report.
[redacted]. As HAQ scores are used to determine utility values in the model, the baseline HAQ score will directly influence the total number of QALYs a patient gains over their lifetime. During the filgotinib appraisal it was shown that the baseline characteristics of the population (baseline HAQ score) can impact the cost-effectiveness results, as selecting the mean DAS score from FINCH 1 resulted in patients progressing faster to severe disease and will ultimately result in fewer QALYs generated by the model.

5. No cost-effectiveness results are reported in the Assessment Report

Pfizer believes that not providing any cost-effectiveness results goes against the practice NICE has been following for the consideration of comparator discounts and at least ICER ranges to indicate likelihood of cost-effectiveness, net benefits or total costs at list price should have been possible to report. We think this goes against one of NICE's key values, transparency, because stakeholders cannot know what cost-effectiveness evidence the Appraisal Committee going to base its decision on. This practice also goes against NICE's rules for handling confidential comparator prices, which recommends including list price analyses in the documentation in case of confidential comparator PASs (section 3.8.8 Single technology appraisal: User guide for company evidence submission template 2017).

References:

1. Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J*, et al.* Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. *Health Technol Assess* 2016;20:1-610.
2. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367(6):508-19.
3. Combe B, Kivitz A, Tanaka Y, van der Heijde D, Matzkies F, Bartok B, et al. Efficacy and safety of filgotinib for patients with rheumatoid arthritis with inadequate response to methotrexate: FINCH 1 primary outcome results. Ann Rheum Dis 2019; 78 (supplement 2):A77.

Sandoz UK RESPONSE TO NICE TA375 Assessment Report and Economic Model

Sandoz would like to thank NICE for having the opportunity to comment on the assessment and economic model produced by ScHARR and the collaborative approach that has been taken to the partial updating of the NICE technology appraisal 375 (TA 375) considering the cost-effectiveness of biologic disease – modifying anti-rheumatic drugs (bDMARDs) in patients with moderate to severe rheumatoid arthritis.

GENERAL CONSIDERATIONS

Overall, the current model shows consistency with prior Technology Appraisals (TA), amongst those are: TA375 (1), TA195 (2), TA466 (3), TA480 (4) and TA665 (5); which guarantees minimizing differential bias across different TAs and timelines.

SANDOZ has performed a considered review of the model in the context of testing its reliability and informing our understanding of the process of the appraisal. Our findings and suggestions are described below.

DRIVERS OF THE MODEL'S RESULTS

SANDOZ analyzed the impact of the following parameters on the different runs (5,000 patients each one, deterministic analysis):

- **Drug Acquisition Costs** (only SANDOZ's biosimilar): This is the most influential driver of the results, due to the difference between list and actual prices
- **Increase/decrease in HAQ-DI and DAS28 relationship**. This is a very important parameter, because it predicts the healthcare resource consumption and associated costs (which is based on the HAQ-DI scale) (6).
- **EULAR response**: derived from Stevenson et al (7), which is the proxy for the transition probabilities across treatments in the algorithm; in line with current British Rheumatology Guidelines (8)

SANDOZ'S FINDINGS

We have run a first round of simulations, based only on SANDOZ biosimilar average contract prices (Commercial in Confidence)[1] and fully acknowledging we are unable to consider confidential information such as third party's Patient Access Schemes (PAS**).**

After running the scenarios, we came to the following results:

Scenario 1 → EULAR as per current TA375. Two prior mono csDMARDs

Treatment	QALY	Costs	ICER
csDMARDs	8.51	[redacted]	[redacted]
ABT	9.09		
ABT SC	9.11		
ADA	9.14		
ETN	9.24		
IFX	9.13		

[1] Please treat all data highlighted in green in this document as commercial in confidence and therefore should be redacted if you make this response publically available.

Scenario 2 → EULAR as per current TA375. One prior mono csDMARDs

Treatment	QALY	Costs	ICER
csDMARDs	8.49	[redacted]	[redacted]
ABT	9.11		
ABT SC	9.10		
ADA	9.10		
ETN	9.23		
IFX	9.10		

Scenario 3 → EULAR as per current TA375. One prior combo csDMARDs

Treatment	QALY	Costs	ICER
csDMARDs	8.46	[redacted]	[redacted]
ABT	9.09		
ABT SC	9.09		
ADA	9.12		
ETN	9.21		
IFX	9.09		

Scenario 4 → EULAR as per current TA375. No prior csDMARDs (COMET trial population (24))

Treatment	QALY	Costs	ICER
csDMARDs	8.46	[redacted]	[redacted]
ABT	9.41		
ABT SC	9.41		
ADA	9.47		
ETN	9.60		
IFX	9.40		

All of the results have:

- First line treatment in every sequence
- All of the above treatments include concomitant MTX, as per current guidelines

The above scenarios implies a cost-effectiveness ratio below the commonly accepted threshold of £30,000 / QALY, with the exception of ERELZI® (Sandoz Etanercept biosimilar).

Of note, the ICER is lower (mostly because of the increased QALYs) when it comes to the csDMARDs naïve population (COMET trial population (24)) or one prior csDMARD combo; in line with existing literature providing with evidence of extended benefits for patients in when biologics are started earlier in time.

Next, we ran the scenarios where the relationship between HAQ-DI and DAS28 (increment / decrement of 0.125 HAQ-DI scores versus DAS28 CRP) was varied. We took the pragmatic approach of revisiting all the historical Randomized Controlled Trials (RCT) following a Systematic Literature Review (unpublished yet) , and running a linear regression(where the HAQ-DI and DAS28 CRP were the independent and dependent variable, respectively) See full table of trials below:

Note: Those are the trials EXPLICITLY reporting both incremental HAQ-DI and incremental DAS28-CRP from baseline to month 6. We have not used any algorithm to derive either of them. A conservative scenario is modelled by assuming patients are either bDMARD naïve, or bDMARD-IR.

Table: 1

Study Name	Arm	incr. DAS28 CRP (6 months vs. baseline), Average	incr. HAQ-DI (6m vs. baseline), Average	Reference
RA-BEAM	**BAR+MTX**	-2.53	-0.75	(9)
RA-BEAM	**ADA+MTX**	-2.27	-0.60	(9)
RA-BEAM	**MTX**	-1.10	-0.35	(9)
RA-BUILD	**BAR+csDMARDs**	-2.30	-0.63	(10)
RA-BUILD	**csDMARDs**	-1.30	-0.38	(10)
ORAL-SCAN	**TOF+MTX**	-2.40	-0.47	(11)
ORAL-SCAN	**MTX**	-1.50	-0.22	(11)
ORAL-STRATEGY	**TOF**	-2.31	-0.52	(12)
ORAL-STRATEGY	**TOF+MTX**	-2.31	-0.58	(12)
ORAL-STRATEGY	**ADA+MTX**	-2.50	-0.54	(12)
ORAL-STANDARD	**TOF+MTX**	-1.92	-0.58	(13)
ORAL-STANDARD	**ADA+MTX**	-1.68	-0.52	(13)
ORAL-STANDARD	**MTX**	-1.59	-0.26	(13)
ORAL-SYNC	**TOF+csDMARDs**	-2.30	-0.53	(14)
ORAL-SYNC	**csDMARDs**	-1.60	-0.18	(14)
ARMADA	**ADA+MTX**	-2.55	-0.62	(15)
ARMADA	**MTX**	-1.16	-0.27	(15)
REFLECTIONS	**INF+MTX**	-2.14	-0.62	(16)
REFLECTIONS	**INF+MTX**	-2.12	-0.59	(16)
DE019	**ADA+MTX**	-1.95	-0.56	(17)
DE019	**MTX**	-0.24	-0.24	(17)
EQUIRA	**Erelzi+MTX**	-2.78	-0.57	(18)
EQUIRA	**ETN+MTX**	-2.70	-0.64	(18)
TEMPO	**ETN+MTX**	-3,20	-0,85	(19)
TEMPO	**MTX**	-2.50	-0.60	(19)

ACQUIRE	**ABTSC+MTX**	-2.57	-0.69	(20)
ACQUIRE	**ABTIV+MTX**	-2.55	-0.70	(20)
AIM	**ABTIV+MTX**	-2.38	-0.59	(21)
AIM	**MTX**	-1.29	-0.39	(21)
ETN309	**ETN**	-2.46	-0.60	(22)
ETN309	**ETN+csDMARDs**	-2.58	-0.64	(22)
ETN309	**csDMARDs**	-0.46	-0.31	(22)
SELECT-COMPARE	**UPA+MTX**	-2.80	-0.70	(23)
SELECT-COMPARE	**ADA+MTX**	-2.30	-0.59	(23)
SELECT-COMPARE	**MTX**	-1.20	-0.28	(23)
SERENE	**RITX+MTX**	-1.71	-0.42	(24)
SERENE	**MTX**	-0.75	-0.24	(24)
ARABESC	**FKB327+MTX**	-2.58	-0.59	(25)
ARABESC	**ADA+MTX**	-2.58	-0.54	(25)
PLANETRA	**CTP-13+MTX**	-2.10	-0.50	(26)
PLANETRA	**INF+MTX**	-2.10	-0.60	(26)
ADMYRA	**HYR+MTX**	-2.60	-0.63	(27)
ADMYRA	**ADA+MTX**	-2.80	-0.59	(27)
REFLECTIONS B538	**PF-06410293+MTX**	-2.70	-0.65	(28)
REFLECTIONS B539	**ADA+MTX**	-2.80	-0.67	(28)
GO-FURTHER	**GOLIV+MTX**	-2.00	-0.53	(29)
GO-FURTHER	**MTX**	-0.80	-0.21	(29)
RA-MONARCH	**SAR**	-2.86	-0.60	(30)
RA-MONARCH	**ADA**	-1.97	-0.40	(30)
DARWIN-1	**FIL+MTX**	-2.80	-0.82	(31)
DARWIN-1	**MTX**	-1.18	-0.37	(31)
DARWIN-2	**FIL**	-2.62	-0.85	(31)

Note: BAR= Baricitinib, MTX= Methotrexate, ADA= Adalimumab, TOF= Tofacitinib 5mg BID, csDMARDs = conventional disease modifiers drugs, Zessly® = SANDOZ Infliximab, Erelzi® = Sandoz Etanercept, HYR= Hyrimoz®, SANDOZ Adalimumab, INF= Infliximab, ETN= Etanercept, UPA= Upadacitinib 15m QD, FKB327= Fresenius Adalimumab, CTP-13= Celltrion Infliximab,

PF06410293, Pfizer Adalimumab, ABTSC= Subcutaneous Abatacept, ABTIV= Intravenous Abatacept, SAR= Sarilumab 200 mg QD, FIL= Filgotinib 200 mg QD, GOLIV= Intravenous Golimumab, RITX= Rituximab

Running a simple regression with all average values yields the following result, taking HAQ-DI as independent predictor of DAS28 CRP increment / decrement at 6 months:

Table: 2

	Coefficients	*Standard Error*	*t Stat*	*P-value*
Intercept	-0.250207	0.160336	-1.5605198	0.124944901
incr. HAQ-DI (6m vs. baseline)	3.487488	0.290373	12.01038233	2.38408E-16
Regression Statistics				
Multiple R	0.86174172			
R Square	0.742599			
Adjusted R Square	0.737451			
Standard Error	0.34843116			
Observations	52			

This shows a strong, statistically significant correlation between both (note: this is based on a pure linear regression with mean values from the trials above and linear regression equation is DAS28 = Intercept + Coefficient*HAQ-DI, where HAQ-DI= 0.125, as per the NICE guidance – DAS28= -0.25+3.48* (-0.125) = -0.69), hence, for a given increase/decrease of HAQ-DI of 0.125 points, this equates to -0.69 increase/decrease on DAS28 CRP at month 6 (95% CI: -0.44 to -0.94).

This figure departs from the Assessment Group's base case, however -0.48 is within the confidence interval of our proposal. If we change this relationship in the model, in addition to the prior assumptions, then the results are as follows:

Scenario 5→ Two prior mono csDMARDs (HAQ-DI vs. DAS relationship 0.7)

Treatment	QALY	Costs	ICER
csDMARDs	8.60	[redacted]	[redacted]
ABT	9.51	[redacted]	[redacted]
ABT SC	9.51	[redacted]	[redacted]
ADA	9.49	[redacted]	[redacted]
ETN	9.65	[redacted]	[redacted]
IFX	9.52	[redacted]	[redacted]

Scenario 6→ One prior mono csDMARD (HAQ-DI vs. DAS relationship 0.7)

Treatment	QALY	Costs	ICER
csDMARDs	8.58	[redacted]	[redacted]
ABT	9.44	[redacted]	[redacted]
ABT SC	9.45	[redacted]	[redacted]
ADA	9.45	[redacted]	[redacted]
ETN	9.60	[redacted]	[redacted]
IFX	9.44	[redacted]	[redacted]

Scenario 7→ Sandoz Prices, no other PAS, EULAR as per current TA375. One prior combo csDMARD (HAQ-DI vs. DAS relationship 0.7, as per average DAS28 published trials)

Treatment	QALY	Costs	ICER
csDMARDs	8.81	[redacted]	[redacted]
ABT	9.62	[redacted]	[redacted]

ABT SC	9.64	[redacted]	[redacted]
ADA	9.65		
ETN	9.80		
IFX	9.63		

Scenario 8→ Sandoz Prices, no other PAS, EULAR as per current TA375. No prior csDMARDs (COMET Trial population (24), HAQ-DI vs. DAS relationship 0.7, as per average DAS28 published trials)

Treatment	QALY	Costs	ICER
csDMARDs	8.59	[redacted]	[redacted]
ABT	9.50		
ABT SC	9.47		
ADA	9.49		
ETN	9.66		
IFX	9.48		

The Assessment Group report notes that there is a wide range and considerable uncertainty in the estimated change in DAS28 score associated with a 0.125 change in HAQ score (-6.50 to 0.90). We would like to suggest that the estimated value proposed, 0.48, is likely to underestimate the impact of the relationship. Based on our own analysis (outlined in Table 1 & 2), running a simple regression with all average values (table 2), HAQ-DI as independent predictor of DAS28 CRP increment / decrement at 6 months yields a value of 0.7.

Using this assumption, the ICERS from the simulated scenarios are consistently reduced. The mean of the ICERs for Adalimumab, Etanercept and Infliximab are below the ICER threshold in all but one scenario.

We believe that this approach results in a more accurate reflection of the value of biosimilar versions of the molecules within the scope of this review and contributes to the case for earlier use of these medicines in patients with moderate to severe disease.

REFERENCES

(1) Overview | Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed | Guidance | NICE [accessed 31st January 2020

(2) Overview | Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor | Guidance | NICE [accessed 31st January 2020]

(3) Overview | Baricitinib for moderate to severe rheumatoid arthritis | Guidance | NICE [accessed 31st January 2020]

(4) Overview | Tofacitinib for moderate to severe rheumatoid arthritis | Guidance | NICE [accessed 31st January 2020]

(5) Overview | Upadacitinib for treating severe rheumatoid arthritis | Guidance | NICE [accessed 31st January 2020]

(6) Rationale and impact | Rheumatoid arthritis in adults: management | Guidance | NICE [accessed 31st January 2020]

(7) Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J, et al. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. Health Technol Assess 2016;20(35).

(8) Jo Ledingham, Nicola Gullick, Katherine Irving, Rachel Gorodkin, Melissa Aris, Jean Burke, Patrick Gordon, Dimitrios Christidis, Sarah Galloway, Eranga Hayes, Andrew Jeffries, Scott Mercer, Janice Mooney, Sander

van Leuven, James Galloway, on behalf of the BSR and BHPR Standards, Guidelines and Audit Working Group, BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs, *Rheumatology*, Volume 56, Issue 6, June 2017, Pages 865–868, https://doi.org/10.1093/rheumatology/kew479

(9) Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J, Yakushin S, Ishii T, Emoto K, Beattie S, Arora V, Gaich C, Rooney T, Schlichting D, Macias WL, de Bono S, Tanaka Y. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. N Engl J Med. 2017 Feb 16;376(7):652-662. doi: 10.1056/NEJMoa1608345.

(10) Dougados M, van der Heijde D, Chen YC, Greenwald M, Drescher E, Liu J, Beattie S, Witt S, de la Torre I, Gaich C, Rooney T, Schlichting D, de Bono S, Emery P. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. Ann Rheum Dis. 2017 Jan;76(1):88-95. doi: 10.1136/annrheumdis-2016-210094. Epub 2016 Sep 29. Erratum in: Ann Rheum Dis. 2017 Sep;76(9):1634.

(11) van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, Cardiel MH, Cohen S, Nash P, Song YW, Tegzová D, Wyman BT, Gruben D, Benda B, Wallenstein G, Krishnaswami S, Zwillich SH, Bradley JD, Connell CA; ORAL Scan Investigators. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum. 2013 Mar;65(3):559-70. doi: 10.1002/art.37816.

(12) Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z, DeMasi R, Soma K, Zhang R, Takiya L, Tatulych S, Mojcik C, Krishnaswami S, Menon S, Smolen JS; ORAL Strategy investigators. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet. 2017 Jul 29;390(10093):457-468. doi: 10.1016/S0140-6736(17)31618-5. Epub 2017 Jun 16.

(13) van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Meijide JA, Wagner S, Forejtova S, Zwillich SH, Gruben D, Koncz T, Wallenstein GV, Krishnaswami S, Bradley JD, Wilkinson B; ORAL Standard Investigators. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012 Aug 9;367(6):508-19. doi: 10.1056/NEJMoa1112072. Erratum in: N Engl J Med. 2013 Jul 18;369(3):293.

(14) Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, Isaacs JD, Gruben D, Wallenstein G, Krishnaswami S, Zwillich SH, Koncz T, Riese R, Bradley J. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2013 Aug 20;159(4):253-61. doi: 10.7326/0003-4819-159-4-201308200-00006.

(15) Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, Teoh LA, Fischkoff SA, Chartash EK. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003 Jan;48(1):35-45. doi: 10.1002/art.10697. Erratum in: Arthritis Rheum. 2003 Mar;48(3):855. PMID: 12528101.

(16) Cohen SB, Alten R, Kameda H, Hala T, Radominski SC, Rehman MI, Palaparthy R, Schumacher K, Schmitt S, Hua SY, Ianos C, Sewell KL. A randomized controlled trial comparing PF-06438179/GP1111 (an infliximab biosimilar) and infliximab reference product for treatment of moderate to severe active rheumatoid arthritis despite methotrexate therapy. Arthritis Res Ther. 2018 Jul 27;20(1):155. doi: 10.1186/s13075-018-1646-4. PMID: 30053896; PMCID: PMC6063022.

(17) Keystone EC, Kavanaugh A, Weinblatt ME, Patra K, Pangan AL. Clinical consequences of delayed addition of adalimumab to methotrexate therapy over 5 years in patients with rheumatoid arthritis. J Rheumatol. 2011 May;38(5):855-62. doi: 10.3899/jrheum.100752. Epub 2011 Feb 1.

(18) Matucci-Cerinic M, Allanore Y, Kavanaugh A, Buch MH, Schulze-Koops H, Kucharz EJ, Woehling H, Babic G, Poetzl J, Davis A, Schwebig A. Efficacy, safety and immunogenicity of GP2015, an etanercept biosimilar, compared with the reference etanercept in patients with moderate-to-severe rheumatoid arthritis: 24-week results from the comparative phase III, randomised, double-blind EQUIRA study. RMD Open. 2018 Nov 14;4(2):e000757. doi: 10.1136/rmdopen-2018-000757. eCollection 2018.

(19) Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, Martín Mola E, Pavelka K, Sany J, Settas L, Wajdula J, Pedersen R, Fatenejad S, Sanda M; TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis:

double-blind randomised controlled trial. Lancet. 2004 Feb 28;363(9410):675-81. doi: 10.1016/S0140-6736(04)15640-7. PMID: 15001324.

(20) Genovese MC, Covarrubias A, Leon G, Mysler E, Keiserman M, Valente R, Nash P, Simon-Campos JA, Porawska W, Box J, Legerton C 3rd, Nasonov E, Durez P, Aranda R, Pappu R, Delaet I, Teng J, Alten R. Subcutaneous abatacept versus intravenous abatacept: a phase IIIb noninferiority study in patients with an inadequate response to methotrexate. Arthritis Rheum. 2011 Oct;63(10):2854-64. doi: 10.1002/art.30463.

(21) Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, Szechinski J, Li T, Ge Z, Becker JC, Westhovens R. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2006 Jun 20;144(12):865-76.

(22) Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK, Pavelka K, Sambrook PN, Smolen JS, Wajdula J, Fatenejad S; Etanercept European Investigators Network (Etanercept Study 309 Investigators). Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis. 2006 Oct;65(10):1357-62. doi: 10.1136/ard.2005.049650. Epub 2006 Apr 10. PMID: 16606651; PMCID: PMC1798315.

(23) Fleischmann R, Pangan AL, Song IH, Mysler E, Bessette L, Peterfy C, Durez P, Ostor AJ, Li Y, Zhou Y, Othman AA, Genovese MC. Upadacitinib Versus Placebo or Adalimumab in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Results of a Phase III, Double-Blind, Randomized Controlled Trial. Arthritis Rheumatol. 2019 Nov;71(11):1788-1800. doi: 10.1002/art.41032. Epub 2019 Aug 28.

(24) Emery P, Deodhar A, Rigby WF, Isaacs JD, Combe B, Racewicz AJ, Latinis K, Abud-Mendoza C, Szczepanski LJ, Roschmann RA, Chen A, Armstrong GK, Douglass W, Tyrrell H. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). Ann Rheum Dis. 2010 Sep;69(9):1629-35. doi: 10.1136/ard.2009.119933. Epub 2010 May 20. Erratum in: Ann Rheum Dis. 2011 Aug;70(8):1519.

(25) Genovese MC, Glover J, Greenwald M, Porawska W, El Khouri EC, Dokoupilova E, Vargas JI, Stanislavchuk M, Kellner H, Baranova E, Matsunaga N, Alten R. FKB327, an adalimumab biosimilar, versus the reference product: results of a randomized, Phase III, double-blind study, and its open-label extension. Arthritis Res Ther. 2019 Dec 12;21(1):281. doi: 10.1186/s13075-019-2046-0.

(26) Yoo DH, Hrycaj P, Miranda P, Ramiterre E, Piotrowski M, Shevchuk S, Kovalenko V, Prodanovic N, Abello-Banfi M, Gutierrez-Ureña S, Morales-Olazabal L, Tee M, Jimenez R, Zamani O, Lee SJ, Kim H, Park W, Müller-Ladner U. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis. 2013 Oct;72(10):1613-20. doi: 10.1136/annrheumdis-2012-203090. Epub 2013 May 16.

(27) Wiland P, Jeka S, Dokoupilová E, Brandt-Jürgens J, Miranda Limón JM, Cantalejo Moreira M, Cabello RV, Jauch-Lembach J, Thakur A, Haliduola H, Brueckmann I, Gaylis NB. Switching to Biosimilar SDZ-ADL in Patients with Moderate-to-Severe Active Rheumatoid Arthritis: 48-Week Efficacy, Safety and Immunogenicity Results From the Phase III, Randomized, Double-Blind ADMYRA Study. BioDrugs. 2020 Dec;34(6):809-823. doi: 10.1007/s40259-020-00447-6.

(28) Fleischmann RM, Alten R, Pileckyte M, Lobello K, Hua SY, Cronenberger C, Alvarez D, Bock AE, Sewell KL. A comparative clinical study of PF-06410293, a candidate adalimumab biosimilar, and adalimumab reference product (Humira®) in the treatment of active rheumatoid arthritis. Arthritis Res Ther. 2018 Aug 15;20(1):178. doi: 10.1186/s13075-018-1676-y. PMID: 30111357; PMCID: PMC6094896.

(29) Weinblatt ME, Westhovens R, Mendelsohn AM, Kim L, Lo KH, Sheng S, Noonan L, Lu J, Xu Z, Leu J, Baker D, Bingham CO; GO-FURTHER investigators. Radiographic benefit and maintenance of clinical benefit with intravenous golimumab therapy in patients with active rheumatoid arthritis despite methotrexate therapy: results up to 1 year of the phase 3, randomised, multicentre, double blind, placebo controlled GO-FURTHER trial. Ann Rheum Dis. 2014 Dec;73(12):2152-9. doi: 10.1136/annrheumdis-2013-203742. Epub 2013 Sep 3.

(30) Burmester GR, Lin Y, Patel R, van Adelsberg J, Mangan EK, Graham NM, van Hoogstraten H, Bauer D, Ignacio Vargas J, Lee EB. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind,

parallel-group phase III trial. Ann Rheum Dis. 2017 May;76(5):840-847. doi: 10.1136/annrheumdis-2016-210310. Epub 2016 Nov 17.

(31) Westhovens R, Taylor PC, Alten R, Pavlova D, Enríquez-Sosa F, Mazur M, Greenwald M, Van der Aa A, Vanhoutte F, Tasset C, Harrison P. Filgotinib (GLPG0634/GS-6034), an oral JAK1 selective inhibitor, is effective in combination with methotrexate (MTX) in patients with active rheumatoid arthritis and insufficient response to MTX: results from a randomised, dose-finding study (DARWIN 1). Ann Rheum Dis. 2017 Jun;76(6):998-1008. doi: 10.1136/annrheumdis-2016-210104. Epub 2016 Dec 19.

(32) Coy NN, Hyrich K, Pavitt S, et alFRI0684 NOVEL MAPPING FUNCTION ILLUSTRATES NONLINEARITY BETWEEN TRIAL ACR RESPONSE, DAS28 CHANGE AND EULAR RESPONSE CRITERIAAnnals of the Rheumatic Diseases 2019;78:1040-1041.

ANNEX

Out of scope for this review, is another assumption, which affects the model's outcomes as well. This relates to the way the EULAR response is currently derived within the context of TA375. This appraisal uses a mapping algorithm, Stevenson et al. (7), which is based on a male, US cohort, which little exposure to biologics. Therefore, SANDOZ has conducted a sensitivity analysis using a recently published paper by Navarro-Coy (32), focusing on novel mapping relationships between ACRn, DAS28 (ESR, CRP), and EULAR responses. SANDOZ has worked on the equation between the first and the latter (unpublished yet), and, in general terms, EULAR responses derived from this method are almost an exact match to the published ones from trials, with an improvement of around 10% on absolute values versus (7) for biologics, and other non csDMARDs. The latter actually are better represented by (7). Using these results in the prior scenarios, yields the following results:

Scenario 9→ Two prior mono csDMARDs (HAQ-DI vs. DAS relationship 0.7, as per average DAS28 published trials, EULAR response modelled by Navarro-Coy et al. 2020 for biologics)

Treatment	QALY	Costs	ICER
csDMARDs	8.35	[redacted]	[redacted]
ABT	9.19	[redacted]	[redacted]
ABT SC	9.24	[redacted]	[redacted]
ADA	9.23	[redacted]	[redacted]
ETN	9.38	[redacted]	[redacted]
IFX	9.23	[redacted]	[redacted]

Scenario 10→ One prior mono csDMARD (HAQ-DI vs. DAS relationship 0.7, as per average DAS28 published trials, EULAR response modelled by Navarro-Coy et al. 2020 for biologics)

Treatment	QALY	Costs	ICER
csDMARDs	8.22	[redacted]	[redacted]
ABT	9.13	[redacted]	[redacted]
ABT SC	9.12	[redacted]	[redacted]
ADA	9.15	[redacted]	[redacted]
ETN	9.30	[redacted]	[redacted]
IFX	9.12	[redacted]	[redacted]

Scenario 11→ One prior combo csDMARD (HAQ-DI vs. DAS relationship 0.7, as per average DAS28 published trials, EULAR response modelled by Navarro-Coy et al. 2020 for biologics)

Treatment	QALY	Costs	ICER
csDMARDs	8.41	[redacted]	[redacted]
ABT	9.24	[redacted]	[redacted]
ABT SC	9.29	[redacted]	[redacted]
ADA	9.30	[redacted]	[redacted]
ETN	9.46	[redacted]	[redacted]
IFX	9.25	[redacted]	[redacted]

Scenario 12→ Sandoz Prices, no other PAS. No prior combination csDMARD (COMET Trial population (24), HAQ-DI vs. DAS relationship 0.7, as per average DAS28 published trials*, EULAR response modelled by Navarro-Coy et al. 2020 for biologics)

Treatment	QALY	Costs	ICER
csDMARDs	8.33	[redacted]	[redacted]
ABT	9.24		
ABT SC	9.26		
ADA	9.25		
ETN	9.40		
IFX	9.21		

Combining all results, its is clear that the main driver is clearly the prices of the biosimilar, however, subtle, and important issues for future research arise from the way TA375 derives both HAQ-DI vs. DAS28 and ACRn vs. EULAR response mappings, which should be taken into consideration when it comes to other future TAs on this area.

Assessment Report consultation: Rheumatoid arthritis (moderate) – adalimumab, etanercept, infliximab, cetolizumab pegol, golimumab, tocilizumab and abatacept (partial review of TA375) [ID2710]

Response prepared by: [redacted]
On behalf of: British Society for Rheumatology

BSR are grateful for sight of the Assessment Group's analysis of the relationship between HAQ and DAS28 in those with moderately active RA. We agree with the AG that there is uncertainty and we share the concern that the relationship between HAQ and DAS was taken from studies that mostly had decreasing values and acknowledge that there is little data from the relation with increasing HAQ and DAS. We consider the AGs assumptions to be reasonable given the uncertainty. Nevertheless, the report does suggest the reduction in DAS in moderates would have significant clinical benefits. We understand the ICERs are confidential, but as a result have difficulty in commenting in more detail.

We welcome NICE's recent FAD on filgotinib in relation to treatment of moderate RA. We would like to draw the attention of the committee to the similar clinical benefit of filgotinib and adalimumab and note that the access costs of generic adalimumab are below that of filgotinib PAS. We are therefore hopeful that the ICERs for generic bDMARDs in the treatment of moderate RA will have NICE approval.

BBA response to the Assessment Report consultation (TA375)

Introduction

The British Biosimilars Association (BBA) welcomes the opportunity to contribute to NICE's partial review of TA375. As cost-effectiveness data could not be shared due to commercial sensitivities, our comments are limited to some broad policy observations. We have also not sought to provide detailed commentary on the economic modelling.

Summary

As highlighted in the Association's response to the methods review consultation, the BBA welcomes the positive step NICE has taken towards expanding patient numbers in rheumatoid arthritis by taking forward this partial review. The BBA believes it sets an important precedent and paves the way for a more routine approach to re-assessing Technology Appraisals as lower cost treatments become available, such as with biosimilar medicines.

Improving patient outcomes

- Whilst it is difficult to draw firm conclusions from the Assessment Report given that key data has been excluded, it is significant to note the report does suggest that with the earlier use of biosimilar medicines, there are additional QLYs gained and illustrated by the graph on Pg.20

- Given the strong experience that both NICE and the NHS have in the cost savings that biosimilar competition can bring, we encourage the Appraisal Committee to fully explore the wider societal benefits and improved patient outcomes of earlier patient access to medicines for e.g. cost savings associated with preventing surgical interventions

- Furthermore, it is important to note there are other reasons why it maybe pragmatic to re-review a Technology Appraisal, beyond price. This includes updated patient pathways and treatment options, evolving clinical experience, the need to continuously improve the standard of care for patients and to benchmark best practice across healthcare systems.

- These factors should be accounted for as part of any re-review and the Technology Appraisal process should have the necessary flexibility to accommodate this.

Description of technologies under assessment

- Notwithstanding the fee to be paid by manufacturers to participate, it is important that NICE consider all the products on the market, as part of the evaluation process, including the full range of formulations available. This ensures the most accurate representation of the current market.

Pricing

- It is important that NICE uses the discounted (net) price, rather than the published list price to reflect the maximum cost savings that can be delivered through the use of biosimilars.

BRITISH BIOSIMILARS ASSOCIATION

About us

The British Biosimilars Association (BBA) is the expert sector group of the BGMA exclusively focused on biosimilar medicines. The members of the BBA ensure access to high quality, safe and effective biosimilars for the NHS and patients.

Biosimilar medicines are licensed by the medicines regulators (MHRA and EMA) to the same standards of quality, safety and efficacy as the originator product. The increased number of manufacturers helps ensure that the prices of biosimilar medicines are much lower than that of the originator version under patent protection.

Competition from biosimilar medicines also stimulates the research-based pharmaceutical industry to develop new therapies. In keeping medicines affordable for the NHS, this allows further investment in other healthcare priorities, and promotes innovation in the development of new medicines.

Confidential until published

Adalimumab, etanercept, infliximab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]

Produced by	The School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
	Emma Simpson, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
	Gill Rooney, Programme Manager, ScHARR, University of Sheffield, Sheffield, UK
	Ruth Wong, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK
	Christopher J Edwards, Consultant Rheumatologist, NIHR Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, SO16 6YD
Correspondence Author	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
Date completed	Date completed (25/02/2021)

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 14/66/01.

Declared competing interests of the authors

Chris Edwards declares that he has received honoraria, provided consultancy or been part of a speaker's bureau for AbbVie, Pfizer, BMS, Celltrion, Fresenius Kabi, Biogen and Janssen in relation to rheumatoid arthritis interventions. None of the remaining authors have any conflicts of interest to declare.

Acknowledgements

We would like to thank Andrew Metry, for help in discussing the project.

Rider on responsibility for report

'This report was commissioned by the NIHR Evidence Synthesis Programme. The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Stevenson M, Simpson E, Rooney G, Wong R, Edwards CJ. Adalimumab, etanercept, infliximab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]. February 2021

Contributions of authors

Emma Simpson and Gill Rooney undertook the systematic review. Emma Simpson, Gill Rooney and Matt Stevenson evaluated the clinical evidence related to the relationship between changes in HAQ score and DAS28 score. Matt Stevenson amended the health economic model and generated the results. Ruth Wong generated the search strategy used. Chris Edwards provided clinical advice. All authors were involved in drafting and commenting on the final report.

Standard copyright statement on the front page of the ERG/AG report:

Table of Contents

List of Tables

List of Figures

1 LIST OF ABBREVIATIONS

ABA	Abatacept
ADA	Adalimumab
bDMARD	Biologic disease-modifying antirheumatic drug
BeST	Behandel Strategieen; in English, treatment strategies
CATCH	Canadian Early Arthritis Cohort
csDMARD	Conventional Synthetic Disease-Modifying Antirheumatic Drug
DAS	Disease Activity Score
DAS28	Disease Activity Score 28 joints
DAS28-CRP	Disease Activity Score 28 joints - C-Reactive Protein
DAS28-ESR	Disease Activity Score 28 joints - Erythrocyte Sedimentation Rate
DAS44	Disease Activity Score 44 joints
DCP	Data from daily clinical practice
DMARD	Disease-Modifying Antirheumatic Drug
EQ-5D	European Quality of Life 5-Dimensions
ERAS	Early Rheumatoid Arthritis Study
ETN	Etanercept
EULAR	European League Against Rheumatism
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire Disability Index
IFX	Infliximab
IQR	Interquartile Range
IV	Intravenously
J-HAQ	Japanese version of the Health Assessment Questionnaire
MTX	Methotrexate
NOAR	Norfolk Arthritis Register
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
PAS	Patient Access Scheme
QALY	Quality-adjusted life years
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trial
RTX	Rituximab
TA	Technology Appraisal
T2T	Treat to Target

TCZ	Tocilizumab
TNFi	Tumour Necrosis Factor inhibitor
UK	United Kingdom
USA	United States of America

2. EXECUTIVE SUMMARY

This work has been undertaken to partially update NICE technology appraisal 375 (TA375) to consider the cost-effectiveness of biologic disease-modifying antirheumatic drugs (bDMARDs) in patients with moderate-to-severe rheumatoid arthritis (RA). Moderate-to-severe RA is defined as a Disease Activity Score (28 joints) (DAS28) score between 3.2 and 5.1. The manufacturers of four bDMARDs (abatacept, adalimumab, etanercept and infliximab) paid to be considered within the partial update of NICE TA375.

In addition to updating the prices of bDMARDs due to the emergence of biosimilars, the model used for TA375 was updated to account for the fact that patients with moderate-to-severe RA would receive bDMARDs when their RA was deemed severe, with a DAS28 score greater than 5.1. To action this change, the relationship between changes in Health Assessment Questionnaire (HAQ) score and changes in DAS28 scores was required. A systematic search of literature was conducted to source information on this parameter, focussing primarily on people with moderate-to-severe RA. One database was searched: Ovid MEDLINE 1946 to the 1st of October 2020. The systematic review was supplemented by company submissions and papers identified by clinical experts.

Nine published studies were identified meeting the inclusion criteria, with data reserved for consideration in sensitivity analyses provided in ten other published studies (as well as subgroups from two of the nine included studies). Furthermore, unpublished data presented by AbbVie in its submission to NICE has been included.

Estimates in the change in DAS28 score per 0.125 change in HAQ score was derived using graphical software where necessary. There was a wide range in the estimated change in DAS28 score associated with a 0.125 change in HAQ score which ranged from -6.50 to 0.70. The Assessment Group believed that the best estimate to populate the base case was a value of 0.48 which was taken from a study with the intention of estimating the relationship between changes in DAS28 scores and HAQ scores in patients receiving csDMARDs and provided a value near the middle of other estimates. Sensitivity analyses were conducted using a lower value of [redacted] and an upper value of 0.70.

Cost-effectiveness results cannot be provided in this document due to the commercial-in-confidence nature of the prices of biosimilars and due to confidential patient access schemes. These results are contained in a confidential addendum. However, the value used for the

estimated change in DAS28 score associated with a 0.125 change in HAQ score did not noticeably change the ICER.

3 BACKGROUND

3.1 Changes between this report and the earlier version of the report (January 2021)

An earlier version of this report was circulated to stakeholders to comment upon.[1] These comments have resulted in multiple changes being made most noticeably to the sequence of biologic disease-modifying antirheumatic drugs (bDMARDs) as rituximab (RTX) is not licenced to be used in patients with moderate rheumatoid arthritis (RA) and tocilizumab (TCZ) was implicitly being used in the same group of patients, contrary to NICE recommendations. This sequence has now been changed as detailed in Section 6.1.

Many comments received from stakeholders were related to NICE processes or were contrary to NICE guide to the methods of technology appraisal;[2] these have not been discussed in this document. There was a request to update the underlying background mortality data, which is not the most recent. However, to update one parameter without updating the remaining parameters was deemed to be deviate from the pragmatic update requested by NICE and was not actioned. Further detail has been added to this report to answer remaining comments from stakeholders.

3.2 Brief description of health problem

RA is a chronic inflammatory disease which is characterised by progressive and irreversible joint damage, impaired joint function, pain and tenderness caused by swelling of the synovial lining of joints.[3] RA is manifested with increasing disability and reduced quality of life. Further details are provided in Stevenson et al.[4]

3.3 Current service provision

NICE Technology Appraisal (TA375)[5] recommended adalimumab (ADA), etanercept (ETN), infliximab (IFX), certolizumab pegol, golimumab, TCZ, and abatacept (ABA) in combination with methotrexate (MTX) for treating patients with RA only if: 1) RA is severe, that is a Disease Activity Score 28 joints (DAS28) score greater than 5.1; 2) the disease has not responded to intensive therapy with a combination of conventional synthetic disease-modifying antirheumatic drug (csDMARDs); and 3) that the agreed patient access schemes (PAS) for ABA, certolizumab pegol, golimumab and TCZ are provided. ADA, ETN, certolizumab pegol or TCZ can be used as monotherapy for people who cannot take MTX because it is contraindicated or because of intolerance. NICE also stated that treatment should be started with the least expensive drug.

3.4 Description of technologies under assessment

Whilst NICE TA375 provided recommendations on seven interventions, the update only focuses on four: ABA, ADA, ETN, and IFX, as the manufacturers of the omitted interventions did not pay the fee required by NICE for the intervention to be appraised.

ABA 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. It is provided in two formulations, intravenously (iv) and subcutaneously (sc). The dose regimen for ABA iv is 500 mg below 60 kg, 750 mg between 60 kg and 100 kg, 1000 mg above 100 kg; 0, 2 and 4 weeks, then every 4 weeks thereafter. For ABA sc the dose regimen is 125 mg weekly following a loading dose of 500mg below 60 kg, 750mg between 60 kg and 100 kg, 1000 mg above 100 kg.

ADA, ETN and IFX, all inhibit the activity of tumour necrosis factor alpha, a pro-inflammatory mediator that is partly responsible for damage to the joints in RA. ADA and ETN are provided sc, whereas IFX can be provided as an iv administration. ADA is provided at doses of 40mg every other week, ETN at doses of 50mg every week, and IFX is provided at 3mg/kg at weeks 0, 2 and 6 and then every 8 weeks. A sc version of IFX is also available, but is not considered within the partial update.

All four drugs being appraised are subject to PAS or pricing for biosimilars that are deemed commercial in confidence. As such, the prices cannot be reported in this document, but are contained in a confidential addendum.

4 DEFINITION OF THE DECISION PROBLEM

The focus of this partial update is on estimating the cost-effectiveness of ABA, ADA, ETN, and IFX, all used with MTX, when used to treat patients with moderate-to-severe RA, which is defined as those patients with a DAS28 score between 3.2 and 5.1. Due to the emergence of biosimilars, and the resulting falls in acquisition price for a number of the technologies, it is anticipated that bDMARDs will now be more cost-effective than at the time of TA375. NICE has requested that all parameters values preferred by the NICE Appraisal Committee when it produced guidance for TA375 should be maintained with the exception of three elements which are discussed below.

1) Updating of the prices, where applicable, of ABA, ADA, ETN, IFX, rituximab (RTX) and TCZ.

This has been undertaken to ensure that any price reductions that have occurred since the introduction of biosimilars into the market, or through any changes in PAS are considered. Due to the sequence of interventions modelled, RTX and TCZ are also incorporated as these treatments would be used following discontinuation of the first bDMARD.

2) Amending the mathematical model to ensure that patients with moderate-to-severe RA who do not receive bDMARDs, will receive bDMARDs when their RA becomes severe.

In the model constructed for TA375, patients with moderate-to-severe RA were modelled as having two potential treatment pathways. 1) receive bDMARDs immediately and then progress through a sequence that comprised of RTX, TCZ and then csDMARDs or 2) to forever stay on csDMARDs. This omitted the option for the patient to remain on csDMARDs until their RA became severe, at which point in accordance with NICE recommendations, bDMARDs could be provided. In order to action this change, the model needed to estimate the relationship between changes in Health Assessment Questionnaire (HAQ) score, which was the key metric used in the modelling, and changes in DAS28 score, which is the metric used to determine the severity of RA. The relationship between changes in the parameters were deemed more pertinent for the work than relationships between absolute HAQ and DAS28 scores, as the model explicitly monitors changes in HAQ, which is a scale from zero to 3.0 with steps of 0.125.

Once a relationship between changes in HAQ and changes in DAS28 has been assumed, the amended model monitors the DAS28 score of the patient. If the patient is on the csDMARD-first strategy they will be provided with a bDMARD once the patient reaches a DAS28 score greater than 5.1. Further details of the mechanics of this change are provided in Section 6.

3) To insert csDMARDs after the first bDMARD intervention for patients with moderate-to-severe RA and prescribing bDMARDs only once the patient had severe RA.

Following consultation comments, it became apparent that the sequences used for patients with moderate-to-severe RA needed updating as the modelled sequences were not permitted within NICE recommendations and/or the marketing authorisation of RTX. As such, the bDMARD-first sequences were amended such that following failure of the first bDMARD patients reverted to csDMARDs until their RA was classed as severe using the method described in Section 6.

5 ASSESSMENT OF CLINICAL EFFECTIVENESS

This chapter details the methods used to identify evidence related to the relationship between changes in HAQ and changes in DAS28, and also presents the results found.

5.1 Methods for reviewing effectiveness

A systematic search of literature was conducted to source information on the relationship between the change in HAQ score and the change in DAS28 score.

Searches

One database was searched: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to the 1st of October, 2020.

The MEDLINE search strategy is shown in Table 1:

Table 1 MEDLINE search strategy: Search conducted October 01 2020

#	Searches	Results
1	exp Arthritis, Rheumatoid/	113387
2	((rheumatoid or early) adj arthritis).tw.	107028
3	1 or 2	149310
4	(("disease activity score" or das*) adj5 ("health assessment questionnaire" or haq*)).tw.	738
5	(relationship or associat* or corrolat*).tw.	5263889
6	3 and 4 and 5	332
7	limit 6 to english language	328

Additionally, references provided within company submissions were checked and papers known to our clinical expert added. The reference lists of relevant studies were checked. All identified citations from the electronic searches and other resources were imported into, and managed using, Endnote X9 software (Clarivate analytics 2020 TM).

Study selection

All titles and abstracts were independently examined for inclusion by two reviewers. Any citations that clearly did not meet the inclusion criteria were excluded. Full text articles were sourced and independently checked by two reviewers. Disagreements were resolved by

discussion, with involvement of a third member of the team. Study selection was based on the following inclusion and exclusion criteria.

Inclusion criteria

Population

Adults (aged 18 years and over) with active RA. If data allow, there is a preference for studies reporting on patients with moderate-to-severe RA (DAS28 3.2-5.1). If there are insufficient data, then any severity of RA would be considered.

Outcome

Change in HAQ/ Health Assessment Questionnaire Disability Index (HAQ-DI) and the associated change in DAS28 (DAS28-erythrocyte sedimentation rate (DAS28-ESR) or DAS28-c-reactive protein (DAS28-CRP).

Study design

Studies were required to provide relevant data, and were not required to be designed solely to address the question of relative changes in HAQ and DAS28.

Exclusion criteria

Population

Children. Studies of several types of arthritis where data not available separately for RA.

Outcomes

Data that cannot be used to calculate change in HAQ and the associated change in DAS28, over the same time period, and in the same group of RA patients. Cross-sectional data (data at one time period only). No DAS28 data reported (disease activity score 44 joints (DAS44) is excluded). No HAQ / HAQ-DI data reported (The Japanese version of the Health Assessment Questionnaire (J-HAQ) is excluded as overall disability index higher in the J-HAQ than in the original HAQ[6]).

Study design

Animal models; preclinical and biological studies; narrative reviews, editorials, opinions; and non-English-language papers. Publication type: articles published as abstracts only where insufficient information is available on outcomes or methods.

Where data meeting inclusion criteria are lacking, some allowance may be given (in severity of RA or prior treatment with biologics) for studies to be used in sensitivity analyses.

Data extraction and synthesis

Data relevant to the decision problem were extracted by one reviewer, and checked by another. Data were extracted without blinding to authors or journal. Graphical data of change in HAQ or DAS28 were estimated using Engauge software [version 12.1; Mark Mitchell, Los Angeles, CA, USA (2011)]. Data of change in HAQ and DAS28 over the same time period, in the same population of patients, were used to calculate an estimated change in DAS28 for a change in HAQ of 0.125 points.

5.2 Results

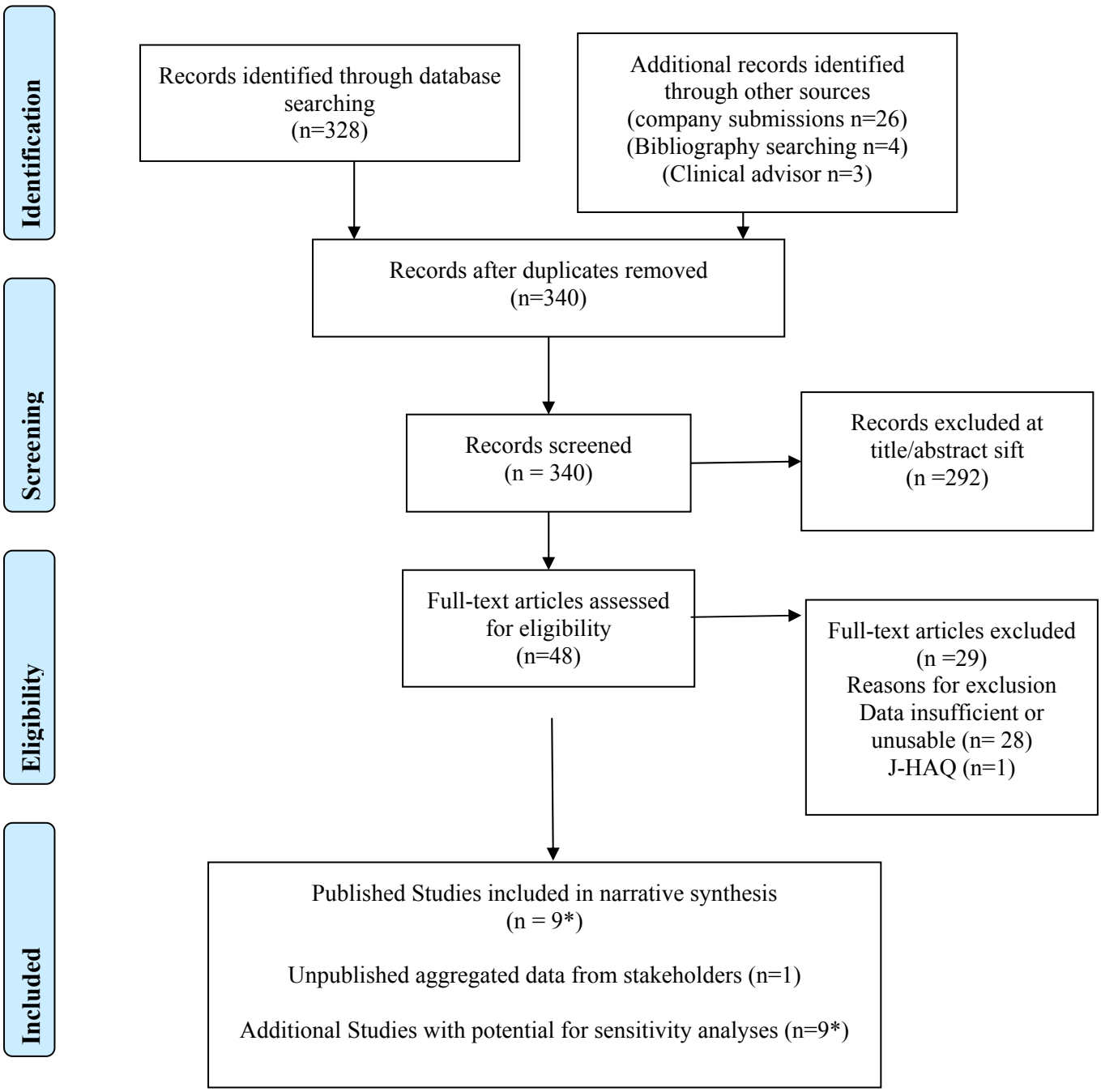
The MEDLINE search was conducted on the 1st of October 2020. It identified 328 records (without removing duplicates). Twenty-six articles were referenced by company submissions, three articles were recommended by our clinical advisor. The bibliography search yielded four additional articles. The search total, following removal of duplicates was 340 (Figure 1).

Following title/abstract sift, 48 full-text articles were checked. The 29 studies excluded at the full-text stage are listed (with rationale for exclusion) in Appendix 1, leaving 19 studies containing relevant information. Of these nine published studies met the inclusion criteria, of which two also provided data that would be considered for sensitivity analyses if the included studies could not provide sufficient data. Nine additional published studies also provided data that could be considered for sensitivity analyses. Results from the studies which met the inclusion criteria are provided in the main text, whereas data for studies which provide data considered for sensitivity analyses are shown in Appendix 2. The reasons for exclusion were having patients with an average baseline DAS28 score > 5.1 (n=9), using DAS44 rather than DAS28, (n=2) and having patients with an average baseline DAS28 score <3.2 (n=1).

Additionally, AbbVie provided data (company submission 6th of Oct 2020), which was believed initially to include patients with a baseline DAS28 score > 5.1, but was confirmed by the company (8th of Feb 2021), to have only included patients with moderate-to-severe RA.

Characteristics of included studies are shown in Table 2 together with the Abbvie data. Only one paper (Boyd et al 2013[7]) had a primary outcome to investigate the relationship between function and disease activity over time, and this was a sub-study of the Canadian Early Arthritis Cohort (CATCH). In all nine studies, HAQ and DAS28 were assessed by qualified clinicians (rheumatologists or rheumatology nurses), as part of ongoing patient care, and are unlikely to be subject to biases. As validated, widely used measures, HAQ and DAS28 were not subject to change throughout the follow-up periods of studies.

Figure 1 Flow diagram of study selection (based on PRISMA guidelines http://prisma-statement.org/)



*Two studies provided data for narrative synthesis and sensitivity analysis.

Table 2 Included study characteristics

Reference	Study type	Study objective	Sample size	Follow-up (months)
Abbvie	Aggregated data from four randomised controlled trials (RCTs)	To ascertain the relative efficacy of upadacitinib	[redacted]	[redacted]
Ariza-Ariza et al 2006[8]	Prospective multicentre study	To compare the utility values and quality-adjusted life years (QALYs) obtained by the Time Trade-Off instrument (TTO) and the European Quality of Life -5 Dimensions (EQ-5D)	300	12
Augustsson et al 2010[9]	Database study	Investigating Tumour Necrosis Factor inhibitor (TNFi) and workforce participation	594	60
Boyd et al 2013[7]	Data from Canadian Early Arthritis Cohort (CATCH)	Sub-study investigating function and disease activity in early arthritis	1,143	24
de Andrade et al 2017[10]	Single centre prospective cohort study	Investigating disease activity and physical function after treat-to-target strategy	229	108
Fioravanti et al 2019 [11]	Prospective cohort from two centres in Italy	Investigating TCZ therapy	44	6
Gwinnutt et al 2020[12]	the Rheumatoid Arthritis Medication Study, a UK multicentre cohort study	Investigating clusters of symptoms associated with poor outcomes in early RA	1,127	12
Ling et al 2016[13]	data from two cohorts: the Norfolk Arthritis Register (NOAR); and the Early Rheumatoid Arthritis Study (ERAS)	Investigating effect of HLA-DRB1 on disease activity	NOAR n=2,158 ERAS n=329	60
Nair et al 2014[14]	data from clinical practice from the observational Nijmegen Early Rheumatoid Arthritis inception cohort	Investigating whether treatment effects of pragmatic clinical trials are generalisable to data from daily clinical practice (DCP),	DCP n=198	6
Twigg et al 2017[15]	Data from Yorkshire Early Arthritis Register (YEAR)	To assess patient-reported variables as predictors of change in	1,415	12

Reference	Study type	Study objective	Sample size	Follow-up (months)
		disease activity and disability		

TNFi=tumour necrosis factor inhibitor; TCZ=tocilizumab; DCP=Data from daily clinical practice; NOAR= Norfolk Arthritis Register; ERAS = Early Rheumatoid Arthritis Study

Baseline variables of included trials are shown in Table 3. Mean/median DAS28 scores were between 3.2 and 5.1 (that is, moderate-to-severe) in all nine studies although, this was only for one of the two cohorts in Nair et al 2014[14]).

Baseline ages were similar across studies, with the lowest mean age 40 years,[9] and highest age median 60 years.[12] All six studies had a majority of female patients, as is to be expected from prevalence of RA. Baseline disease duration ranged from six months[13 7] to 10.6 years.[10] This is considered by our clinical advisor to be generalisable to the RA population seeking treatment in England.

The estimated change in DAS28 associated with a 0.125 change in HAQ are provided in Table 4. These values were calculated by dividing the reported / digitised estimation of change in DAS28 from baseline, by the reported / digitised estimation change in HAQ score from baseline values and then multiplying by 0.125. In all studies apart from Ariza-Ariza *et al*.[8] and for cluster 6 of Gwinnutt *et al*., [12] HAQ and DAS28 scores decreased indicating an improvement, on average, in the condition of the patients. As such, the assessment group has had to assume that the relationship between decreases in HAQ score and in decreases in DAS28 are generalisable to when there are increases in the HAQ score.

A wide range was observed in the estimated relationship between the change in DAS28 score when HAQ changes. Ariza-Ariza *et al*.[8] reported a large, negative correlation whilst a positively correlated estimate of 0.70 was derived from Twigg *et al*.[15] The ERG believes that the most appropriate estimate (0.48) would be provided by Boyd *et al*.[7] which has the advantage of the relationship being the primary outcome of the study, having a reasonable long follow-up of 24 months, where patients did not have bDMARDs, and with an estimate that was not too removed from the remaining studies.

Acknowledging the uncertainty in the parameter the ERG ran two sensitivity analyses using a higher value and a lower value. The higher value (0.70) was estimated from Twigg *et al.*[15] which was a fairly recent, large, study of reasonable length where patients did not use bDMARDs. For the lower value, the ERG used the values estimated by AbbVie which

regressed change in DAS28 on HAQ score using individual patient data from four RCTs of upadacitinib. The reason for choosing this source is that the estimated value ([redacted]) is amongst the lowest observed, that individual patient data had been used, and importantly, that this was the only source where both HAQ and DAS score was assumed to increase.

In consultation comments, Sandoz UK provided the result from an analysis of historic RCTs and using linear regression to determine a relationship between change in HAQ and change in DAS28. Whilst this method has limitation in that all data points are weighted equally ignoring the size or date of the study, and assuming that the relationship was the same for bDMARDs and bDMARDs, the results supported those of by Boyd *et al*.[7] The coefficient for change in DAS28 based on a one step change in HAQ was 0.436, similar to the 0.480 estimated from Boyd. Note, Sandoz UK incorrectly interpret their regression analysis in the commentator comments.

Table 3 Baseline characteristics of included studies

Reference	Study Sample size	Baseline DAS28*	Baseline HAQ	Prior Treatment	Treatment during study	Baseline age (years)	Gender (% female)	Baseline disease duration
Abbvie	[redacted]	DAS28-CRP Mean Range ([redacted]) SD Range ([redacted])	HAQ Mean Range [redacted] SD Range ([redacted])	Range of prior bDMARD use [redacted]	Upadacitinib (either 15mg QD or 30mg QD), placebo, MTX and ADA.	Mean Range [redacted]) SD Range ([redacted])	Range [redacted])	Months Mean Range ([redacted]) SD Range ([redacted])
Ariza-Ariza *et al.* 2006[8]	300	DAS28-ESR Mean 4.5 SD 1.5	HAQ Mean 1.2 SD0.9	csDMARDs, or bDMARDs at physician discretion	csDMARDs, or bDMARDs at physician discretion	Mean 59.6 SD 13.3	82	Years Mean 10.3 SD 8.7
Augustsson *et al.* 2010[9]	594	DAS28 Mean 4.7 SD 1.4 N=521	HAQ Mean 1.0 SD 0.6 N=528	No prior bDMARD	First treatment with TNFi IFX (52.9%) ETN (34.5%) ADA (12.6%)	Mean 40.0 SD 9.3	66	Years Mean 9.4 SD 8.5
Boyd *et al.* 2013[7]	1,143	DAS28 mean 4.53 SD 1.99	HAQ Mean 0.94 SD 0.72	csDMARDs with or without prednisone (physician discretion) or csDMARD naive	csDMARDs with or without prednisone (physician discretion)	Mean 52.2 SD 15.8	71.2	Months Mean 6.3 SD 3.7
de Andrade *et al.* 2017[10]	229	DAS28 Mean 4.6 SD 1.5	HAQ-DI Mean 1.4 SD 0.05	csDMARD	T2T strategy, two courses of csDMARDs followed by bDMARD (TNFi, with physician discretion for ABA, TCZ, RTX)	Mean 55 SD 11	83.8	Years Mean 10.6 SD 7.4
Fioravanti *et al.* 2019[11]	44	DAS28-ESR Median 4.630 IQR 4.23-5.25	HAQ Median 1.68 IQR 1.04-2.38	At least two csDMARDs	TCZ (n=20); TCZ+MTX (n=24)	Median 58.50 IQR 48-69.75	86.4	Years Median 8 IQR 5-15
Gwinnutt *et al.* 2020[12]	1,127	DAS28-CRP median 4.1 IQR 3.2, 5.2	HAQ Median 1.00 IQR 0.38, 1.63	MTX naive	Starting MTX	Median 60 IQR 50, 69	63.4	Months Median 6, IQR 4, 10

Reference	Study Sample size	Baseline DAS28*	Baseline HAQ	Prior Treatment	Treatment during study	Baseline age (years)	Gender (% female)	Baseline disease duration
Ling *et al.* 2016[13]	2,158 NOAR cohort; 329 ERAS cohort	DAS28-ESR NOAR Median 3.76 IQR 2.79, 4.78 ERAS Median 5.06 IQR 4.19, 5.84	HAQ NOAR Median 0.875 IQR 0.25, 1.5 ERAS Median 1 IQR 0.625, 1.6875	csDMARDs, and/or corticosteroids	csDMARDs, and/or corticosteroids	Age at symptom onset NOAR Median 55 IQR 43–67 ERAS Median 54 IQR 44–62	NOAR 65 ERAS 67	Months NOAR Median 6 IQR 3, 12 ERAS Median 6 IQR 3, 11
Nair *et al.* 2014[14]	198 Data from DCP	DAS28 DCP Mean 5.0 SD 1.3	HAQ DCP Mean 0.8 SD 0.7	csDMARD naive, no prior corticosteroids	csDMARDs, NSAIDS and/or corticosteroids, and/or biologics	DCP Mean 54.7 SD 15.2	DCP 61.3	<1 year
Twigg *et al.* 2017[15]	1,415	DAS28-CRP Mean 5.01 SD 1.33	HAQ-DI Mean 1.22 SD0.57	csDMARDs	csDMARDs, and/or corticosteroids	Mean 57.7 SD 14.2	66	Months Mean 7.1 SD 4.3

*unless otherwise stated, unclear if calculated with ESR or CRP

DAS28=Disease Activity Score 28 joints; ESR= erythrocyte sedimentation rate; CRP= C-reactive protein; HAQ = Health Assessment Questionnaire; HAQDI = Health Assessment Questionnaire Disease Index; csDMARD=conventional synthetic disease-modifying antirheumatic drug; NOAR= Norfolk Arthritis Register; ERAS = Early Rheumatoid Arthritis Study; DCP=Data from daily clinical practice;

TNFi=tumour necrosis factor inhibitor; MTX=methotrexate; ABA=abatacept; TCZ=tocilizumab; RTX=rituximab; IQR=interquartile range; IFX=infliximab; ADA=adalimumab; ETN=etanercept; NSAIDS=non-steroidal anti-inflammatories; T2T=treat-to-target

Table 4 Step changes estimated

Reference	Sample size [providing data]	Baseline DAS	Baseline HAQ	Treatment during study	Follow-up (Months)	Change in DAS associated with 0.125-point change in HAQ
Ariza-Ariza *et al.* 2006[8]	163	DAS28-ESR Mean 4.5 SD1.5	HAQ Mean 1.2 SD0.9	csDMARDs, or bDMARDs at physician discretion	12	-6.5 DAS28 decrease HAQ increase
Augustsson *et al.*2010[9]	528	Mean 4.7 SD 1.4 N=521	Mean 1.0 SD 0.6 N=528	First treatment with TNFi IFX (52.9%) ETN (34.5%) ADA (12.6%)	60	0.59* HAQ and DAS28 score decrease
Boyd *et al.* 2013[7]	214	mean 4.53 SD 1.99	Mean 0.94 SD 0.72	DMARDs with or without prednisone (physician discretion)	24	0.48* HAQ and DAS28 score decrease
de Andrade *et al.* 2017[10]	229 [156 at year 9]	Mean 4.6 SD 1.5	Mean 1.4 SD 0.05	T2T strategy, two courses of csDMARDs followed by biologic (TNFi, with physician discretion for ABA, TCZ, RTX)	108	0.39* HAQ and DAS28 score decrease
Fioravanti *et al.* 2019[11]	44	Median 4.630 IQR 4.23-5.25	Median 1.68 IQR 1.04-2.38	TCZ (n=20); TCZ+MTX (n=24)	6	0.34 HAQ and DAS28 score decrease
Gwinnutt *et al.* 2020[12]	Cluster 5 71 Cluster 6 46	DAS28-CRP Cluster 5 Median 3.4 Cluster 6 Median 3.8 [at month 6 of study – baseline of calculation]	Cluster 5 HAQ Median 1.5 Cluster 6 HAQ Median 1.25 [at month 6 of study – baseline of calculation]	Starting MTX	6 [change from months 6 to 12 of the study]	Cluster 5 0.18 HAQ and DAS28 score decrease Cluster 6 Not calculable No change in HAQ, DAS28

Reference	**Sample size [providing data]**	**Baseline DAS**	**Baseline HAQ**	**Treatment during study**	**Follow-up (Months)**	**Change in DAS associated with 0.125-point change in HAQ**
						score decrease
Ling *et al.* 2016[13]	NOAR 2,158 ERAS 329	NOAR Median 3.76 IQR 2.79, 4.78 ERAS Median 5.06 IQR 4.19, 5.84	NOAR Median 0.875 IQR 0.25, 1.5 ERAS Median 1 IQR 0.625, 1.6875	csDMARDs, and/or corticosteroids	60	Not calculable
Nair *et al.* 2014[14]	198 (DCP)	Mean 5.0 SD 1.3	HAQ Mean 0.8 SD 0.7	csDMARDs, NSAIDS and/or corticosteroids, and/or biologics	6	0.37 HAQ and DAS28 score decrease
Twigg *et al.* 2017[15]	1,415	5.01	1.22	csDMARDs, and/or corticosteroids	12	0.70 HAQ and DAS28 score decrease

*estimated from graph
DCP=Data from daily clinical practice; TNFi=tumour necrosis factor inhibitor; NOAR= Norfolk Arthritis Register; ERAS = Early Rheumatoid Arthritis Study;

6 INDEPENDENT ECONOMIC ASSESSMENT

6.1 Methods

As stated, NICE requested that that all parameters values preferred by the NICE Appraisal Committee when it produced guidance for TA375 should be maintained bar updating the prices of interventions and allowing patients to receive bDMARDs when their DAS28 score was greater than 5.1. Comprehensive details of the modelling approach are provided in Stevenson *et al.*[4] In TA375, the sequence after the first bDMARD was accepted, to be the use of RTX and then TCZ, providing TCZ was not used earlier in the treatment sequence then csDMARDs. Although subsequently it has been identified that this sequence is not allowable.

In consultation with NICE and on the advice of our clinical expert the following strategy has instead been used. A bDMARD used initially (one of ABA iv, ABA sc, ADA, ETN, and IFX) which would be followed by csDMARDs until a patient had severe RA, at which point ADA, followed by RTX and then TCZ reverting to csDMARDs following the failure of TCZ would be provided, unless the first intervention was ADA, in which case, IFX would be used later in the sequence. The comparator arm was csDMARDs until a patient reached a DAS score of greater than 5.1 where a sequence of ADA, RTX and TCZ was used. For all analyses it was assumed that MTX was used in combination with the bDMARD, and that following TA375 guidance, the results for combination therapy would also be used to generalise to the bDMARDs being used in monotherapy. A sensitivity analysis was conducted removing MTX after TCZ in line with that of the recent filgotinib appraisal.[16] When MTX is removed the trajectory of HAQ is unaltered but the patient does not have a possibility of a HAQ improvement (and rebound) at initiation (and cessation) of MTX.

The model operationalises the change to bDMARD when the RA of the patient becomes severe by calculating the number of HAQ increases, in steps of 0.125, that would be required for the DAS28 score of the patient to be greater than 5.1. Once these net number of HAQ step increases have been reached the patient is assumed to receive ADA (or IFX if ADA was used earlier in the sequence).

The model structure has the capacity to run 10 cohorts of patients. Having evaluated early results, the Assessment Group decided that 2 cohorts would be used for the csDMARD strategy, 2 for each of the ADA, ETN, and IFX strategies and 1 each for ABA iv and ABA sc. This was because more precision may be needed for the interventions with biosimilars available as the

uncertainty associated with the simulated experience of identical patients (often referred to as first-order uncertainty) would be reduced by apportioning two cohorts.

50,000 patients per cohort were simulated, at that point the Monte Carlo sampling error was low, as shown in the earlier report.[1] A commentator noted that controlling for random numbers could decrease the number of patients required by reducing Monte Carlo sampling error, this is acknowledged but not operationalised due to the time requirements of introducing this change.

Only deterministic results were run as there were shown to be little difference between probabilistic and deterministic results in TA375. Each simulation took in the order of 9 hours to complete.

The base case analyses use the cheapest formulation of each intervention. An additional analysis was run at the request of NICE which used the third cheapest biosimilar price for ADA to reflect potentially different prices within the UK. A further scenario was run using the cost of Humira® rather than the cost of the cheapest ADA biosimilar. In the 'Humira' scenario, it was assumed that IFX would be used as the first bDMARD when a patient was classified as having severe RA, with ETN used when IFX was used in patients with moderate RA.

6.2 The assumed efficacy of the interventions.

The assumed midpoint efficacy of each intervention used in the model is provided in Table 5, this provides the values shown in pictorial form in Stevenson *et al.*[1] (Figure 102). No uncertainty within these values have been considered. A good European League Against Rheumatism (EULAR) response is better for a patient than a moderate EULAR response, which is better than no response. In line with TA375, both ABA sc and RTX was assumed to have the same efficacy of ABA iv. csDMARDs are assumed to produce no EULAR response.

Table 5: Assumed efficacy associated with each treatment, all bDMARDs with MTX

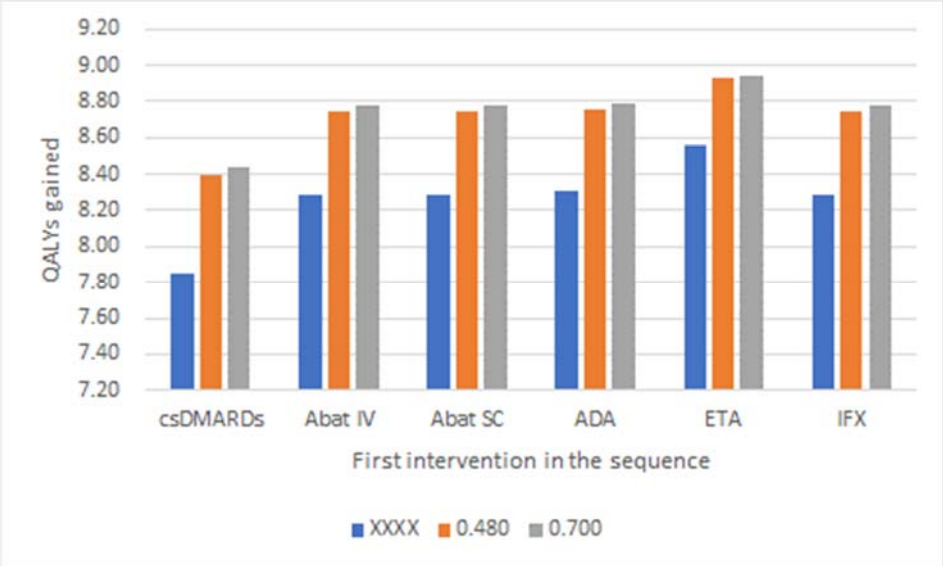
EULAR response	ABA iv + MTX	ADA + MTX	MTX	ETA + MTX	IFX + MTX	TCZ + MTX
Good	26.3%	28.1%	9.7%	53.0%	25.6%	57.2%
Moderate	41.4%	40.5%	35.5%	32.4%	42.8%	33.0%
No response	32.3%	31.4%	54.8%	14.6%	31.6%	9.8%

Further details on the consequences of each EULAR response is provided in Stevenson *et al.*[4] If there is no EULAR response to a bDMARD after 6 months the next treatment in the strategy is used.

6.3 Model results

As the prices for all interventions bar csDMARDs are commercial in confidence, full results cannot be provided here but are supplied to the NICE Appraisal Committee in a confidential addendum. However, to provide some transparency, the QALYs gained by each strategy, are provided in Figure 2 for each relationship between change in HAQ and change in DI. It is seen that when the DAS score of patients with moderate-to-severe RA increases more rapidly, more QALYs are gained due to the earlier use of bDMARDs. Figure 2 shows the QALYs gained using the efficacy values in Table 5 and uncertainty in these estimates have not been considered.

Figure 2: QALYs gained by each strategy compared to the csDMARD-first strategy



As stated, the cost-effectiveness results cannot be presented in this document due to commercial-in-confidence pricing. However, the results were not overly sensitive to the choice of parameter value for the relationship between HAQ score changes and DAS28 changes as increased QALY gains were correlated with the increased costs associated with the earlier use of bDMARDs.

The QALY gains compared to a csDMARD-first strategy when MTX was removed following TCZ were very similar to the base case and had little impact on the ICER.

7 CONCLUSIONS

There appears to be considerable uncertainty in the relationship between changes in HAQ scores and changes in DAS28 scores. A limitation within the published literature is that HAQ score was increasing in few studies; as such the Assessment Group had to assume that the relationship associated with decreasing HAQ scores would also apply when HAQ scores increased.

Our best estimate (0.48) is that reported by Boyd *et al.*[7] which was a study designed for the purpose of establishing such a relationship and provided a value near the middle of other estimates. Sensitivity values were provided for higher (0.70) and lower values ([redacted]) for this relationship.

Cost-effectiveness results cannot be provided in this document, but the incremental cost-effectiveness results were not overly sensitive to the assumed relationship between change in HAQ score and change in DAS28 score nor to whether MTX was assumed to be used after TCZ. All ICERs increased when the price of Humira® was used instead of the cheapest ADA biosimilar.

8 REFERENCES

1. Stevenson M, Simpson E, Rooney G, Wong R, Edwards CJ. Adalimumab, etanercept, infliximab and abatacept for moderate rheumatoid arthritis after conventional DMARDs only have failed (partial review of TA375) [ID2710]. 2021.
2. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013.; 2013. https://www.nice.org.uk/process/pmg9/chapter/foreword (Accessed
3. Scott DL, Steer S. The course of established rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2007;21:943-67.
4. Stevenson M, Archer R, Tosh J, Simpson E, Everson-Hock E, Stevens J, *et al.* Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: systematic review and economic evaluation. *Health Technol Assess* 2016;20:1-610.
5. National Institiute for Health and Care Excellence. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. 2016. https://www.nice.org.uk/guidance/ta375 (Accessed 23/12/2020).
6. Matsuda Y, Singh G, Yamanaka H, Tanaka E, Urano W, Taniguchi A, *et al.* Validation of a Japanese version of the Stanford Health Assessment Questionnaire in 3,763 patients with rheumatoid arthritis. *Arthritis Rheum* 2003;49:784-8.
7. Boyd TA, Bonner A, Thorne C, Boire G, Hitchon C, Haraoui BP, *et al.* The Relationship Between Function and Disease Activity as Measured by the HAQ and DAS28 Varies Over Time and by Rheumatoid Factor Status in Early Inflammatory Arthritis (EIA). Results from the CATCH Cohort. *The open rheumatology journal* 2013;7:58-63.
8. Ariza-Ariza R, Hernandez-Cruz B, Carmona L, Dolores Ruiz-Montesinos M, Ballina J, Navarro-Sarabia F, *et al.* Assessing utility values in rheumatoid arthritis: a comparison between time trade-off and the EuroQol. *Arthritis & Rheumatism* 2006;55:751-6.
9. Augustsson J, Neovius M, Cullinane-Carli C, Eksborg S, van Vollenhoven RF. Patients with rheumatoid arthritis treated with tumour necrosis factor antagonists increase their participation in the workforce: potential for significant long-term indirect cost gains (data from a population-based registry). *Annals of the Rheumatic Diseases* 2010;69:126-31.
10. de Andrade NPB, da Silva Chakr RM, Xavier RM, Viecceli D, Correa RHB, de Oliveira Filho CM, *et al.* Long-term outcomes of treat-to-target strategy in established rheumatoid arthritis: a daily practice prospective cohort study. *Rheumatology International* 2017;37:993-7.

11. Fioravanti A, Tenti S, Bacarelli MR, Damiani A, Li Gobbi F, Bandinelli F, *et al.* Tocilizumab modulates serum levels of adiponectin and chemerin in patients with rheumatoid arthritis: potential cardiovascular protective role of IL-6 inhibition. *Clinical & Experimental Rheumatology* 2019;37:293-300.

12. Gwinnutt JM, Hyrich KL, Lunt M, Co-Investigators R, Barton A, Verstappen SMM. Long-term outcomes of patients who rate symptoms of rheumatoid arthritis as 'satisfactory'. *Rheumatology* 2020;59:1853-61.

13. Ling SF, Viatte S, Lunt M, Van Sijl AM, Silva-Fernandez L, Symmons DP, *et al.* HLA-DRB1 Amino Acid Positions 11/13, 71, and 74 Are Associated With Inflammation Level, Disease Activity, and the Health Assessment Questionnaire Score in Patients With Inflammatory Polyarthritis. *Arthritis & Rheumatology* 2016;68:2618-28.

14. Nair SC, Kievit W, Janse RW, Bijlsma JW, Fransen J, Lafeber FP, *et al.* Generalization and extrapolation of treatment effects from clinical studies in rheumatoid arthritis. *Arthritis care & research* 2014;66:998-1007.

15. Twigg S, Hensor EMA, Emery P, Tennant A, Morgan AW, Yorkshire Early Arthritis Register C. Patient-reported Outcomes as Predictors of Change in Disease Activity and Disability in Early Rheumatoid Arthritis: Results from the Yorkshire Early Arthritis Register. *Journal of Rheumatology* 2017;44:1331-40.

16. National Institiute for Health and Care Excellence. Filgotinib for treating moderate to severe rheumatoid arthritis ID1632. 2021. https://www.nice.org.uk/guidance/indevelopment/gid-ta10541 (Accessed 16/02/2021).

17. Adams R, Walsh C, Veale D, Bresnihan B, FitzGerald O, Barry M. Understanding the relationship between the EQ-5D, SF-6D, HAQ and disease activity in inflammatory arthritis. *Pharmacoeconomics* 2010;28:477-87.

18. Baganz L, Richter A, Albrecht K, Schneider M, Burmester GR, Zink A, *et al.* Are prognostic factors adequately selected to guide treatment decisions in patients with rheumatoid arthritis? A collaborative analysis from three observational cohorts. *Seminars in Arthritis & Rheumatism* 2019;48:976-82.

19. Bechman K, Tweehuysen L, Garrood T, Scott DL, Cope AP, Galloway JB, *et al.* Flares in Rheumatoid Arthritis Patients with Low Disease Activity: Predictability and Association with Worse Clinical Outcomes. *Journal of Rheumatology* 2018;45:1515-21.

20. Bergstra SA, Couto MC, Govind N, Chopra A, Salomon Escoto K, Murphy E, *et al.* Impact of the combined presence of erosions and ACPA on rheumatoid arthritis disease activity over time: results from the METEOR registry. *RMD Open* 2019;5:e000969.

21. Boers M, Buttgereit F, Saag K, Alten R, Grahn A, Storey D, *et al.* What Is the Relationship Between Morning Symptoms and Measures of Disease Activity in Patients With Rheumatoid Arthritis? *Arthritis care & research* 2015;67:1202-9.

22. Bremander A, Forslind K, Eberhardt K, Andersson MLE. Importance of Measuring Hand and Foot Function Over the Disease Course in Rheumatoid

Arthritis: An Eight-Year Follow-Up Study. *Arthritis care & research* 2019;71:166-72.

23. Campbell RC, Batley M, Hammond A, Ibrahim F, Kingsley G, Scott DL. The impact of disease activity, pain, disability and treatments on fatigue in established rheumatoid arthritis. *Clinical Rheumatology* 2012;31:717-22.

24. Carvalho PD, Ferreira RJO, Landewe R, Vega-Morales D, Salomon-Escoto K, Veale DJ, *et al.* Association of 17 Definitions of Remission with Functional Status in a Large Clinical Practice Cohort of Patients with Rheumatoid Arthritis. *Journal of Rheumatology* 2020;47:20-7.

25. Drossaers-Bakker KW, de Buck M, van Zeben D, Zwinderman AH, Breedveld FC, Hazes JM. Long-term course and outcome of functional capacity in rheumatoid arthritis: the effect of disease activity and radiologic damage over time. *Arthritis Rheum* 1999;42:1854-60.

26. Fatima S, Schieir O, Valois MF, Bartlett SJ, Bessette L, Boire G, *et al.* Health Assessment Questionnaire at One Year Predicts All-Cause Mortality in Patients with Early Rheumatoid Arthritis. *Arthritis & Rheumatology* 2020;06:06.

27. Heinimann K, von Kempis J, Sauter R, Schiff M, Sokka-Isler T, Schulze-Koops H, *et al.* Long-Term Increase of Radiographic Damage and Disability in Patients with RA in Relation to Disease Duration in the Era of Biologics. Results from the SCQM Cohort. *Journal of Clinical Medicine* 2018;7:13.

28. Lee KE, Choi SE, Xu H, Kang JH, Park DJ, Lee SS. HAQ score is an independent predictor of sustained remission in patients with rheumatoid arthritis. *Rheumatology International* 2017;37:2027-34.

29. Linde L, Sorensen J, Ostergaard M, Horslev-Petersen K, Rasmussen C, Jensen DV, *et al.* What factors influence the health status of patients with rheumatoid arthritis measured by the SF-12v2 Health Survey and the Health Assessment Questionnaire? *Journal of Rheumatology* 2009;36:2183-9.

30. Michaud K, Wallenstein G, Wolfe F. Treatment and nontreatment predictors of health assessment questionnaire disability progression in rheumatoid arthritis: a longitudinal study of 18,485 patients. *Arthritis care & research* 2011;63:366-72.

31. Nikiphorou E, Norton S, Young A, Carpenter L, Dixey J, Walsh DA, *et al.* Association between rheumatoid arthritis disease activity, progression of functional limitation and long-term risk of orthopaedic surgery: combined analysis of two prospective cohorts supports EULAR treat to target DAS thresholds. *Annals of the Rheumatic Diseases* 2016;75:2080-6.

32. Norton S, Sacker A, Dixey J, Done J, Williams P, Young A, *et al.* Trajectories of functional limitation in early rheumatoid arthritis and their association with mortality. *Rheumatology* 2013;52:2016-24.

33. Norton S, Fu B, Scott DL, Deighton C, Symmons DPM, Wailoo AJ, *et al.* Health Assessment Questionnaire disability progression in early rheumatoid arthritis: systematic review and analysis of two inception cohorts. *Seminars in arthritis and rheumatism* 2014;44:131-44.

34. Pan Y, Norton S, Gwinnutt JM, Kearsley-Fleet L, Symmons DPM, Lunt M, *et al.* Not all moderate disease is the same - Identification of disability trajectories

among patients with rheumatoid arthritis and moderate disease activity. *PLoS ONE [Electronic Resource]* 2019;14:e0215999.

35. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44-8.

36. Rydell E, Forslind K, Nilsson JA, Jacobsson LTH, Turesson C. Smoking, body mass index, disease activity, and the risk of rapid radiographic progression in patients with early rheumatoid arthritis. *Arthritis Research & Therapy* 2018;20:82.

37. Scott DL, Pugner K, Kaarela K, Doyle DV, Woolf A, Holmes J*, et al.* The links between joint damage and disability in rheumatoid arthritis. *Rheumatology (Oxford)* 2000;39:122-32.

38. Shadick NA, Gerlanc NM, Frits ML, Stolshek BS, Brady BL, Iannaccone C*, et al.* The longitudinal effect of biologic use on patient outcomes (disease activity, function, and disease severity) within a rheumatoid arthritis registry. *Clinical Rheumatology* 2019;38:3081-92.

39. Sokka T, Kankainen A, Hannonen P. Scores for functional disability in patients with rheumatoid arthritis are correlated at higher levels with pain scores than with radiographic scores. *Arthritis Rheum* 2000;43:386-9.

40. Tanaka E, Mannalithara A, Inoue E, Hara M, Tomatsu T, Kamatani N*, et al.* Efficient management of rheumatoid arthritis significantly reduces long-term functional disability. *Annals of the Rheumatic Diseases* 2008;67:1153-8.

41. Ten Klooster PM, Oude Voshaar MAH, Fakhouri W, de la Torre I, Nicolay C, van de Laar M. Long-term clinical, functional, and cost outcomes for early rheumatoid arthritis patients who did or did not achieve early remission in a real-world treat-to-target strategy. *Clinical Rheumatology* 2019;38:2727-36.

42. van der Heijde D, Klareskog L, Singh A, Tornero J, Melo-Gomes J, Codreanu C*, et al.* Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. *Ann Rheum Dis* 2006;65:328-34.

43. Ward MM, Guthrie LC, Alba MI. Measures of arthritis activity associated with patient-reported improvement in rheumatoid arthritis when assessed prospectively versus retrospectively. *Arthritis care & research* 2015;67:776-81.

44. Welsing PM, van Gestel AM, Swinkels HL, Kiemeney LA, van Riel PL. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. *Arthritis & Rheumatism* 2001;44:2009-17.

45. Tanaka E, Mannalithara A, Inoue E, Iikuni N, Taniguchi A, Momohara S*, et al.* Effects of long-term corticosteroid usage on functional disability in patients with early rheumatoid arthritis, regardless of controlled disease activity. *Rheumatology International* 2012;32:749-57.

46. Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L*, et al.* Baricitinib in Patients with Refractory Rheumatoid Arthritis. *New England Journal of Medicine* 2016;374:1243-52.

47. Wendler J, Burmester GR, Sorensen H, Krause A, Richter C, Tony HP*, et al.* Rituximab in patients with rheumatoid arthritis in routine practice (GERINIS): six-year results from a prospective, multicentre, non-interventional study in 2,484 patients. *Arthritis Research & Therapy* 2014;16:R80.

48. Koizumi R, Koyama K, Wako M, Ohba T, Takayama Y, Haro H. Clinical conditions needed to acquire sustained functional remission in rheumatoid arthritis patients. *Clinical Rheumatology* 2020; 10.1007/s10067-020-05451-3.

49. Baker JF, Conaghan PG, Emery P, Baker DG, Ostergaard M. Relationship of patient-reported outcomes with MRI measures in rheumatoid arthritis. *Annals of the Rheumatic Diseases* 2017;76:486.

50. van der Kooi E, Klarenbeek NB, Guler-Yuksel M, Kerstens PJ, van der Lubbe PA, Westedt ML*, et al.* A decrease in disease activity score (DAS) level is associated with a decrease in health assessment questionnaire (HAQ) score, independent of follow-up duration, during 5 years of tightly controlled treatment: results from the BeSt study. *Annals of the Rheumatic Diseases* 2011;70:168-71.

51. Andersson MLE, Forslind K, Hafstrom I, Group BS. Patients with Early Rheumatoid Arthritis in the 2000s Have Equal Disability and Pain Despite Less Disease Activity Compared with the 1990s: Data from the BARFOT Study over 8 Years. *Journal of Rheumatology* 2017;44:723-31.

52. Behrens F, Koehm M, Schwaneck EC, Schmalzing M, Gnann H, Greger G*, et al.* Use of a "critical difference" statistical criterion improves the predictive utility of the Health Assessment Questionnaire-Disability Index score in patients with rheumatoid arthritis. *BMC Rheumatology* 2019;3:51.

53. Nair SC, Bijlsma JW, van der Werf JH, van der Veen MJ, Linn-Rasker SP, Vreugdenhil S*, et al.* Do radiographic joint damage and disease activity influence functional disability through different mechanisms? Direct and indirect effects of disease activity in established rheumatoid arthritis. *Journal of Rheumatology* 2013;40:1505-12.

54. Radner H, Alasti F, Smolen JS, Aletaha D. Physical function continues to improve when clinical remission is sustained in rheumatoid arthritis patients. *Arthritis Research & Therapy* 2015;17:203.

9 APPENDICES

Appendix 1: Excluded studies with rationale for exclusion

Full-text articles excluded (n =29)

Reasons for exclusion

Data insufficient or unusable *(e.g.* data from one time period only) *(n= 28)*
Adams *et al*. 2010[17]
Baganz *et al*. 2019[18]
Bechman *et al*. 2018[19]
Bergstra *et al*. 2019[20]
Boers *et al*. 2015[21]
Bremander *et al*. 2019[22]
Campbell *et al*. 2012[23]
Carvalho *et al*. 2020[24]
Drossaers-Bakker *et al*. 1999[25]
Fatima *et al*. 2020[26]
Heinimann *et al*. 2018[27]
Lee *et al*. 2017[28]
Linde *et al*. 2009[29]
Michaud *et al*. 2011[30]
Nikiophorou *et al*. 2016[31]
Norton *et al*. 2013[32]
Norton *et al*. 2014[33]
Pan *et al*. 2019[34]
Prevoo *et al*. 1995[35]
Rydell *et al*. 2018[36]
Scott *et al*. 2000[37]
Shadick *et al*. 2019[38]
Sokka *et al*. 2000[39]
Tanaka *et al*. 2008[40]
Ten Klooster *et al*. 2019[41]
van der Heijde *et al*. 2006[42]
Ward *et al*. 2015[43]
Welsing *et al*. 2001[44]

J-HAQ *(n=1)*
Tanaka *et al*. 2012[45]

Appendix 2 Potential sensitivity analyses

Studies with potential for inclusion in sensitivity analyses

Eleven published studies, and confidential data provided from AbbVie, were considered as having potential for inclusion.

Eleven published studies were considered for sensitivity analyses if the included studies could not provide sufficient data. Data from a cohort presented in one of the included studies, Nair et al 2014 [14] had baseline DAS over 5.1 and is presented in this appendix. Clusters 5 and 6 of Gwinnutt et al. 2020[12] were included in the narrative synthesis, whereas data from clusters 1-4 had baseline DAS over 5.1 and are in this appendix. Details are provided in Table 6.

Most of the studies had a population with no prior biologic treatment, however three studies included patients with prior biologics at baseline (Genovese et al 2016[46] Wendler et al 2014.[47] Koizumi et al 2020[48]).

In all eleven studies, HAQ and DAS were assessed by physicians. Blinding of outcome assessors was explicit in two studies[49] [46] and a third study had DAS calculations by a blinded research nurse.[50]

Table 6Study characteristics of studies providing data, but excluded

Reference	Study	Sample size	Follow-up	Reason not meeting inclusion criteria
Andersson *et al*. 2017[51]	Comparing outcomes of two cohorts of RA patients, data from the BARFOT study	Cohort 1 n=928 Cohort 2 n=1010	8 years	Baseline DAS28 score > 5.1
Baker *et al*. 2017[49]	MRI sub-study of GOBEFORE, RCT of golimumab among methotrexate-naïve patients	291	12 months	Baseline DAS28 score > 5.1
Behrens *et al*. 2019[52]	Data from multicentre observational trial, full cohort and restricted cohort data, to determine a statistically defined critical difference for HAQ-DI	2740	6 months	Baseline DAS28 score > 5.1 (for cohort providing data)

Reference	**Study**	**Sample size**	**Follow-up**	**Reason not meeting inclusion criteria**
Genovese *et al*. 2016[46]	Investigating baricitinib treatment, RA-BEACON RCT	527	24 weeks	Baseline DAS28 score > 5.1
Gwinnutt *et al*. 2020[12] Clusters 1-4	Investigating clusters of symptoms associated with poor outcomes in early RA in the Rheumatoid Arthritis Medication Study, a UK multicentre cohort study	455	12 months 6 months of HAQ and DAS28 score changes	Baseline DAS28 score > 5.1
Koizumi *et al*. 2020[48]	Investigating factors for maintaining long-term functional remission, data from database of patient records	205 (of whom Remission n=154; No remission n=51)	1 year	Baseline DAS28 score < 3.2. Data from Japanese treatment, and so probably J-HAQ (not HAQ)
Nair *et al*. 2013[53]	Investigating disease activity and functional disability in T2T of RA, data from three cohorts, Netherlands	1, 034 (of whom Pyramid cohort n=551; CAMERA I n=299; CAMERA II n=236)	120 months	Baseline DAS28 score > 5.1
Nair *et al*. 2014[14]	Investigating whether treatment effects of pragmatic clinical trials are generalisable to clinical practice, data from pragmatic clinical trials of the Utrecht Rheumatoid Arthritis Cohort	Data from RCTs n=398;	6 months	Baseline DAS28 score > 5.1
Norton *et al*. 2013[32]	to identify subgroups with distinct trajectories of functional (HAQ) progression, Consecutive patients diagnosed with RA with symptoms <2 years (median 6 months) and prior to disease-modifying treatment were recruited into the Early	1460	10 years	DAS44 used (not DAS28)

Reference	Study	Sample size	Follow-up	Reason not meeting inclusion criteria
	RA Study (ERAS)			
Radner *et al*. 2015[54]	investigating the course of physical function in patients with sustained (24 weeks) DAS28 remission (DAS28CRP≤2.6), Information from clinical trials in RA patients and newly introduced TNFi or csDMARDs	610	24 weeks	Baseline DAS28 score > 5.1
van der Kooi *et al*. 2011[50]	Investigating DAS and functional ability during DAS-steered treatment, data from BeST RCT	508	5years	DAS44 used (not DAS28)
Wendler *et al*. 2014[47]	Investigating RTX in RA, prospective observational study (GERINIS study)	1658	8 months	Baseline DAS28 score > 5.1