NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Overview

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 (review of technology appraisal guidance 130, 186, 224, 280 and a part review of technology appraisal guidance 225 and 247)

This overview is a summary of:

- the evidence and views submitted by the manufacturers, the consultees and their nominated clinical specialists and patient experts and
- the assessment report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before comments on the assessment report have been received.

Key issues for consideration

Clinical effectiveness

- Current NICE guidance has not been able to distinguish between the biologic DMARDs on the basis of effectiveness. A number of head to head trials of biologic DMARDs are now available and the Assessment Group has completed a network meta-analysis that includes each of the interventions in the appraisal. What is the Committee's view on the relative clinical effectiveness of the biologic DMARDs?
- Current NICE guidance restricts use of the biologic DMARDs to people with severe active disease. The previous and new submissions indicate a paucity of clinical evidence for the moderately active disease group. What is the Committee's view of the effectiveness of biologic DMARDs in the

different populations (moderate to severe active disease, severe active disease) based on the updated evidence?

- The existing NICE guidance accepts the clinical effectiveness of the biologic DMARDs compared to either placebo or to existing conventional DMARDs. Further evidence is now available for both the methotrexate experienced and the methotrexate naïve populations. Does the new evidence change the Committee consideration of the effectiveness of the biologic DMARDs?
- There is no current NICE guidance for either the use of golimumab not previously treated with methotrexate or the use of subcutaneous abatacept. What is the Committee's opinion on the effectiveness of these technologies?
- The Assessment Group conducted NMA sensitivity analyses expanding the network to include studies that included a proportion of patients who previously received biologic DMARDs and/or a mixed population of people who previously received methotrexate and people who were methotrexate-naïve. What is the Committee's view on the inclusion of the patient populations in the trials in the NMA? What is the Committee's view on the inclusion of the larger group of trials in the NMA?

Cost effectiveness

- The Assessment Group developed their model based on EULAR response criteria, rather than the ACR response criteria that has been used in previous NICE appraisals. The ACR response criteria (ACR20, 50 and 70). require a specified improvement in tender joint count, swollen joint count, global assessments, pain, disability and an acute-phase reactant while the EULAR response criteria use the degree of change in DAS28 score and the DAS28 score reached to determine good, moderate or non-response Given this, how should the topic of EULAR and ACR response criteria be addressed in the economic modelling?
- The key driver of the economic modelling is the assumed long-term disease progression trajectory for people receiving treatment with conventional DMARDs. Previous appraisals have used a linear assumption

of disease progression which has been included in the manufacturers' submissions. What is the Committee's view of the Assessment Group's presentation of an alternative assumption on non-linear progression based on the Early Rheumatoid Arthritis Study (ERAS) dataset?

- The Assessment Group also included ICERs that varied based on assumptions about HAQ to utility mapping. What is the Committee's view on the most appropriate assumptions in the cost effectiveness analyses?
- For the population of people with severe active disease not previously treated with methotrexate, the Assessment Group assume that the ICERs for adalimumab will be representative of the other biologic DMARDs. Does the Committee consider that this assumption is appropriate?
- The ICERs presented by the Assessment Group and the manufacturers vary:
  - What is the Committee's view on the most appropriate ICERs for different populations by disease activity (moderate and severe)?
  - What is the Committee's view on the most appropriate ICERs for different populations by prior methotrexate use?
- The AG note that for many of the biologic DMARDs there are small differences between the total cost and QALYs. What is the Committee's view on the relative cost effectiveness of the interventions?

1 Background: clinical need and practice

1.1 Rheumatoid arthritis is a 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. It is a systemic disease and inflammatory disease outside the joints can affect other organs, including the lungs, heart and eyes. Rheumatoid arthritis is associated with increased mortality, and increasing disability which has a severe impact on quality of life. It is associated with substantial costs both direct (associated with drug acquisition and hospitalisation) and indirect due to reduced productivity.

1.2 Estimates of the prevalence of rheumatoid arthritis vary between 400,000 and 580,000 people in England. Of these, approximately 15% have severe disease. It is about two- to four-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.

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

1.4 Treatment for rheumatoid arthritis usually includes: non-steroidal anti-inflammatory drugs which reduce pain, fever and joint swelling/inflammation, and disease modifying anti-rheumatic drugs (DMARDs). DMARDs slow the disease process and reduce joint damage. Traditionally people received conventional DMARDs (cDMARDs) including methotrexate, leflunomide and sulfasalazine. More recently, a group of drugs have been developed 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 biologic DMARDs. Corticosteroids are also be used to control inflammation.

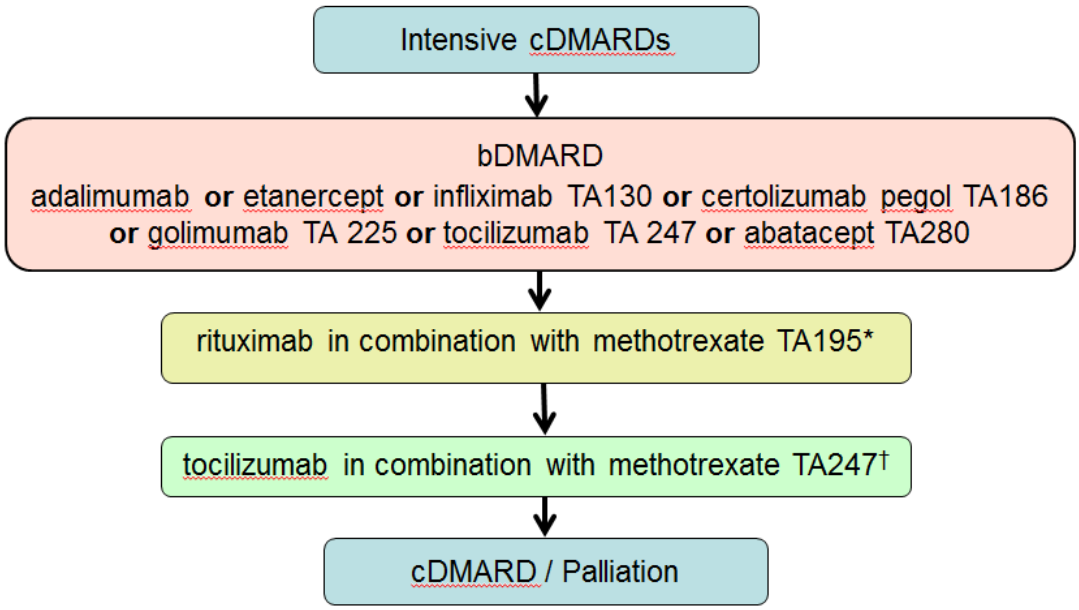
1.5 For people with newly diagnosed rheumatoid arthritis, 'Rheumatoid arthritis: the management of rheumatoid arthritis in adults' (NICE clinical guideline 79) recommends a combination of cDMARDs (including methotrexate and at least one other cDMARD plus short term glucocorticoids) as first-line treatment, ideally beginning within 3 months of the onset of persistent

symptoms. Where combination therapies are not appropriate cDMARD monotherapy is used.

1.6 NICE guidance does not recommend biologic DMARDs in newly diagnosed disease, but these may be used after the failure of two cDMARDs, including methotrexate. NICE guidance (TA130, TA186, TA225, TA247 and TA280) recommends the use of one of etanercept, infliximab, adalimumab, certolizumab pegol, golimumab, abatacept or tocilizumab in people with rheumatoid arthritis, and who have a disease activity severity (DAS28) score greater than 5.1 (see paragraph 1.8 for a definition of DAS28). The guidance states that the least costly option should be used taking into account administration costs, required dose and product price per dose. Treatment should only be continued at 6 months if there is an improvement in disease activity measured by a change DAS28 score of 1.2 or more, and treatment should be withdrawn if an adequate response is not maintained. Treatments should normally be used in combination with methotrexate. Adalimumab, etanercept and certolizumab pegol monotherapy may be used where continued methotrexate is not appropriate. The guidance described in this paragraph (that is, use of first biologic DMARD) is the subject of this appraisal review.

1.7 A proportion of people will have disease that does not respond to DMARD treatment and for others the effect of DMARD treatment reduces over time. Therefore people require a series of treatments. NICE has also issued guidance (TA195, TA225 and TA 247) on the treatment of rheumatoid arthritis after the failure of a TNF inhibitor which is shown in a simplified format in figure 1. A review of this guidance is not included in this appraisal (see appendix A for NICE guidance).

Figure 1: Simplified diagram of current DMARD treatment



*If rituximab and methotrexate (MTX) is contraindicated or withdrawn due to adverse events then the following can be used: adalimumab or etanercept or infliximab or abatacept in combination with MTX; adalimumab or etanercept monotherapy TA195 : tocilizumab in combination with MTX TA 247, assuming these have not been used previously in the sequence.

Note: Rituximab is only licensed and recommended in NICE guidance for use where there is an inadequate response or intolerance to other DMARDs including one or more tumour necrosis factor (TNF) inhibitor therapies

†Would not be used if tocilizumab has been used previously in the sequence

1.8 Measures to assess 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 DAS28 score 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. The Stanford Health Assessment Questionnaire (HAQ) is one component of the ACR criteria and scores physical disability and pain from 0 (least disability) to 3 (most severe disability). The

modified Total Sharp Score (mTSS) is a measure of joint damage as assessed radiographically, and is based on joint space narrowing and erosions.

2 The technologies

2.1 The different technologies have different mechanisms of action. Adalimumab, etanercept, infliximab, certolizumab pegol and golimumab all inhibit the activity of TNF-α, a pro-inflammatory mediator that is partly responsible for damage to the joints in rheumatoid arthritis and are referred to as TNF inhibitors. Tocilizumab inhibits the activity of the cytokine interleukin-6 (IL-6), a pro-inflammatory 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. The marketing authorisations for each of the technologies for use in rheumatoid arthritis are below, and are summarised in table 1.

Adalimumab

2.2 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, with the possibility of dose escalation up to 40mg per week for patients who experience a decrease in their response. It is administered subcutaneously.

2.3 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, leucopaenia, anaemia, lipids increased, 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.

Etanercept

2.4 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. It is administered subcutaneously.

2.5 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.

Infliximab

2.6 Infliximab (Remicade, Merck Sharp & Dohme), in combination with methotrexate, has a UK marketing authorisation for the reduction of signs and symptoms 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. It is administered by intravenous infusion.

2.7 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, pain. For full details of adverse reactions and contraindications, see the summary of product characteristics.

Certolizumab pegol

2.8 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 adult patients 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. It is administered subcutaneously.

2.9 Certolizumab pegol is contraindicated in people with active tuberculosis or other severe infections such as sepsis or opportunistic infections and 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 belonged to the system organ classes infections and infestations. For full details of adverse reactions

and contraindications, see the summary of product characteristics.

Golimumab

2.10 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 adult patients 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. It is administered subcutaneously.

2.11 Golimumab is contraindicated in people with active tuberculosis or other severe infections such as sepsis or opportunistic infections and moderate or severe heart failure. The summary of product characteristics notes the following adverse reactions as very common: upper respiratory tract infection. For full details of adverse reactions and contraindications, see the summary of product characteristics.

Abatacept

2.12 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 adult patients who responded inadequately to previous therapy with one or more DMARDs including methotrexate or a tumour necrosis factor-alpha inhibitor. It is administered by intravenous infusion or subcutaneous injection.

2.13 Abatacept is contraindicated in people with severe and uncontrolled infections such as sepsis and opportunistic infections. The summary of product characteristics notes the following adverse reactions as very common: upper respiratory

tract infections. For full details of adverse reactions and contraindications, see the summary of product characteristics.

Tocilizumab

2.14 Tocilizumab (RoActemra, Roche), in combination with methotrexate, has a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more DMARDs or tumour necrosis factor antagonists. In these patients, tocilizumab can be given as monotherapy in case of intolerance to methotrexate or where continued treatment with methotrexate is inappropriate. Tocilizumab is administered by intravenous infusion.

2.15 Tocilizumab is contraindicated in people with severe and uncontrolled 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.

2.16 The manufacturers of abatacept, certolizumab pegol, golimumab and tocilizumab have agreed patient access schemes with the Department of Health. The Department of Health considered that these patient access schemes do not constitute an excessive administrative burden on the NHS.

Table 1. Summary of licensed indications

	Adalimumab	Etanercept	Infliximab	Certolizumab pegol	Golimumab	Abatacept	Tocilizumab
Method of administration	sc	sc	iv	sc	sc	iv or sc	iv
Licensed as monotherapy where methotrexate use inappropriate	x	x		x			x
Licensed as combination therapy with MTX	x	x	x	x	x	x	x
Licensed for disease that is MTX naïve	x	x	x		x		
Licensed for disease that is MTX experienced	x	x	x	x	x	x	x
sc = subcutaneous; iv = intravenous infusion; MTX = methotrexate							

Table 2. Summary description of technologies

Non-proprietary name	Adalimumab	Etanercept	Infliximab	Certolizumab pegol	Golimumab	Abatacept iv	Abatacept sc	Tocilizumab
Proprietary name	Humira	Enbrel	Remicade	Cimzia	Simponi	Orencia	Orencia	RoActembra
Manufacturer	AbbVie	Pfizer	MSD	UCB	MSD	BMS	BMS	Roche
Dose	40 mg; every other week	50 mg; every week or 25 mg twice weekly	3 mg/kg: 0, 2, 6 then every 8 weeks	400 mg per week initially, repeated at weeks 2and 4 weeks followed by a maintenance dose of 200 mg every 2 weeks	50 mg below 100 kg per month. For patients who weigh more than 100kg, 100mg per month may be considered if they have an inadequate clinical response after 3-4 doses	**Intravenous infusion:** 500 mg below 60 kg, 750 mg between 60-100 kg, 1000 mg above 100 kg; 0, 2 and 4 weeks then every 4 weeks thereafter	**Subcutaneous injection:** Following a single IV infusion (schedule left),125mg should be given within a day followed by 125mg once weekly	8 mg/kg every four weeks
Acquisition cost (BNF September 2013)	net price 40-mg prefilled pen or prefilled syringe = £352.14; 40 mg/0.8-mL vial = £352.14	net price 25-mg prefilled syringe = £89.38; 50-mg prefilled pen or prefilled syringe = £178.75	net price 100-mg vial = £419.62	net price 200-mg prefilled syringe = £357.50	net price 50-mg prefilled pen or prefilled syringe = £762.97	net price 250-mg vial = £302.40,	net price 125-mg pre-filled syringe = £302.40	net price 4 mL (80-mg) vial = £102.40, 10 mL (200-mg) vial = £256.00, 20 mL (400-mg) vial = £512.00
Patient access scheme	N/A	N/A	N/A	Initial 10 doses free	100mg dose provided at the same price as the 50mg dose	[redacted]	[redacted]	[redacted]

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept within their licensed indications for the treatment of rheumatoid arthritis[1].

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Population	Adults with severe active rheumatoid arthritis not previously treated with methotrexate, or other DMARDs. Adults with severe active rheumatoid arthritis that has been previously treated with conventional DMARDs only, including methotrexate (unless contraindicated or inappropriate) Adults with moderate to severe active rheumatoid arthritis that has been previously treated with conventional DMARDs only, including methotrexate (unless contraindicated or inappropriate)	The AG in their report amended the populations to be: Population 1: Adults with severe active rheumatoid arthritis not previously treated with methotrexate. Population 2: Adults with severe active RA that have been previously treated with cDMARDs only, including methotrexate (unless contraindicated or inappropriate) Population 3: Adults with moderate to severe active RA that have been previously treated with cDMARDs only, including methotrexate (unless contraindicated or inappropriate)

The definition of population 1 was amended by the AG to include people who had not received methotrexate but could have received a different cDMARD to

[1] This appraisal includes a review of: Technology Appraisal No. 130, October 2007, Guidance on the use of infliximab, etanercept and adalimumab for the treatment of rheumatoid arthritis; Technology Appraisal No. 186, February 2010, Certolizumab pegol for the treatment of rheumatoid arthritis; Technology Appraisal No. 224 (Terminated June 2011), Golimumab for the treatment of methotrexate-naïve rheumatoid arthritis; Technology Appraisal No. 280, Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs; and a partial review of Technology Appraisal No. 225, June 2011, Golimumab for the treatment of rheumatoid arthritis after the failure of a conventional DMARD; and Technology Appraisal No. 247 (rapid review of TA 198), February 2012, Tocilizumab for the treatment of rheumatoid arthritis.

ensure that evidence for this group would not be excluded from consideration in the appraisal. The AG deviated from the scope because the groups as defined in the scope were mutually exclusive but not exhaustive, The AG defined severe active RA by a DAS28 score of ≥5.1, and moderate to severe active RA as a DAS28 score between 3.2 and 5.1.

	Final scope issued by NICE	**Additional comments or specifications in the Assessment Group's protocol**
Intervention	For rheumatoid arthritis not previously treated with methotrexate, or other DMARDs: • Adalimumab • Etanercept • Infliximab • Golimumab For rheumatoid arthritis that has been previously treated with conventional DMARDs only: • Adalimumab • Etanercept • Infliximab • Certolizumab pegol • Golimumab • Abatacept (intravenous and subcutaneous formulations) • Tocilizumab	The AG evaluated the interventions in combination with methotrexate, as per their licensed indications. Four products were also considered as monotherapy where methotrexate is contraindicated or inappropriate: Adalimumab, certolizumab pegol, etanercept, tocilizumab

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Comparators	For severe active rheumatoid arthritis not previously treated with methotrexate, or other DMARDs: • Combination therapy with conventional DMARDs (including methotrexate and at least one other DMARD, such as sulfasalazine and leflunomide), or DMARD monotherapy with dose escalation • The interventions will be compared to each other For severe active rheumatoid arthritis that has been previously treated with conventional DMARDs only: • Management strategies involving further conventional DMARDs (for example sulfasalazine, leflunomide), NSAIDs and corticosteroids. • The interventions will be compared to each other • Tofacitinib, subject to NICE guidance For moderate to severe active arthritis that has been previously treated with conventional DMARDs only: • Management strategies involving further conventional DMARDs (for example sulfasalazine, leflunomide), NSAIDs and corticosteroids. • The interventions will be compared to each other • Tofacitinib, subject to NICE guidance	The Assessment group reflected the scope of the appraisal in their analysis. The appraisal of tofacitinib is currently suspended following receipt of negative CHMP opinion. Two studies of tofacitinib provided supplementary linkages in the network meta-analysis.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Outcomes	The outcome measures to be considered include: • disease activity • physical function • joint damage • pain • mortality • fatigue • radiological progression • extra-articular manifestations of disease • adverse effects of treatment • health-related quality of life.	The Assessment Group included the outcomes in the scope in their analysis.

The AG also collected data on a number of variables such as disease duration, number of previous cDMARDs, and the percentage of patients who had received prior biologic DMARDs in case there was sufficient variation in baseline measurements that these could be investigated as treatment effect modifiers within the data synthesis.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The Assessment Group reflected the scope in their analysis

4 Clinical-effectiveness evidence

4.1 60 randomised controlled trials were identified by the Assessment Group as meeting the criteria for inclusion in the systematic review. Six trials were head-to-head comparisons of biologic DMARDs, one was an unpublished trial comparing TNF-α inhibitors (as a group) with cDMARDs (TACIT), and 53 were trials of individual biologic DMARDs compared with placebo or cDMARDs. An additional 12 trials were included in sensitivity analyses. These included trials where a small proportion of patients in the trial had had prior exposure to biological DMARDs or low prior exposure to methotrexate. Two trials of tofacitinib in comparison with placebo were also included in the sensitivity analyses and provided supplementary linkages in the network meta-analysis. In total the AG drew on 74 trials in their assessment of clinical effectiveness.

4.2 The AG reported that many of the trials included in the systematic review were of good quality, and had a reasonably low risk of bias. The AG noted that there may be issues with generalisability to the UK, as some of the trials conducted in Japan used low dose methotrexate treatment prior to randomization, which could affect the rate of methotrexate response among the trial populations. The AG also noted that the application of strict trial inclusion criteria resulted in narrower study populations than in clinical practice in England and Wales, and that randomized controlled trials may not capture rare adverse events. For the AG the primary outcomes of interest were American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) data. The EULAR response criteria use the degree of change in DAS28 score and the DAS28 score reached to determine good, moderate or non-response.

Head to head biologic DMARD trials

4.3 There were 6 head to head trials of biologic DMARDs (table 3), of which two were excluded from the network meta-analysis (Kume, 2011 and RED-SEA). Of the six studies there were 4 studies with adalimumab arms, 3 studies with etanercept arms, 2 studies with infliximab arms, 2 studies with abatacept arms, and 1 study with a tocilizumab arm. One trial was included in the development of the abatacept guidance TA280.

4.4 The AG identified one head to head trial completed in patients with disease that was methotrexate naïve (Kume 2011). This trial did not report either ACR or EULAR data. The outcome in the trial was mean change from baseline in DAS28 which was reported to be similar for adalimumab and etanercept monotherapy. For the methotrexate experienced population, 4 of the trials provided ACR response data. In the ATTEST trial statistically significantly greater proportions of patients achieved ACR20, ACR50 and

ACR70 responses in the infliximab plus methotrexate and intravenous abatacept plus methotrexate groups than in the placebo plus methotrexate group. In ADACTA, statistically significantly greater proportions of patients achieved ACR responses in the tocilizumab monotherapy group than in the adalimumab monotherapy group.

4.5 Three trials provided EULAR data for the methotrexate experienced population. The ATTEST trial reported that abatacept plus methotrexate and infliximab plus methotrexate had similar EULAR outcomes at six months follow-up. No statistically significant differences were reported between the abatacept and infliximab groups. The RED-SEA trial reported that adalimumab plus cDMARDs and etanercept plus cDMARDs had similar EULAR outcomes at one year follow-up. However, the ADACTA study reported that significantly more patients in the tocilizumab monotherapy group achieved a good EULAR response compared to adalimumab monotherapy at six months follow-up. Four trials for the methotrexate experienced population reported change in DA28. Similar changes in DAS 28 were observed for abatacept and infliximab (ATTEST), abatacept and adalimumab monotherapy (AMPLE) and adalimumab and etanercept both in combination with cDMARDs (RED-SEA). ADACTA reported higher DAS28 change for tocilizumab monotehrapy than adalimumab monotherapy.

4.6 Four head to head trials (ATTEST, AMPLE, ADACTA and DeFilippis 2004) including people previously treated with methotrexate showed improvements in HAQ-DI for all arms. Abatacept had similar reslts to infliximab (ATTEST) and adalimumab (AMPLE). Tocilizumab monotherapy had slightly more improvement than adalimumab monotherapy (ADACTA). Etanercept had slightly better results than infliximab (De Filippis).

Table 3. Key results for head to head biologic DMARD studies

Study	N	Intervention and comparator	Follow-up (mths)	ACR 20/50/70 (%)	EULAR response None/ mod/ good (%)	Mean change HAQ (SD)
Methotrexate naive disease (trials in italics with an asterisk are NOT included in the NMA main analysis)						
*Kume 2011**	*43*	*ADA mono* *ETN mono*	*6*	*NR* *NR*	*NR* *NR*	*NR* *NR*
Methotrexate experienced disease (trials in italics with an asterisk are NOT included in the NMA main analysis)						
ADACTA	326	ADA mono TCZ mono	6	45/35/20 22/26/52	35/20/55 26/52/78	-0.5 (NR) -0.7 (NR)
AMPLE	646	ADA mono ABTsc mono	7	65/42/23 66/46/24	NR NR	NR NR
*RED-SEA**	*120*	*ADA +cDMARD* *ETN +cDMARD*	*12*	*NR* *NR*	*40/33/26* *52/17/32*	*NR* *NR*
DeFilippis 2006	32	ETN + MTX IFX + MTX	5.5	60/26/7 60/33/7	NR NR	NR NR
ATTEST	431	ABT+MTX IFX+MTX PBO+MTX	6.5	67/40/21 59/37/24 42/20/9	23/57/20 34/43/23 45/44/11	NR NR NR

Abbreviations: ADA adalimumab; cDMARD conventional disease-modifying anti-rheumatic drugs; PBO placebo; NR not reported; ACR American College of Rheumatologist score; EULAR European League Against Rheumatism score; HAQ Health Assessment Questionnaire; MTX methotrexate; ETN etanercept; ABT abatacept; CTZ certolizumab pegol; GOL golimumab; TCZ tocilizumab; TOF tofacitinib; SSZ sulfasalazine; DAS Disease Activity Score; IFX infliximab; MP methylprednisolone; sc subcutaneous; IV intravenous

Trials shaded in grey were previously considered in developing the original guidance. ATTEST was included in the appraisal of abatacept TA280 but not that of infliximab TA130.

Adalimumab

4.7 Thirteen trials compared adalimumab with placebo or cDMARDs: 6 completed in people who were methotrexate naive, and 7 completed in people who had previously received methotrexate (table 4). Three of the 13 trials were not included in the NMA. One further study was excluded from the systematic review due to a proportion of patients having had prior biologic DMARDs but was included in sensitivity analyses. Five of the trials were previously considered in the development of the guidance for TA130.

4.8 For patients who had not previously received methotrexate, 5 trials included ACR data and 4 reported statistically significant differences in ACR response favouring biologic treatment over comparator. Two trials included EULAR data, GUEPARD reported a significantly better EULAR response for adalimumab plus methotrexate compared with methotrexate alone at 12 weeks follow-up but at one year follow-up when both groups had undergone step-up therapy based on their DAS28 score, both groups had similar outcomes. OPERA reported similar EULAR responses for adalimumab plus methotrexate and steroid and for placebo plus methotrexate and steroid at one year follow-up.

4.9 For patients who had previously received methotrexate, statistically significant findings were reported in 4 adalimumab trials for ACR response favouring biologic over comparator treatment. Two adalimumab trials (AUGUST II in combination with methotrexate, monotherapy in van de Putte) reported EULAR data and both reported significantly better EULAR results for adalimumab than placebo.

Table 4. Key results for adalimumab studies

Study	**N**	**Intervention and comparator**	**Follow-up (mths)**	**ACR 20/50/70 (%)**	**EULAR response None/ mod/ good (%)**	**Mean change HAQ (SD)**
Methotrexate naive disease (trials in italics with an asterisk are NOT included in the NMA base case)						
*Bejarano 2008**	*148*	*ADA + MTX* *PBO + MTX*	*12*	*NR* *NR*	*NR* *NR*	*NR* *NR*
*GUEPARD**	*65*	*ADA + MTX* *MTX*	*3*	*84/66/44* *50/27/19*	*NR/NR/64* *NR/NR/25*	*-0.82 (NR)* *-0.51 (NR)*
HIT HARD	172	ADA + MTX PBO + MTX	6	79/64/48 68/49/27	NR NR	-0.91(NR) -0.58 (NR)
*OPERA**	*180*	*ADA + MTX+steroid* *PBO + MTX+steroid*	*12*	*86/80/65* *78/63/45*	*11/82/93* *20/74/94*	*-0.88* (NR) *-0.63* (NR)
OPTIMA	103	ADA + MTX	6.5	70/52/35	NR	-0.89 (0.74)

	2	PBO + MTX		57/34/17	NR	-0.66 (0.73)
PREMIER	799	ADA + MTX ADA mono PBO + MTX	6.5	69/59/43 53/35/20 62/41/22	NR NR NR	-1.1 (0.6) -0.8 (0.7) -0.8 (0.6)
Methotrexate experienced disease (trials in italics with an asterisk are NOT included in the NMA base case)						
ARMADA	129	ADA + MTX PBO + MTX	6	67/55/27 15/8/5	NR NR	0.57 (NR) 0.27(NR)
AUGUST II	155	ADA + MTX PBO + MTX	6.5	71/38/18 46/15/5	19/NR/NR 41/NR/NR	NR NR
CHANGE	178	ADA mono PBO	6	44/24/12 14/6/1	NR	-0.2(0.6) 0.1(0.6)
DE019	407	ADA + MTX PBO + MTX	6	63/39/21 30/10/3	NR	-0.59 (0.57) -0.25(0.56)
Kim 2007	128	ADA + MTX PBO + MTX	6	62/43/22 37/14/8	NR NR	NR NR
STAR	636	ADA +cDMARD PBO +cDMARD	6	53/29/15 35/11/4	NR NR	NR NR
Van de Putte 2004	223	ADA mono PBO	6.5	46/22/12 19/8/2	NR/NR/9 NR/NR/0.4	-0.38 (0.60) -0.07(0.49)
Trials not eligible for the systematic review but providing additional evidence for NMA sensitivity analyses (disease methotrexate experienced)						
ORAL Standard	697	ADA+MTX TOF5+MTX TOF10+MTX PBO+MTX	6	47/27/10 52/36/20 53/33/23 28/12/2	NR NR NR NR	NR NR NR NR

Abbreviations: ADA adalimumab; cDMARD conventional disease-modifying anti-rheumatic drugs; PBO placebo; NR not reported; ACR American College of Rheumatologist score; EULAR European League Against Rheumatism score; HAQ Health Assessment Questionnaire; MTX methotrexate; ETN etanercept; ABT abatacept; CTZ certolizumab pegol; GOL golimumab; TCZ tocilizumab; TOF tofacitinib; SSZ sulfasalazine; DAS Disease Activity Score; IFX infliximab; MP methylprednisolone; sc subcutaneous; IV intravenous; TOF5 tofacitinib 5mg; TOF10 tofacitinib 10mg

Trials shaded in grey were previously considered in developing the original guidance.

Etanercept

4.10 There were 12 studies that that compared etanercept with placebo or cDMARDs: 2 were completed in people who were methotrexate naive, and 10 in people who were methotrexate experienced (table 5). An additional trial was conducted comparing etanercept in combination with methotrexate with etanercept monotherapy. An additional 2 studies (TEMPO and TEAR) were not eligible for inclusion in the systematic review (due to the mix of patients who had and had not received

methotrexate) but were included in the NMA sensitivity analyses. Five of the 13 trials were not included in the NMA. Seven of the trials were considered in the development of the guidance for TA130.

4.11 For patients not previously treated with methotrexate, bothstudies reported ACR data, and both reported statistically significant differences in ACR response favouring biologic treatment over comparator. Neither of the etanercept trials reported EULAR data.

4.12 For patients previously treated with methotrexate, statistically significant findings were reported in 8 trials for ACR response favouring etanercept over comparator treatment. Four etanercept trials (JESMR, ADORE, LARA and APPEAL) reported EULAR results. JESMR reported statistically significantly better results for etanercept combination therapy than for etanercept monotherapy at six months and one year, while ADORE found similar responses at 16 weeks. LARA showed statistically significant results for etanercept combination therapy compared with methotrexate in combination with DMARDs, while APPEAL did not.

Table 5. Key results for etanercept studies

Study	N	Intervention and Comparator	Follow-up (mth)	ACR 20/50/70 ((%)	EULAR response None/ mod/ good (%)	Mean change HAQ (SD)
Methotrexate naive disease (trials in italics with an asterisk are NOT included in the NMA ma analysis)						
*COMET**	*542*	*ETN +MTX* *PBO + MTX*	*12*	*86/71/48* *67/49/28*	*NR* *NR*	*-1.02 (NR)* *-0.72 (NR)*
ERA	424	ETN mono MTX	6	65/40/21 58/32/14	NR NR	-0.73 (NR) -0.76 (NR)
Methotrexate experienced disease (trials in italics with an asterisk are NOT included in the NMA main analysis)						

*ADORE**	*314*	*ETN mono* *ETN+MTX*	*4*	*71/42/17* *67/40/18*	*80*** *82***	*-0.59 (0.69)* *-0.59 (0.58)*
*APPEAL**	*300*	*MTX+DMARD, ETN+MTX*	*4*	*58/35/7* *79/57/19*	*74*** *88***	*NR* *NR*
ETN Study 309	254	ETN + SSZ ETN mono SSZ mono	6	74/52/25 74/47/21 28/14/2	NR NR NR	NR NR NR
IIBCREATE	129	ETN + cDMARD PBO + cDMARD	6	66/47/23 32/17/5	NR NR	NR NR
JESMR	151	ETN mono ETN+MTX	6	64/48/26 90/64/38	29/38/33 4/44/52	-0.4 (NR) -0.5 (NR)
*Lan 2004**	*58*	*ETN +MTX* *MTX+PBO*	*3*	*90/66/24* *34/10/0*	*NR* *NR*	*-0.65 (NR* *-0.24 (NR)*
LARA	423	ETN + MTX cDMARD + MTX	6	83/62/35 50/23/11	8/NR/47 35/NR/12	-0.5 (NR)* -0.9 (NR)*
Moreland 1999	158	ETN mono PBO	6	59/40/15 11/5/1	NR NR	-0.59 -0.12
RACAT	353	ETN + MTX MTX + SSZ + HCQ	6	55/36/16 56/26/5	NR NR	-0.51(0.84) -0.44(0.77)
*Wajdula 2000**	*216*	*ETN mono* *PBO*	*3*	*70/NR/NR* *12/NR/NR*	*NR* *NR*	*1.30 (0.60)* *1.70 (0.60)*
Weinblatt 1999	89	ETN + MTX PBO + MTX	6	71/39/15 27/3/0	NR NR	NR NR
Trials not eligible for the systematic review but providing additional evidence for NMA sensitivity analyses (both methotrexate experienced disease)						
TEAR	755	ETN+MTX MTX+SSZ+HCQ MTX mono	6	56/32/12 55/31/9 39/19/3	NR NR NR	NR NR NR
TEMPO	682	ETN mono ETN+MTX MTX mono	6	72/41/18 83/60/37 74/41/16	NR NR NR	NR NR NR

Abbreviations: ADA adalimumab; cDMARD conventional disease-modifying anti-rheumatic drugs; PBO placebo; NR not reported; ACR American College of Rheumatologist score; EULAR European League Against Rheumatism score; HAQ Health Assessment Questionnaire; MTX methotrexate; ETN etanercept; ABT abatacept; CTZ certolizumab pegol; GOL golimumab; TCZ tocilizumab; TOF tofacitinib; HCQ hydroxychloroquine; SSZ sulfasalazine; DAS Disease Activity Score; IFX infliximab; MP methylprednisolone; sc subcutaneous; IV intravenous * adjusted ** moderate and good response combined

Trials shaded in grey were previously considered in developing the original guidance.

Infliximab

4.13 There were 12 studies that compared infliximab with placebo or cDMARDs: 5 were completed in people who were methotrexate naive, and 7 in people who were methotrexate experienced (table

6). Seven of the 12 trials were not included in the NMA. Four of the trials were previously considered in the development of the TA130 guidance.

4.14 In the trials of people not previously treated with methotrexate, ACR response was reported in 4 studies and statistically significant differences in ACR response favouring infliximab over comparator were reported for 2 studies. None of the trials reported EULAR data.

4.15 In the trials of people previously treated with methotrexate, statistically significant differences were reported in 5 trials for ACR response favouring infliximab over comparator treatment. EULAR response data was included in 1 trial. Swefot reported infliximab plus methotrexate having significantly better EULAR response than triple therapy with at one year, but this was not statistically significant at six months and two years.

Table 6. Key results for infliximab studies

Study	N	Intervention and comparator	Follow-up (mths)	ACR 20/50/70 (%)	EULAR response None/ mod/ good (%)	Mean change HAQ (SD)
Methotrexate naive disease (trials in italics with an asterisk are NOT included in the NMA bas case)						
*ASPIRE**	*571*	*IFX + MTX* *PBO + MTX*	*12.5*	*62/46/33* *54/32/21*	*NR* *NR*	*0.80 (0.65)* *0.68 (0.63)*
BeST	508	Initial combination therapy with IFX Sequential monotherapy Step-up combination therapy Initial combination therapy with prednisone	6	74/NR/31 50/NR/16 60/NR/12 74/NR/31	NR NR NR NR	NR NR NR NR
Durez 2007	44	IFX + MTX MTX MTX + MP	5.5	87/67/34 28/8/0 NR/NR/NR	NR NR NR	NR NR NR
*IDEA**	*122*	*IFX + MTX* *MTX + MP*	*6*	*NR* *NR*	*NR* *NR*	*NR* *NR*
*Quinn 2005**	*20*	*IFX + MTX* *PBO + MTX*	*3.5*	*60/60/60* *20/0/0*	*NR* *NR*	*NR* *NR*
Methotrexate experienced disease (trials in italics with an asterisk are NOT included in the NMA base case)						
*Abe 2006**	*96*	*IFX + MTX* *PBO + MTX*	*3.5*	*61/31/10* *23/9/0*	*NR* *NR*	*NR* *NR*
ATTRACT	174	IFX + MTX PBO + MTX	7.5	54/27/8 22/5/0	NR NR	NR NR
*Durez 2004**	*26*	*IFX + MTX* *MTX + MP*	*3.5*	*67/44/0* *8/0/0*	*NR* *NR*	*NR* *NR*
START	723	IFX + MTX PBO + MTX	5.5	58/32/14 26/10/5	NR NR	-0.39 (NR) -0.11 (NR)
Swefot	258	IFX + MTX SSZ + HCQ + MTX	5.5 for EULAR, 12 for ACR	42/25/12 28/15/7	NR/NR/34 NR/NR/24	NR NR
*Wong 2009**	*26*	*IFX + MTX* *PBO + MTX*	*4*	*NR* *NR*	*NR* *NR*	*NR* *NR*
*Zhang 2006**	*173*	*IFX + MTX* *PBO + MTX*	*4.5*	*76/44/23* *49/26/14*	*NR* *NR*	*-0.76 (NR)** *-0.45 (NR)**
Abbreviations: ADA adalimumab; cDMARD conventional disease-modifying anti-rheumatic drugs; PBO placebo; NR not reported; ACR American College of Rheumatologist score; EULAR European League						

Against Rheumatism score; HAQ Health Assessment Questionnaire; MTX methotrexate; ETN etanercept; ABT abatacept; CTZ certolizumab pegol; GOL golimumab; TCZ tocilizumab; TOF tofacitinib; HCQ hydroxychloroquine; SSZ sulfasalazine; DAS Disease Activity Score; IFX infliximab; MP methylprednisolone; sc subcutaneous; IV intravenous * Unclear if mean reported

Trials shaded in grey were previously considered in developing the original guidance.

Certolizumab pegol

4.16 There were 2 trials comparing certolizumab pegol with placebo or cDMARDs: both completed in people who had previously received methotrexate (table 7). An additional 4 studies were not eligible for inclusion in the systematic review due to a proportion of patients having had prior biologic DMARDs but which were included in sensitivity analyses. One of the 2 trials was not included in the NMA. The CERTAIN trial was specifically completed in people with low to moderate disease activity. Two of the additional trials identified by the AG, but neither of the trials included in the AG systematic review were considered in TA186.

4.17 Statistically significant differences were reported in 1 certolizumab pegol trial for ACR response favouring certolizumab pegol over comparator treatment. EULAR response data were not reported by the AG for either trial.

Table 7. Key results for certolizumab pegol studies

Study	N	Intervention and comparator	Follow-up (mths)	ACR 20/50/70 (%)	EULAR response None/ mod/ good (%)	Mean change HAQ (+/- SD)
Methotrexate experienced disease (trials in italics with an asterisk are NOT included in the NMA main analysis)						
CERTAIN	194	CTZ+ cDMARDs PBO+ cDMARDs	6	37/21/9 16/8/3	NR NR	[redacted] [redacted]
*REALISTIC **	*163*	*CTZ+ cDMARDs* *PBO+ cDMARDs*	*3*	*55/NR/NR* *21/NR/NR*	*NR* *NR*	*-0.48(NR)* *-0.10(NR)*
Trials not eligible for the systematic review but providing additional evidence for NMA sensitivity analyses (all methotrexate experienced disease)						
JRAPID	159	CTZ+MTX PBO+MTX	6	73/55/29 25/17/1	85* 30*	NR NR
RA0025	121	CTZ+MTX PBO+MTX	6	67/43/17 28/20/3	NR NR	NR NR
RAPID1	586	CTZ+MTX PBO+MTX	6	59/37/21 14/8/3	[redacted] [redacted]	NR NR
RAPID2	373	CTZ+MTX PBO+MTX	6	57/33/16** 9/3/1	NR NR	NR NR

Abbreviations: ADA adalimumab; cDMARD conventional disease-modifying anti-rheumatic drugs; PBO placebo; NR not reported; ACR American College of Rheumatologist score; EULAR European League Against Rheumatism score; HAQ Health Assessment Questionnaire; MTX methotrexate; ETN etanercept; ABT abatacept; CTZ certolizumab pegol; GOL golimumab; TCZ tocilizumab; TOF tofacitinib; SSZ sulfasalazine; DAS Disease Activity Score; IFX infliximab; MP methylprednisolone; sc subcutaneous; IV intravenous *moderate or good ** ORs from logistic regression

Trials shaded in grey were previously considered in developing the original guidance.

Golimumab

4.18 There were 4 trials comparing golimumab with placebo or conventional DMARDs: 1 completed in people who were methotrexate naive, and 3 completed in people who had previously received methotrexate (table 8). One of the 4 trials was not included in the NMA. Two of the studies were previously considered in TA225.

4.19 In the trial (GO-BEFORE) including people not previously treated with methotrexate, statistically significant differences in ACR response were reported favouring golimumab over comparator. GO-BEFORE reported significantly better EULAR response at 24

weeks for golimumab combined with methotrexate than for placebo with methotrexate.

4.20 In the trials of people previously treated with methotrexate, statistically significant findings were reported in all 3 trials for ACR response favouring golimumab over comparator treatment. In terms of EULAR response GO-FORWARD reported statistically significantly better results for golimumab in combination with methotrexate than methotrexate in combination with placebo.

Table 8. Key results for golimumab studies

Study	N	Intervention and Comparators	Follow-up (mths)	ACR 20/50/70 (%)	EULAR response None/ mod/ good (%)	Mean change HAQ (SD)
Methotrexate naive disease (trials in italics with an asterisk are NOT included in the NMA main analysis)						
GO-BEFORE	319	GOL+MTX PBO+MTX	6	62/40/24 49/29/16	73* 61*	NR NR
Methotrexate experienced disease (trials in italics with an asterisk are NOT included in the NMA main analysis)						
GO-FORTH	179	GOL+MTX PBO+MTX	6	71/42/27 33/15/6	NR NR	0.33 (0.42) 0.03 (0.58)
GO-FORWARD	222	GOL+MTX PBO+MTX	6	60/37/20 28/14/5	72* 42*	0.47 (0.55) - 0.13 (0.58)
*Kay 2008**	*70*	*GOL+MTX* *PBO + MTX*	*4*	*60/37/9* *37/6/0*	*NR* *NR*	*NR* *NR*

Abbreviations: ADA adalimumab; cDMARD conventional disease-modifying anti-rheumatic drugs; PBO placebo; NR not reported; ACR American College of Rheumatologist score; EULAR European League Against Rheumatism score; HAQ Health Assessment Questionnaire; MTX methotrexate; ETN etanercept; ABT abatacept; CTZ certolizumab pegol; GOL golimumab; TCZ tocilizumab; TOF tofacitinib; SSZ sulfasalazine; DAS Disease Activity Score; IFX infliximab; MP methylprednisolone; sc subcutaneous; IV intravenous *moderate or good response

Trials shaded in grey were previously considered in developing the original guidance.

Abatacept

4.21 There were 3 trials comparing abatacept with placebo or conventional DMARDs, all completed in people who had previously received methotrexate (table 9). Two of the 3 trials were not included in the NMA. An additional 2 studies were

excluded from the systematic review due to a proportion of patients having had prior biologic DMARDs but were included in sensitivity analyses.

4.22 The AIM study reported statistically significant differences for ACR responses favouring abatacept over the comparator. EULAR response data were not reported.

Table 9. Key results for abatacept studies

Study	N	Intervention and comparator	Follow-up (mths)	ACR 20/50/70 (%)	EULAR response None/ mod/ good (%)	Mean change HAQ (SD)
Methotrexate experienced disease (trials in italics with an asterisk are NOT included in the NMA main analysis)						
AIM	652	ABT+MTX PBO+MTX	6	68/40/20 40/17/7	NR NR	-0.68(0.03)* -0.50(0.05)*
*ASSET**	*50*	*ABT+MTX* *PBO+MTX*	*4*	*NR* *NR*	*NR* *NR*	*NR* *NR*
*ASSURE**	*1274*	*ABT+cDMARDs* *PBO+cDMARDs*	*12*	*NR* *NR*	*NR* *NR*	*-0.47 (NR)* *-0.26 (NR)*
Trials not eligible for the systematic review but providing additional evidence for NMA sensitivity analyses						
ACQUIRE	1457	ABTsc +PBO+MTX ABTiv +PBO+MTX	6.5	75/50/26 74/49/24	NR NR	NR NR
NCT00254293	234	ABT+MTX PBO+MTX	6.5	60/37/17 35/12/2	NR NR	NR NR

Abbreviations: ADA adalimumab; cDMARD conventional disease-modifying anti-rheumatic drugs; PBO placebo; NR not reported; ACR American College of Rheumatologist score; EULAR European League Against Rheumatism score; HAQ Health Assessment Questionnaire; MTX methotrexate; ETN etanercept; ABT abatacept; CTZ certolizumab pegol; GOL golimumab; TCZ tocilizumab; TOF tofacitinib; SSZ sulfasalazine; DAS Disease Activity Score; IFX infliximab; MP methylprednisolone; sc subcutaneous; IV intravenous *adjusted

Trials shaded in grey were previously considered in developing the original guidance.

Tocilizumab

4.23 There were 6 trials comparing tocilizumab with placebo or conventional DMARDs all completed in people who had previously received methotrexate (table 10). Three additional studies were identified that were not eligible for inclusion in the systematic review due to a proportion of patients having had prior

biologic DMARDs (AMBITION, LITHE, OPTION), and a mix of patients who had and had not received methotrexate (the AMBITION trial only), but which were included in sensitivity analyses. Two of the 6 trials were not included in the NMA. One of the trials included in the AG systematic review and all 3 of the additional trials identified by the AG were considered in TA247.

4.24 Statistically significant differences were reported in 4 tocilizumab trials for ACR response favouring tocilizumab over comparator treatment. In terms of EULAR response ACT-RAY reported that tocilizumab monotherapy and tocilizumab in combination with methotrexate were similar at 6 months. Further, tocilizumab monotherapy had statistically significantly improved EULAR results compared with placebo in Nishimoto 2004. The TOWARD trial reported significantly better EULAR responses for tocilizumab in combination with cDMARDS than for placebo in combination with cDMARDS at six months.

Table 10. Key results for tocilizumab studies

Study	N	Intervention and comparator	Follow-up (mths)	ACR 20/50/70 (%)	EULAR response None/ mod/ good (%)	Mean change HAQ (SD)
Methotrexate experienced disease (trials in italics with an asterisk are NOT included in the NMA main analysis)						
ACT-RAY	553	TCZ mono TCZ+MTX	6	70/40/25 72/46/25	NR/35/51 NR/28/62	-0.54 (NR) -0.56 (NR)
*MEASURE**	*138*	*TCZ+MTX* *PBO+MTX*	*3*	*51/17/10* *25/6/3*	*NR* *NR*	*NR* *NR*
*Nishimoto 2004**	*108*	*TCZ mono* *PBO*	*3*	*78/40/16* *11/2/0*	91* 19*	*NR* *NR*
SAMURAI	302	TCZ mono cDMARDs	6	82/57/34 39/18/7	NR NR	NR NR
SATORI	125	TCZ+PBO PBO+MTX	6	80/54/33 25/17/11	NR NR	NR NR
TOWARD	1220	TCZ+cDMARDs PBO+cDMARDs	6	61/38/21 25/9/3	80* 38*	-0.5 (NR) -0.2 (NR)
Trials not eligible for the systematic review but providing additional evidence for NMA sensitivity analyses						
AMBITION	524	TCZ mono MTX mono	6	72/40/28 48/31/16	18/45/38 35/50/15	NR NR
LITHE	791	TCZ+MTX PBO+MTX	6	56/32/13 27/10/2	NR NR	NR NR
OPTION	409	TCZ+MTX PBO+MTX	6	59/44/22 26/11/2	21/41/38 65/32/3	NR NR

Abbreviations: ADA adalimumab; cDMARD conventional disease-modifying anti-rheumatic drugs; PBO placebo; NR not reported; ACR American College of Rheumatologist score; EULAR European League Against Rheumatism score; HAQ Health Assessment Questionnaire; MTX methotrexate; ETN etanercept; ABT abatacept; CTZ certolizumab pegol; GOL golimumab; TCZ tocilizumab; TOF tofacitinib; SSZ sulfasalazine; DAS Disease Activity Score; IFX infliximab; MP methylprednisolone; sc subcutaneous; IV intravenous *moderate or good response

Trials shaded in grey were previously considered in developing the original guidance.

4.25 The TACIT trial compared grouped biologic DMARDs (adalimumab, etanercept and infliximab) combined with a cDMARD with combination cDMARDs in people who had previously been treated with cDMARDs. TACIT provided EULAR data for the NMA. In TACIT, treatment with grouped biologics had more moderate/good EULAR responders (80%) than combination DMARDs (47%) at six months (no significance testing available).

4.26 Thirteen trials comparing biologic DMARDs with placebo of cDMARDs and including people not previously treated with methotrexate reported mean DAS28 change or remission data, while 20 such trials including people previously treated with methotrexate reported mean DAS28 change or remission data. Mean DAS28 improved slightly in all interventions, including control cDMARD arms. Biologic treatments arms reported higher percentages of patients meeting pre-defined DAS28 remission (usually <2.6) than non-biologic control arms with one or two cDMARDs or background cDMARDs. Statistically significantly more patients met DAS28 remission criteria or had statistically significantly improved DAS28 scores than baseline for biologic interventions than control in 7 trials including people not previously treated with methotrexate and 15 trials including people previously treated with methotrexate.

4.27 Ten trials including people not previously treated with methotrexate showed improvements in HAQ-DI for most treatments, both interventions and controls. Improvements in HAQ tended to be larger for the biologic DMARDs in most cases. In 27 other trials reporting HAQ-DI in trials including people previously treated with methotrexate, there was some improvement in HAQ-DI for all trial arms, with more improvement for biologics than control arms. In TACIT, treatment with grouped biologics had slightly smaller reductions in HAQ-DI from baseline compared with intensive cDMARDs at six months.

Network meta-analysis (NMA)

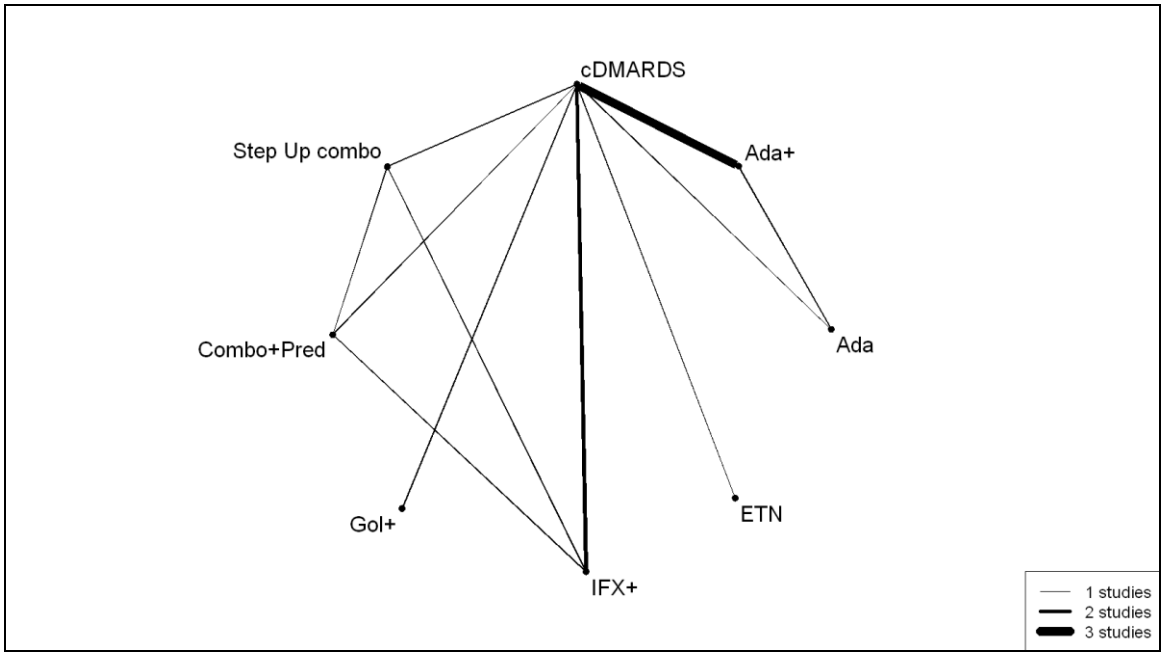
4.28 The AG conducted a network meta analysis including 37 studies for the outcomes of ACR response and EULAR response. An additional 12 trials with a small proportion of patients with previous biological DMARD use and those in which the patients have low background methotrexate use were included in

sensitivity analyses. Two further trials of tofacitinib were included in sensitivity analyses to create further linkages.

Methotrexate naïve disease

4.29 For the population of people not previously treated with methotrexate, the AG conducted an NMA of ACR response that included 7 trials. The network enabled a comparison of the effects of adalimumub (with and without methotrexate), etanercept monotherapy, infliximab in combination with methotrexate, golimumab in combination with methotrexate, intensive cDMARDs in combination with prednisolone, and step-up combination cDMARDs relative to cDMARDs (Figure 1). Data were not available to complete an analysis using EULAR response.

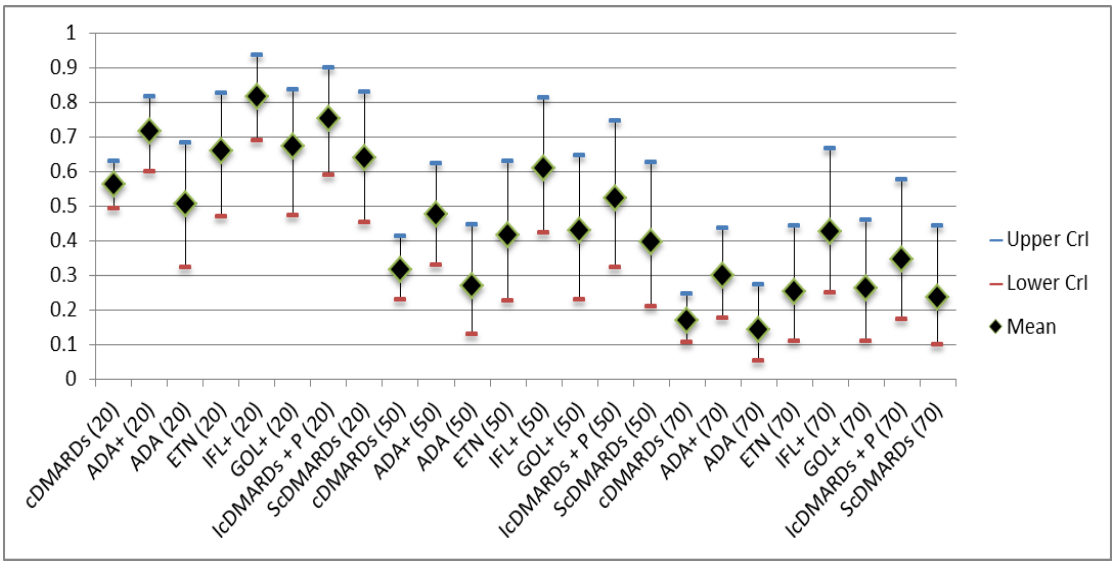
Figure 1: ACR – Network of evidence



4.30 The results were presented on the probit scale and showed that all interventions except for adalimumab monotherapy were associated with beneficial treatment effects relative to cDMARDs. However, compared to cDMARDs the treatment effects were only statistically significant ($p<0.05$) for adalimumab in combination

with methotrexate, infliximab in combination with methotrexate and intensive cDMARDs in combination with prednisolone. The probability of ACR 20, 50 and 70 response for each treatment (calculated by combining the treatment effects estimated from the network meta-analysis with the estimates of the cDMARDs 'no response' rate) are shown in Figure 2.

Figure 2. Probability of ACR 20, 50 and 70 response in the methotrexate naive population (derived from tables 26, 27 and 28 of AR)



Abbreviations: ADA adalimumab; cDMARD conventional disease-modifying anti-rheumatic drugs; PBO placebo; ETN etanercept; GOL golimumab; IFX infliximab; P prednisolone; + with methotrexate; IcDMARDs Intensive cDMARDS; ScDMARDs stepped up cDMARDs; 20 ACR20 response; 50 ACR 50 response; 70 ACR 70 response.

Median estimates were similar to mean estimates can be found in the AR tables referenced

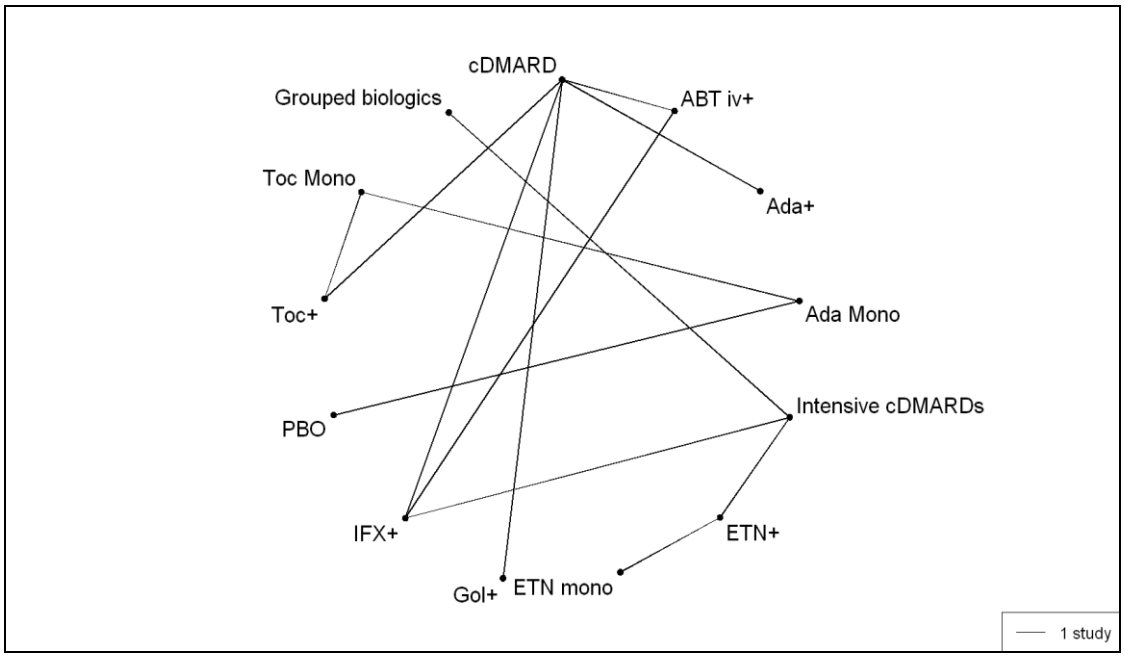
Methotrexate experienced

4.31 For the population of people previously treated with methotrexate, the AG conducted NMAs for EULAR and ACR responses, as well as sensitivity analyses which also included the additional trials that were excluded from the systematic review.

4.32 The AG included 11 trials in their NMA for EULAR response to compare the effects of intravenous abatacept combined with methotrexate, adalimumab (with and without methotrexate), intensive cDMARDs, etanercept (with and without methotrexate),

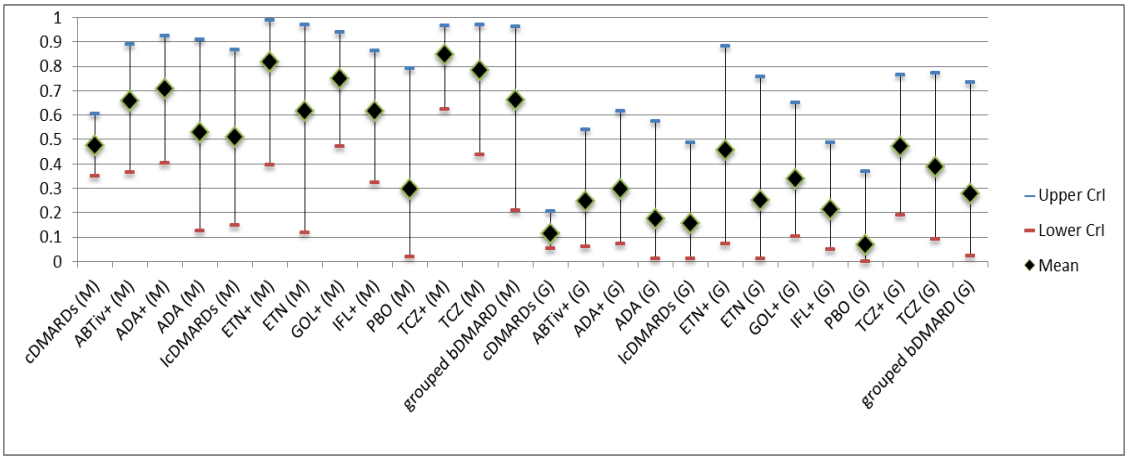
golimumab combined with methotrexate, infliximab combined with methotrexate, placebo, tocilizumab (with and without methotrexate) and the grouped biologics from the TACIT trial, relative to cDMARDs (Figure 3).

Figure 3: EULAR (Main Trials) – Network of evidence



4.33 Results were presented on the probit scale and showed that all interventions except for placebo were associated with beneficial treatment effects relative to cDMARDs. However, compared to cDMARDs the treatment effects were only statistically significant for golimumab combined with methotrexate and tocilizumab in combination with methotrexate at $p<0.05$. The probability of EULAR responses (calculated by combining the treatment effects estimated from the network meta-analysis with the estimates of the cDMARDs 'no response' rate) in the methotrexate experienced population are shown in Figure 4.

Figure 4. Probability of EULAR response in methotrexate experienced population (derived from AR tables 32 and 33)

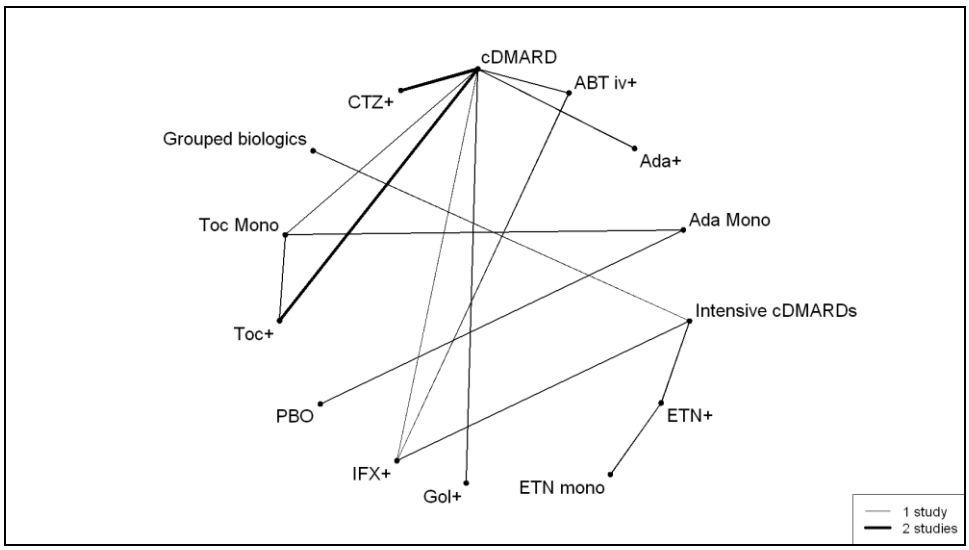


Abbreviations: ADA adalimumab; cDMARD conventional disease-modifying anti-rheumatic drugs; PBO placebo; ETN etanercept; ABT abatacept; GOL golimumab; IcDMARDs intensive cDMARDs; TCZ tocilizumab; IFX infliximab; IV intravenous; + with methotrexate; grouped bDMARDs data from the TACIT trial; M moderate EULAR response; G good EULAR response.

Median estimates were similar to mean estimates can be found in the AR tables referenced

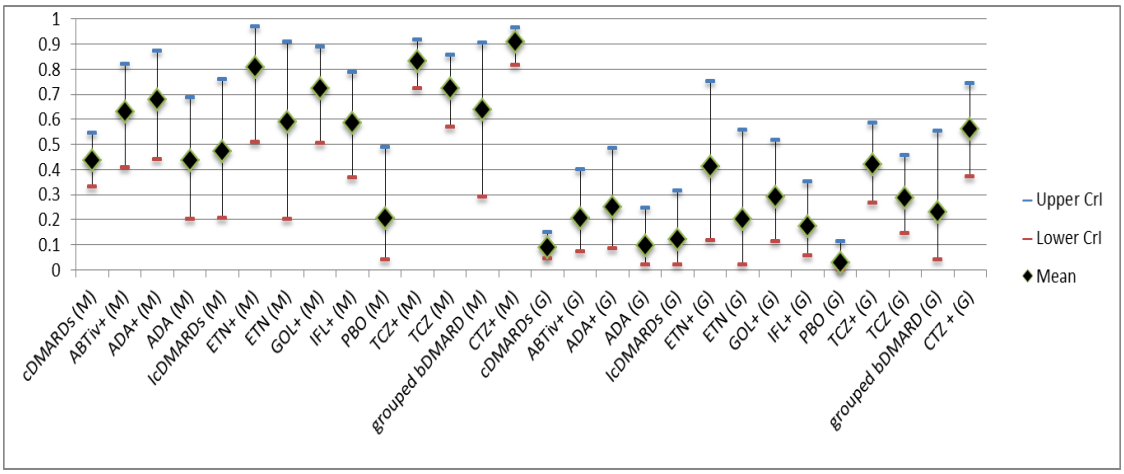
4.34 The AG conducted a sensitivity analysis including trials which included patients with previous use of biologic DMARDs, and also the AMBITION study which included a proportion of patients who had previously used biologic DMARDS and also included some patients who may not have had methotrexate. Expanding the inclusion criteria for the network meta-analysis enabled the inclusion of certolizumab pegol (figure 5). There were 13 treatment effects estimated from 15 studies.

Figure 5. EULAR (Main Trials plus Prior Biologics with AMBITION) – Network of evidence



4.35 Data were presented on the probit scale and showed that all interventions except for adalimumab monotherapy and placebo were associated with beneficial treatment effects relative to cDMARDs. The treatment effects were statistically significant for abatacept, adalimumab, etanercept, golimumab, tocilizumab and certolizumab pegol each in combination with methotrexate and also tocilizumab monotherapy. The inclusion of the additional studies reduced the uncertainty associated with each treatment effect, and reduced the effects of adalimumab monotherapy, placebo and tocilizumab. The additional studies also allowed the inclusion in the network of certolizumab pegol in combination with methotrexate. The probability of EULAR moderate and good responses (calculated by combining the treatment effects estimated from the network meta-analysis with the estimates of the cDMARDs 'no response' rate) are shown in Figure 6.

Figure 6. Probability of EULAR response in methotrexate experienced population (including patients who had received prior biologic DMARDs and AMBITION) (derived from AR tables 37 and 38)



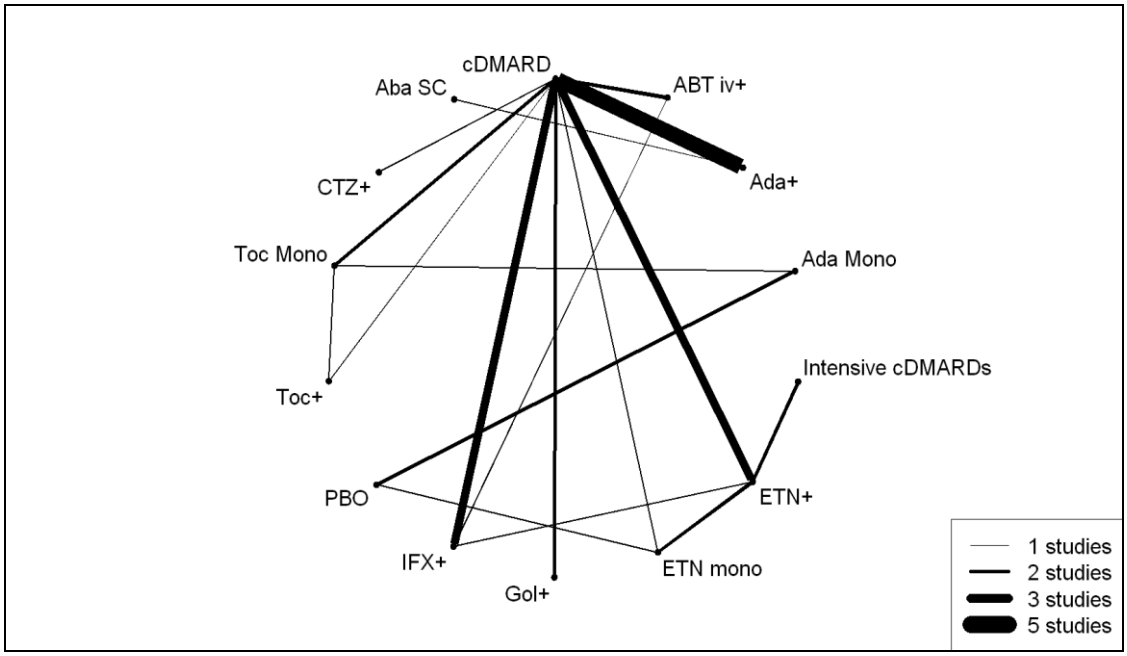
Abbreviations: ADA adalimumab; cDMARD conventional disease-modifying anti-rheumatic drugs; PBO placebo; ETN etanercept; ABT abatacept; GOL golimumab; TCZ tocilizumab; IFX infliximab; IV intravenous; CTZ certolizumab pegol; IcDMARDs intensive cDMARDs; + with methotrexate; grouped bDMARDs data from the TACIT trial; M moderate EULAR response; G good EULAR response.

Median estimates were similar to mean estimates can be found in the AR tables referenced

4.36 The AG also completed an analysis which included the trials where patients had prior biologics use, but excluded the AMBITION study. The AG reported that the exclusion of the AMBITION study had little impact on the estimate of the between study standard deviation, and that it resulted in a small increase in the results for adalimumab, placebo and tocilizumab relative to cDMARDs.

4.37 The AG conducted an NMA including the studies in its main analysis to compare the effect of the interventions on the ACR score which was the outcome reported in a larger proportion of studies. There were 13 treatment effects estimated from 28 studies (Figure 7).

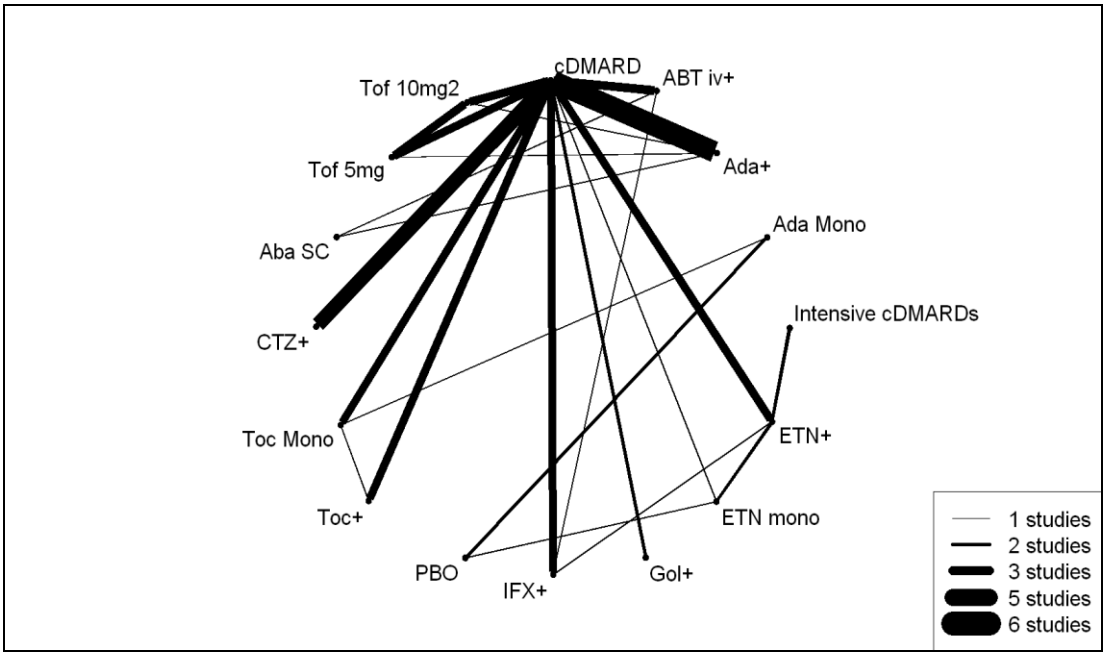
Figure 7. ACR (Main Trials) – Network of evidence



4.38 Results were presented on the probit scale and showed that all interventions except for placebo were associated with beneficial treatment effects relative to cDMARDs. The treatment effects were statistically significant for all interventions except for adalimumab monotherapy and placebo at $p<0.05$. The probability of ACR 20, 50 and 70 responses (calculated by combining the treatment effects estimated from the network meta-analysis with the estimates of the cDMARDs 'no response' rate) in the methotrexate experienced population are shown in Figure 9.

4.39 The AG conducted a sensitivity analysis for the NMA which incorporated trials that included patients with prior biologic DMARD use, including the AMBITION trial. Fifteen treatment effects were estimated from 40 trials (Figure 8).

Figure 8. ACR (Main Trials plus Prior Biologics with AMBITION) – Network of evidence



4.40 Data were presented on the probit scale and showed that all interventions except for placebo were associated with beneficial treatment effects relative to cDMARDs. All effects were statistically significant at $p<0.05$ except for placebo and adalimumab monotherapy. The results from the AR analyses for the probability of ACR responses (calculated by combining the treatment effects estimated from the network meta-analysis with the estimates of the cDMARDs 'no response' rate) in the methotrexate experienced population are shown in Figure 10.

Figure 9. Probability of ACR responses in methotrexate experienced population (main analysis) (AR tables 47, 48, 49)

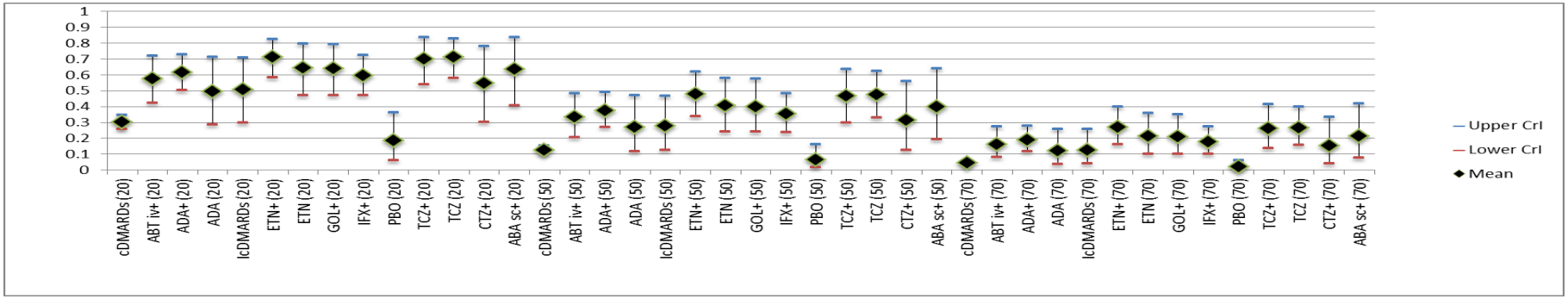
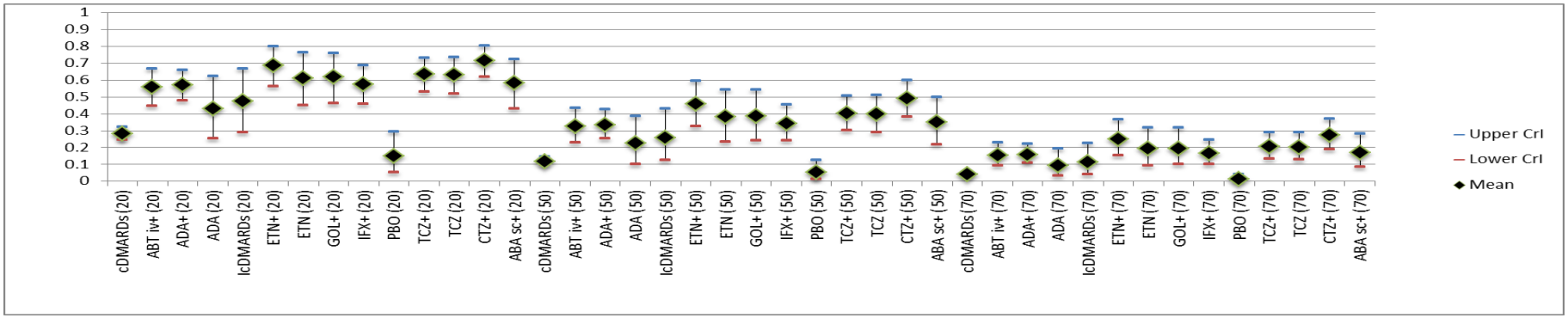


Figure 10. Probability of ACR responses in methotrexate experienced population (biologic DMARDs + AMBITION) (AR tables 53, 54 and 55)



Abbreviations: ADA adalimumab; cDMARD conventional disease-modifying anti-rheumatic drugs; PBO placebo; ETN etanercept; GOL golimumab; IFX infliximab; P prednisolone; iv interavenous infusion; PBO placebo; TCZ tocilizumab; CTZ certolizumab pegol; ABT abatacept; sc subcutaneous; + with methotrexate; IcDMARDs Intensive cDMARDS; 20 ACR20 response; 50 ACR 50 response; 70 ACR 70 response.

Median estimates were similar to mean estimates can be found in the AR tables referenced

Other outcomes data

4.41 The AG extracted data relating to discontinuations due to adverse events, number of patients experiencing 1 or more adverse events and number of patients 1 or more serious event (table 397 page 657 of the assessment report).

4.42 Nine RCTs reported health-related quality of life results in patients not previously treated with methotrexate. Trial data were available for adalimumab, etanercept and infliximab. Statistically significant differences in SF-36 components and domains favouring biologic treatment over comparator were reported for adalimumab (1 of 4 trials), etanercept (2 of 2 trials) and infliximab (1 of 3 trials). EQ-5D, SF-12 physical component and SF6D differences were also reported in 1 of the adalimumab trials. Statistically significant differences in the Rheumatoid Arthritis Quality of Life score favouring biologic treatment over comparator were reported in one study each for adalimumab and infliximab.

4.43 Twelve RCTs reported health-related quality of life results in people previously treated with methotrexate. Similar improvements were reported for SF-36 components and domains scores among patients receiving subcutaneous abatacept in combination with methotrexate and adalimumab in combination with methotrexate, abatacept in combination with methotrexate, infliximab in combination with methotrexate and methotrexate with placebo in the head to head trials (ATTEST and AMPLE). Significantly greater improvements were reported on SF-36 mental component score among patients receiving tocilizumab arm than in the adalimumab arm in the ADACTA trial. The RED-SEA trial reported similar improvements in EQ-5D score among patients receiving adalimumab and etanercept. Statistically significant differences in SF-36 components and domains scores favouring biologic treatment over cDMARDs or placebo were

reported in 5 of 9 trials collecting SF-36 data. One study each for abatacept, etanercept, golimumab, infliximab and tocilizumab. In TACIT, there was a statistically significantly greater reduction (worsening) in SF-36 component and domain scores in the TNF inhibitor arm. Statistically significant differences in EQ-5D domain scores favouring biologic treatment over comparator were reported in 1 etanercept trial and a further etanercept trial reported a statistically significant improvement in EuroQol Visual Analogue Scale score.

5 Comments from other consultees

5.1 Professional groups commented that the current eligibility criteria in NICE guidance for biologic DMARDs have been based on the British Society for Rheumatology (BSR) guidelines, but that the BSR guidelines have changed to become more inclusive recommending biologic DMARD treatment for people with moderate disease activity. Professional groups highlighted the importance of giving patients cDMARDs and biologic DMARDs according to NICE Clinical Guideline 79 in order to induce remission, and stated that there is evidence that treating people with moderately active rheumatoid arthritis with biological DMARDs produces outcomes comparable to treating people with severely active RA. Professional groups stated that the available evidence did not suggest that any biologic DMARD appeared to have greater clinical effectiveness than others.

5.2 The comments from patient groups emphasised the importance of biologic DMARDs for quality of life, including freedom of movement, reduction in fatigue and pain, as well as resumption of normal daily activities, including work and child care.

5.3 The comments received from NHS organisations were similar to those from professional groups, including endorsements of one

professional group's statement. They were supportive of the potential for use of biologic DMARDs in patients with moderately active RA, and in patients who were DMARD naïve. Consultee groups commented that these treatments can improve peoples' ability to continue working with resultant gains on productivity.

6 Cost-effectiveness evidence

6.1 The AG identified 30 relevant studies in their systematic review of the literature. Twenty three studies evaluated biologic DMARDs in patients who had previously received DMARDs, 6 studies evaluated biologic DMARDs in patients who had not previously received DMARDs, and 1 study evaluated patients in both groups. Most studies were of etanercept, infliximab and adalimumab, with no studies found in certolizumab pegol or golimumab. The studies had a wide range of model methods, time horizons, price years, currencies and discount rates. The AG stated that a detailed analysis of the parameters employed 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 AG's systematic review indicated that in patients who had previously received DMARD therapy, many biologic DMARDs had ICERs close to £30,000 per QALY in both directions, and that the ICERs were often higher for those people not previously treated with DMARDs. No individual biologic DMARD was seen to be consistently more cost effective compared to any other biologic DMARD. The AG noted that some studies identified had been used in previous NICE appraisals (TA 130 and TA 195) (Jobanputra 2002, Barton 2004 and Chen 2006).

6.2 The 6 manufacturers submitted models for each of the 7 drugs. The models for golimumab and infliximab were similar, as they

are both manufactured by MSD. The decision problem addressed by each manufacturer is outlined in Table 11.

Table 11: The decision problem addressed within the manufacturers' submissions (derived from table 74 in the Assessment Report)

	Manufacturer						
Decision Problem	AbbVie (ADA)	BMS (ABT)	MSD (GOL)	MSD (IFX)	Pfizer (ETN)	Roche (TCZ)	UCB (CTZ)
Combination with MTX							
Severe active MTX experienced	✔		✔	✔	✔		✔
Moderate active MTX experienced	✔				✔		✔
Severe active MTX naïve	✔				✔		
General RA Population [Δ]		✔	✔	✔			
Monotherapy							
Severe active MTX experienced	✔				✔		✔
Moderate active MTX experienced	✔						✔
Severe active MTX naive	✔						
MTX intolerant or contraindicated population[†]						✔	

Shaded cells indicate the intervention is not licensed in this population

ADA = adalimumab; ABT = abatacept; GOL = golimumab; IFX = infliximab; ETN = etanercept; TCZ = Tocilizumab; CTZ = certolizumab pegol; MTX = MTX. iv = intravenous; sc = subcutaneous; pop = population

Δ In essence, severe active and moderate active MTX experienced combined

† In essence, severe active and moderate active MTX experienced combined

Model structure and baseline characteristics

AbbVie (adalimumab)

6.3 The AbbVie model was an individual patient simulation in ARENA software. The model used a discrete simulation approach so there were no time cycles. The time horizon of the model was life with the perspective of the NHS/PSS and discounting of 3.5% for costs and benefits. Adalimumab was compared to other biologic DMARDs and to cDMARDs. Costs of serious infections were included.

6.4 Baseline characteristics of patients with severe active disease previously treated with methotrexate were taken from the BSRBR. For patients with moderate active disease previously treated with methotrexate, the ReAct study was used. For patients with severe active disease not previously treated with methotrexate, the source was the PREMIER trial. Patients 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 inhibitor, as well as cDMARDs. The response criterion in the model was ACR 50 and all patients were assumed to stay on treatment for 6 months, unless an adverse event occurred.

BMS (abatacept)

6.5 The BMS cost effectiveness model was an individual patient model implemented in Simul8 and does not require time cycles. The structure of the model was similar to that used in technology appraisal TA195 (the use of biologic DMARDs after the failure of a TNF inhibitor), but added an additional biologic DMARD to the start of the model. The time horizon of the model was life with the perspective of the NHS/PSS and discounting of 3.5% for costs and benefits. Abatacept was compared to other biologic DMARDs and to cDMARDs. Costs and disutilities associated with adverse events were not included.

6.6 Baseline characteristics of patients were based on those used for TA130 from Chen et al. Patients moved through a sequence of treatments based on response which included the use of rituximab and tocilizumab after the failure of a TNF inhibitor, as well as cDMARDs. The response criterion in the model was improvement in DAS28 score of 1.2 and patients were assumed to stay on treatment for 6 months, unless an adverse event occurred.

MSD (golimumab and infliximab)

6.7 For both golimumab and infliximab MSD constructed a cohort Markov model in Excel, with a time cycle of 6 months with half-cycle correction. Separate models were provided for each intervention. The time horizon of the models was 45 years with the perspective of the NHS/PSS and discounting of 3.5% for costs and benefits. Both infliximab and golimumab were compared to other biologic DMARDs and to cDMARDs. Costs and disutilities associated with adverse events were not included.

6.8 Patient baseline characteristics were taken from the GO-FORWARD trial for golimumab and from the ATTRACT trial for infliximab. Patients moved through a sequence of treatments based on response which included the use of rituximab after the failure of a TNF inhibitor, as well as conventional DMARDs. The sequence of treatments did not include tocilizumab. The response criterion in the model was ACR 20 response and all patients were assumed to stay on treatment for 6 months.

Pfizer (etanercept)

6.9 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 time horizon of the model was life with the perspective of the NHS/PSS and discounting of 3.5% for costs and benefits. Etanercept was compared to other biologic DMARDs and to cDMARDs. Costs and disutilities associated with adverse events were included in a scenario analysis.

6.10 For patients with severe active disease who had previously used DMARDs, baseline patient characteristics were sampled from the etanercept BSRBR cohort. For patients with moderate to severe active disease who had previously used DMARDs patient characteristics were based on the PRESERVE trial. For patients

with severe active disease who had not previously received DMARDs patient characteristics were taken from the COMET trial. Patients moved through a sequence of treatments depending on treatments response which included the use of rituximab and tocilizumab after the failure of a TNF inhibitor, as well as cDMARDs. The response criterion in the model was ACR 20 response and all patients were assumed to stay on treatment for 6 months.

Roche (tocilizumab)

6.11 Roche submitted an individual patient level model in Excel. The model used a 6 month cycle length with half cycle correction. The time horizon of the model was life with the perspective of the NHS/PSS and discounting of 3.5% for costs and benefits. The modeled strategies were restricted to patients contraindicated to methotrexate and the sequence of care included three lines of biologic DMARDs (certolizumab pegol, etanercept, adalimumab). Costs and disutilities associated with adverse events were not included.

6.12 Baseline patient characteristics were taken from the ADACTA trial, but instead of the 77kg average patient weight in the ADACTA trial, a 70kg average patient weight was used as previously accepted in TA130, TA195 and TA247. Tocilizumab was inserted as a first-line biologic treatment to create 4 lines of biologic DMARDs (that is a sequence of 4 biologic DMARDs including tocilizumab was compared to a sequence of 3 biologic DMARDs without tocilizumab). Conventional DMARDs were not included in the sequence. The response criterion in the model was ACR 20 response at 6 months, but patients whose disease did not respond to treatment were assumed to only incur costs of treatment for 3 months.

UCB (certolizumab pegol)

6.13 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 employed. The time horizon of the model was 45 years with the perspective of the NHS/PSS and discounting of 3.5% for costs and benefits. Certolizumab pegol was compared to other biologic DMARDs but not to cDMARDs. Costs and disutilities associated with adverse events were not included.

6.14 Baseline patient characteristics for patients with severe active disease previously treated with methotrexate was based on pooled mean estimates from the RAPID 1, RAPID 2 and FAST4WARD trials including both placebo and certolizumab pegol arms. For patients 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 which included the use of rituximab but not tocilizumab after the failure of a TNF inhibitor, as well as cDMARDs. The response criterion in the model could be either ACR 20 response or EULAR response and the time before measurement of response could be changed between 3 and 6 months.

Costs of interventions and administration

6.15 The costs assumed by the manufacturers came from established sources, however, several of the manufacturers did not consider some or all of the patient access schemes – AbbVie did not consider any of them, MSD considered the patient access schemes for golimumab, certolizumab pegol and tocilizumab while Pfizer and UCB only included the patient access schemes for golimumab and certolizumab pegol but not the commercial-in-confidence schemes for tocilizumab and abatacept. All the

manufacturers assumed vial wastage for intravenous abatacept, tocilizumab and infliximab.

6.16 Administration costs were largely comparable, mostly between £100 and £200 per infusion, based on values used in previous NICE appraisals for biologic DMARDs. However, AbbVie used a value of £501 per infusion. Several of the manufacturers included a cost for subcutaneous injections. Often a single cost in the first year for teaching a patient to inject, but in some cases a proportion of patients (10%) were assumed to require visits from a district nurse or other professional to provide the injection. The data for costs are summarised in table 12.

Table 12. Summary of drug and administration costs in manufacturers models

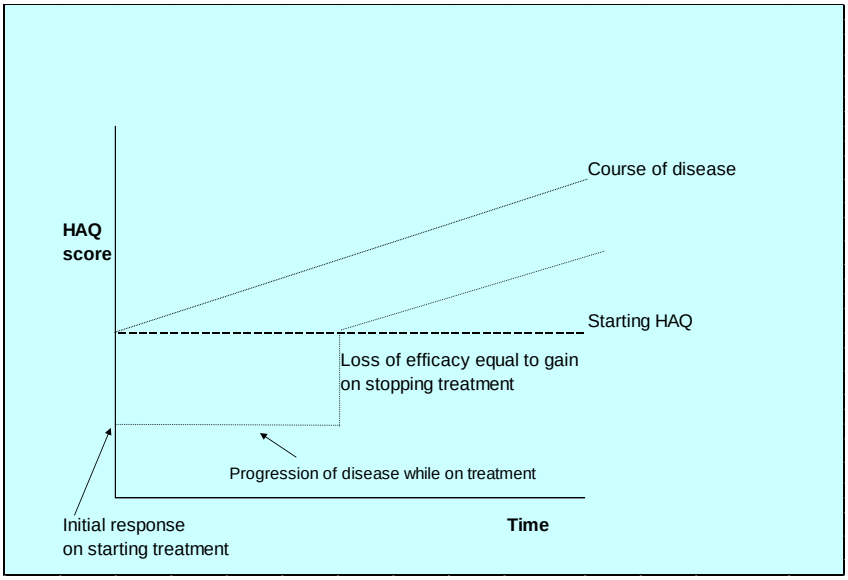
	AbbVie (ADA)	BMS (ABT)	MSD (GOL)	MSD (IFX)	Pfizer (ETN)	Roche (TCZ)	UCB (CTZ)
Include PAS	No	GOL CTZ TCZ ABT	GOL CTZ	GOL CTZ	GOL CTZ	CTZ TCZ	GOL CTZ
Annual cost ABT IV (£)	11,131	[redacted]	11,243	11,243		Not inc	11,390
Annual cost ABT sc (£)	Not included	[redacted]	15,724	15,724		Not inc	Not inc
Annual cost ADA (£)	9156	9187	9,155	9,155		9156	9192
Annual cost ETA (£)	9295	9327	9,295	9,295		9296	9332
Annual cost IFX (£)	7366	8211	7366	7366		Not inc	7354
Annual cost TOC (£)	10,175	[redacted]	[redacted]	[redacted]		[redacted]	12950
Annual cost GOL (£)	11,649	9156	9155	9155		Not inc	9192
Annual cost CTZ (£)	10725	9327	9295	9295		9292	9332
Assumed weight	Weight distribution	70kg	Weight distribution	Weight distribution	Weight distribution	70kg	Weight distribution
Source of weight estimate	BSRBR	TA195	BSRBR	BSRBR	BSRBR, PRESERVE, COMET	TA130 TA195 TA247	CTZ trials
Assumed vial wastage	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Intravenous infusion cost	501.48	136.20	109	109	152	171	126 (outpatient) 441 inpatient
Source of infusion cost	NHS ref costs	NHS ref costs	PSSRU	PSSRU	TA198 / TA247	TA 247	NHS ref costs
Inclusion of	Not given	Yes	Yes	Yes	Yes	10% injectio	Yes

teaching cost for subcutan e-ous injections						ns given by nurse	
Drug costs represent those for the second year onwards and do not include loading doses used in the first year.							

Effects of treatment

6.17 The manufacturers used comparable methods to model the effects of treatment. On starting treatment, a patient either responds or does not respond to treatment. If the patient responds, this is recorded in terms of ACR 20, 50 or 70 response or EULAR moderate and good response. The ACR or EULAR response is then related to a change in HAQ score or HRQOL (if HRQOL data are available). A better response is related to a larger change in HAQ or HRQOL. 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. Where HAQ instead of HRQOL is used, the HAQ change is then mapped to HRQOL data to produce a utility. This effect of treatment is assumed to be lost when treatment is stopped (described as the 'rebound effect'). Treatment is 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 receiving cDMARDs than for a person receiving biologic DMARDs. The overview includes 3 sections describing treatment effects (1) calculation of initial response on starting treatment, (2) relating the initial response to HAQ and HRQOL and (3) progression of disease while on treatment (that is, the trajectory or course of disease).

Figure 11. General approach to modelling treatment effect



This diagram describes the general approach only and does not reflect specific data used by any 1 manufacturer

Initial response to treatment

6.18 AbbVie included a mixed treatment comparison for ACR 20, 50 and 70 response rates. The analyses included controlling for treatment effect modifiers and hurdles to avoid inconsistent results (that is the possibility of a patient being simulated with an ACR50 response but not an ACR20 response). AbbVie stated that median posterior simulated ACR20 responses at 6 months were highest for etanercept and lowest for golimumab in methotrexate experienced patients who receive cDMARDs, while ACR50 responses were highest for etanercept and lowest for infliximab and ACR70 responses were highest for adalimumab and certolizumab pegol and lowest for abatacept and infliximab, but these differences were not statistically significant.

6.19 BMS included a mixed treatment comparison for change in DAS and also for change in HAQ. The analysis did not incorporate possible treatment effect modifiers. Certolizumab pegol and golimumab had the highest probabilities of being the most efficacious treatment for the HAQ score while tocilizumab and infliximab had the lowest probabilities. For the DAS score, certolizumab pegol and subcutaneous abatacept had the highest

probabilities of being the most efficacious treatment while etanercept and infliximab had the lowest probabilities, although these differences were not statistically significant.

6.20 MSD included a mixed treatment comparison for ACR20, 50 and 70. The analysis did not include potential effect modifiers. MSD reported that golimumab and infliximab combination therapy were statistically significantly better than adalimumab monotherapy and tocilizumab monotherapy for ACR20, 50 and 70, as well as etanercept monotherapy for ACR 50 and 70. No statistically significant differences were reported between biologic DMARDs when given in combination with methotrexate.

6.21 Pfizer included MTCs: for ACR20, 50 and 70 response, change in HAQ, withdrawals due to adverse events, patients with serious infection and rates of serious infection. Not all analyses were completed for each of the populations modeled. Only ACR analyses were presented for monotherapy treatment and patients not previously treated with cDMARDs. For combination therapy, Pfizer did not report any statistically significantly different HAQ changes between biologic DMARDs or ACR responses for monotherapy. However, etanercept was reported to be statistically significantly more effective than adalimumab and infliximab and intravenous abatacept for ACR20, 50, and 70 outcomes and subcutaneous abatacept for an ACR20 and 70 outcome. For monotherapy none of the biologic DMARDs were shown to be statistically significantly better than the others.

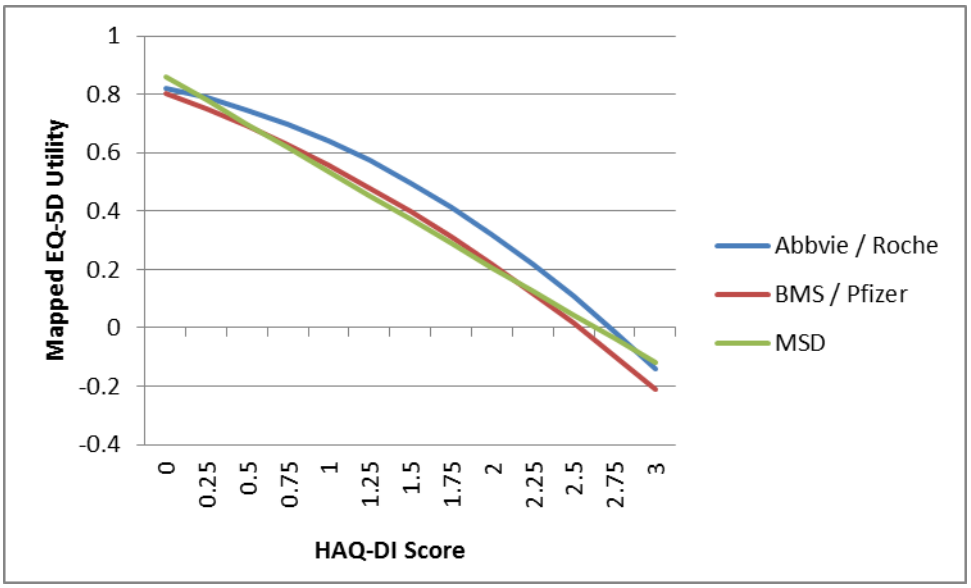
6.22 Roche included an NMA for ACR 20, 50 and 70 response. Tocilizumab monotherapy more effective than adalimumab, certolizumab pegol and etanercept monotherapy for each ACR response measure. However, the differences were not statistically significant.

6.23 UCB included MTCs for ACR 20, 50 and 70 response at 12 and 24 weeks and DAS28 at 24 weeks for biologic DMARDs in combination with methotrexate and as monotherapy. Certolizumab pegol was not statistically significantly more effective than the comparators for biologic DMARDs in combination with methotrexate or as monotherapy.

HAQ/EQ-5D changes in relation to response levels

6.24 The majority of manufacturers related the ACR or EULAR response to a change in HAQ that was then mapped to EQ-5D utility. UCB was the only manufacturer to use directly collected EQ-5D data. Of the mapping equations, those used in the appraisals TA130 (Hurst or Chen) and TA195 (Malottki) were used as the base case by BMS, MSD and Pfizer.

Figure 12: The relationship between HAQ and utility assumed in the manufacturers' models



6.25 AbbVie related the ACR responses calculated in the mixed treatment comparison to a change in HAQ. It was assumed that the HAQ change by ACR response for all biologic DMARDs would be the same as for adalimumab, while the changes associated with conventional DMARDs would be the same as for

methotrexate. Data for the amount of HAQ change for patients who are methotrexate-naïve were taken from PREMIER and from DE019 for patients who are methotrexate experienced. The HAQ change was then mapped to a change in utility based on a regression equation: EQ-5D = 0.82 -0.11*HAQ-DI – 0.07*HAQ-DI^2.

6.26 BMS related the change in DAS score to the change in HAQ calculated in their network meta-analyses. The change in HAQ was therefore treatment dependent (rather than assuming the same change in HAQ based for all biologic DMARDs). The HAQ change was then mapped to a change in utility using the regression equation used in TA195: EQ-5D = 0.804 – 0.203 x HAQ-0.045 x HAQ^2.

6.27 MSD related the ACR responses calculated in the mixed treatment comparison to a change in HAQ. For golimumab the change in HAQ was calculated from the GO-FORWARD and GO-FORTH trials, while for infliximab the change in HAQ was calculated from the START and ATTRACT trials. For both, changes in HAQ were calculated separately for the full rheumatoid arthritis population and for the subgroup of people with severe active disease. The change in HAQ based on ACR response was assumed to be applied to all treatments (treatment independent). The HAQ change was then mapped to a change in utility using the regression equation used in TA130: EQ-5D = 0.862-0.32*HAQ.

6.28 Pfizer related the ACR responses calculated in the mixed treatment comparison to a change in HAQ. The change in HAQ based on ACR response was assumed to be the same for all treatments. However, it differed based on line of treatment and whether the patient had previously received only cDMARDs or if

they had also received biologic DMARDs. These estimates were based on the manufacturer submission to NICE for TA198 (subject to rapid review and replaced by TA247). The HAQ change was then mapped to a change in utility using the regression equation used in TA195: EQ-5D = 0.804 – 0.203 x HAQ-0.045 x HAQ^2.

6.29 Roche related the ACR responses calculated in the mixed treatment comparison to a change in HAQ. The relationship between ACR response and initial HAQ change was based on the ADACTA trial at 24 weeks and is treatment independent. HAQ score was then mapped to EQ-5D utilities using the same method as in their submission to NICE for TA247. The regression equation used was EQ-5D = 0.82 -0.11*HAQ-DI – 0.07*$HAQ\text{-}DI^2$.

6.30 UCB used directly collected EQ-5D data from the RAPID trials for the patients with severe active disease with a regression analysis against ACR response criteria, and from the CERTAIN trial for the patients with moderate to severe active disease with a regression analysis of EQ-5D against EULAR response criteria. The relationship between EULAR response and change EQ-5D was assumed to be treatment independent and applied to all treatments.

HAQ trajectory following initial response

6.31 To model the change in HAQ score as disease progressed, the manufacturers used values from previous NICE appraisals that assumed a linear rate of progression. No progression was assumed to occur for patients on treatment with biologic DMARDs. For patients on treatment with cDMARDs the rate is 0.045 increase (worsening) in HAQ score per year, and for patients on treatment with palliative care the rate is 0.060 increase (worsening) in HAQ score per year. These changes in

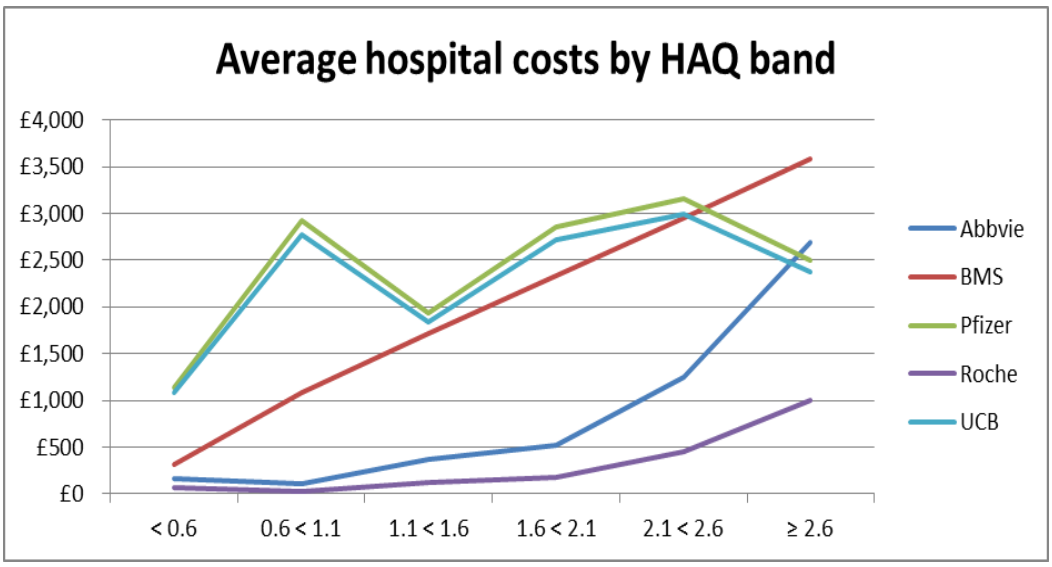
HAQ are also related to a change in utility using the same equations as described above.

6.32 UCB included a different approach and reported that HAQ would decrease (that is, disease would improve) at a rate of 0.0.0963 per 6 months while on first line treatment, but increase (that is, disease would worsen) at a rate of 0.048 per annum for second line biologic DMARD treatment. In the UCB model patients on cDMARDs or palliative care have an annual rate of progression of disease of 0.06 HAQ score. The long term change in HAQ score was related to HRQOL using the equation EQ-5D = -0.2102 x change in HAQ.

NHS costs per HAQ band

6.33 The manufacturers each included NHS costs (in addition to drug costs, administration and monitoring) that were related to HAQ score. AbbVie estimated disease related hospital costs based on the Norfolk Arthritis Register (NOAR) database. BMS assumed a cost per HAQ unit score of £1245 based on those used in TA195. MSD used data from Brennan et al to estimate the number of hospitalisations. Pfizer and UCB used the same data source from Kobelt et al, based on the Early Rheumatoid Arthritis Study to estimate the direct annual costs of medical resource. Roche included inpatient costs and calculated these using NOAR (figure 13).

Figure 13. A summation of the hospital costs assumed associated with each HAQ band



Mortality associated with RA

6.34 All manufacturers included an increased risk of death associated with rheumatoid arthritis. Four manufacturers included an additional risk of death of 1.33 per HAQ score unit (AbbVie, BMS, Roche, UCB) based on Wolfe and used in previous appraisals. MSD used a standardized mortality ratio of 1.65 that was taken from Chenhata et al, and was not HAQ dependent. Pfizer used Brennan et al and assumed an age and gender specific standardized mortality ratio, based on the UK population, and was not HAQ dependent.

Cost effectiveness results within the manufacturers' submissions

Biologic DMARDs in combination with methotrexate

Biologic DMARDs in combination with methotrexate for a population with severe active rheumatoid arthritis previously treated with methotrexate

6.35 Results for biologic DMARDs in combination with methotrexate in patients with severe active rheumatoid arthritis previously treated with methotrexate were provided by AbbVie, MSD, Pfizer and UCB. Each manufacturer concluded that their intervention was cost effective in comparison with conventional DMARDs. For this group MSD provided analyses only against cDMARDs rather than with other biologic DMARDs. UCB provided analyses that included the other biologic DMARDs but did not include conventional DMARDs (table 13).

6.36 Both AbbVie and Pfizer provided incremental analyses. Both suggested that etanercept was the most cost effective biologic DMARD with an ICER of £16,571 and £20,520 per QALY gained respectively. Other biologic DMARDs were dominated or extendedly dominated. The incremental analysis provided by UCB suggested that certolizumab pegol was the most cost effective treatment over a willingness to pay threshold of £4,822 per QALY gained.

Table 13. Pairwise ICERs (cost per QALY gained) for biologic DMARDs in comparison with cDMARDs – severely active disease. methotrexate experienced in combination with methotrexate

	AbbVie	MSD (GOL)	MSD (IFX)	Pfizer*	UCB
cDMARDS	-	-	-	-	cDMARDs not included in the treatment strategy
ABTiv	£24,172	-	-	£46,115	
ABTsc	-	-	-	£56,624	
ADA	£16,650	-	-	£28,451	
CTZ	£17,071	-	-	£20,966	
ETA	£16,571	-	-	£20,518	
GOL	£17,594	£21,013	£24,968	£29,856	
IFX	£18,781	-	-	£30,694	
TOC	£21,405	-	-	£39,240	

*ICERs calculated from incremental costs and QALYs presented in manufacturer submission may be subject to rounding

All biologic DMARDs with methotrexate

Biologic DMARDs in combination with methotrexate for a population moderate active rheumatoid arthritis previously treated with methotrexate

6.37 Results for biologic DMARDs in combination with methotrexate in patients with moderate active rheumatoid arthritis previously treated with methotrexate were provided by AbbVie, Pfizer and UCB. All manufacturers except UCB concluded their intervention was cost effective. The Pfizer analysis only included etanercept and cDMARDs and the UCB analysis only included certolizumab pegol and cDMARDs (table 14). Pfizer stated that there was a paucity of RCT data for the use of biologic DMARDs in a population with truly moderately active disease. The two available trials (PRESERVE and CERTAIN) could not be combined in a NMA. The incremental analysis provided by AbbVie suggested that etanercept was the most cost effective biologic DMARD with an ICER of £18,721 per QALY gained. Other biologic DMARDs were dominated or extendedly dominated.

Table 14. Pairwise ICERs (cost per QALY gained) for biologic DMARDs in comparison with cDMARDs – moderately active disease. methotrexate experienced in combination with methotrexate

	AbbVie	Pfizer	UCB
cDMARDS	-	-	-
ABTiv	£26,952	-	-
ABTsc	-	-	-
ADA	£18,792	-	-
CTZ	£19,217	-	£47,821
ETA	£18,721	£24,727	-
GOL	£19,784	-	-
IFX	£21,000	-	-
TOC	£24,014	-	-
All biologic DMARDs with methotrexate			

Biologic DMARDs in combination with methotrexate for a general population (moderate and severe active rheumatoid arthritis) previously treated with methotrexate

6.38 Results for biologic DMARDs in combination with methotrexate in patients with moderate or severe active rheumatoid arthritis previously treated with methotrexate were provided by BMS and MSD (table 15). BMS did not present an incremental analysis. MSD presented incremental analyses for both golimumab and infliximab. The AG reported that both MSD incremental analyses were completed incorrectly. The analyses in both submissions with the AG 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 biologic DMARDs were either dominated or extendedly dominated.

Table 15. Pairwise ICERs (cost per QALY gained) for biologic DMARDs in comparison with cDMARDs – moderate or severe active experienced combination

	BMS	MSD (Gol)	MSD (IFX)
cDMARDS	-	-	-
ABTiv	[redacted]	£34,953	£43,455
ABTsc	[redacted]	£44,232	£55,234
ADA	[redacted]	£20,769	£23,663
CTZ	[redacted]	£18,817	£21,011
ETA	[redacted]	£25,429	£31,065
GOL	[redacted]	£22,331	£26,512
IFX	[redacted]	£21,278	£25,144
TOC	[redacted]	£24,774	£29,339
All biologic DMARDs with methotrexate			

Biologic DMARDs in combination with methotrexate for a population with severe active rheumatoid arthritis not previously treated with methotrexate (methotrexate naïve)

6.39 Results for biologic DMARDs in combination with methotrexate in patients with severe active rheumatoid arthritis not previously treated with methotrexate were provided by AbbVie and Pfizer (table 16). AbbVie included a comparison with the licensed biologic DMARDs and methotrexate monotherapy and the combination of methotrexate and hydroxychloroquine. Their incremental analyses reported an ICER for methotrexate and hydroxychloroquine compared with methotrexate of £18,381 per QALY gained and an ICER for adalimumab compared with methotrexate and hydroxychloroquine was £69,971 per QALY gained. Other treatment options were dominated. Pfizer only included a comparison of etanercept with cDMARDs, including adalimumab in a secondary analysis. Their incremental analysis suggested that the ICER for etanercept compared with combination cDMARDs was £34,373 per QALY gained with cDMARD monotherapy dominated.

Table 16. Pairwise ICERs (cost per QALY gained) for biologic DMARDs and combination cDMARDs in comparison with cDMARD monotherapy – severe, active naïve combination

	AbbVie	Pfizer
MTX	-	-
MTX+HCQ	£18,381	-
ADA	£30,071	-
ETA	£30,742	£34,373
GOL	£33,044	-
IFX	£33,055	-
All biologic DMARDs with methotrexate		

Biologic DMARDs monotherapy

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

6.40 Results for biologic monotherapy in patients with severe active rheumatoid arthritis previously treated with methotrexate were provided by AbbVie, Pfizer and UCB (table 17). UCB included other biologic DMARDs in their analysis but did not compare certolizumab pegol with conventional DMARDs. The incremental analysis provided by AbbVie suggested that etanercept was the most cost effective biologic DMARD with an ICER of £29,338 per QALY gained with other biologic DMARDs being dominated or extendedly dominated. The incremental analysis provided by Pfizer also suggested that etanercept was the most cost effective biologic DMARD with an ICER £26,335 per QALY gained, but 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 adalimumab was the optimal treatment up to a willingness to pay threshold of £9,587 per QALY gained, with certolizumab pegol being the optimal treatment up to a level of £962,778 per QALY gained.

Table 17. Pairwise ICERs (cost per QALY gained) for biologic DMARDs in comparison with cDMARDs – severe active experienced monotherapy

	AbbVie	Pfizer*	UCB
DMARDs	-	-	cDMARDs not included in the treatment strategy
ADA	£35,641	£30,481	
ETA	£29,338	£26,335	
CTZ	£30,609	-	
TOC	£50,972	£30,277	
*ICERs calculated from incremental costs and QALYs presented in manufacturer submission may be subject to rounding			

Biologic DMARD monotherapy for a population with moderate active rheumatoid arthritis previously treated with methotrexate

6.41 Results for this population were provided by AbbVie and UCB. UCB only included a comparison of certolizumab pegol compared with conventional DMARDs. The incremental analysis provided by AbbVie suggested that etanercept was the most cost effective biologic DMARD with with an ICER of £32,276 per QALY gained and other biologic DMARDs being dominated or extendedly dominated.

Table 18. Pairwise ICERs (cost per QALY gained) for biologic DMARDs in comparison with cDMARDs moderate active experienced monotherapy

	AbbVie	UCB
DMARDs	-	-
ADA	£39,083	-
ETA	£32,276	-
CTZ	£33,791	£49,226
TOC	£55,844	-

Biologic DMARD monotherapy for a general population (moderate and severe active RA) previously treated with methotrexate

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

Biologic DMARD monotherapy for a population with severe active rheumatoid arthritis not previously treated with methotrexate (methotrexate naïve)

6.43 Results for this population were provided by AbbVie (table 19). AbbVie compared adalimumab and etanercept monotherapy and the combination of sulfasalazine and 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.

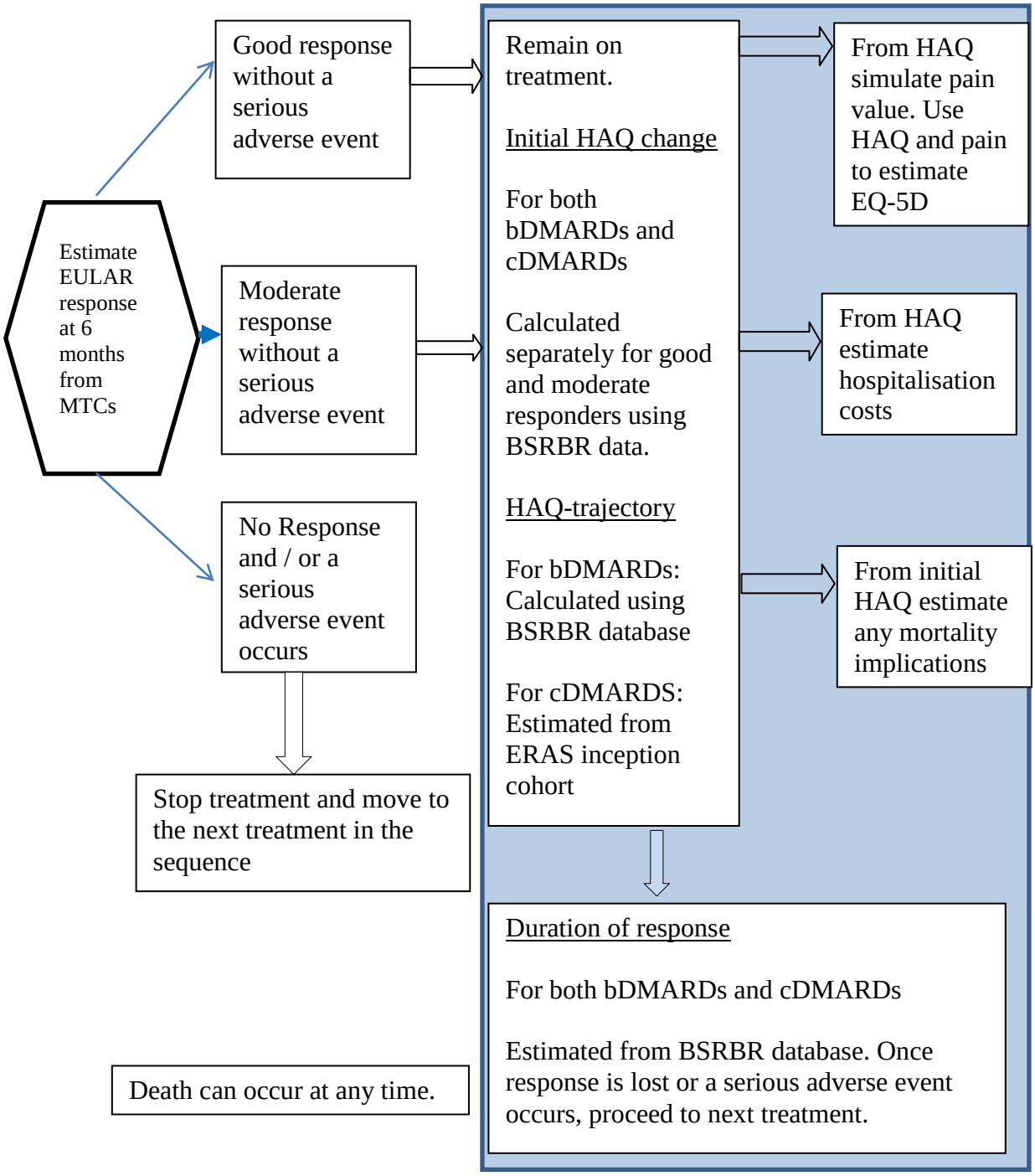
Table 19. Pairwise ICERs (cost per QALY gained) for biologic DMARDs and combination cDMARDs in comparison with cDMARD monotherapy - severe active naïve monotherapy

	AbbVie
DMARDs	-
SSZ + HCQ (followed by ADA)	£18,540
ADA	£918,015
ETA	£201,097

Assessment Group cost effectiveness analysis

6.44 The AG developed an individual-patient based discrete event simulation model for their economic evaluation (see Figure 14). The model incorporated a response criterion based on EULAR response at 6 months to reflect UK clinical practice. The AG modelled patients with severe active disease previously treated with methotrexate, patients with moderate to severe active disease previously treated with methotrexate, and patients with severe active disease not previously treated with methotrexate. These 3 populations were modelled as combination therapy with methotrexate and as monotherapy.

Figure 14. Conceptual simplified schematic of the modelling process.



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

Strategies modelled

6.46 The AG assumed NICE guidance was followed after the failure of the first biologic treatment, which is rituximab in combination with methotrexate followed by tocilizumab in combination with methotrexate for people who can take methotrexate. Although the AG's model could incorporate up to 7 treatments in sequence, they decided for simplicity and due to a paucity of evidence to limit the sequence to intensive cDMARD therapy and/or biologic DMARDs, one further cDMARD (typically methotrexate, but a different cDMARD if methotrexate was unsuitable) before moving to 'non-biologic therapy', a selection of treatments chosen by clinicians for individual patients. Non-biologic therapy was assumed to have no initial EULAR response, unlike methotrexate, which was assumed to have a EULAR response based on the NMA. Table 20 outlines the strategies modelled for each population who could and could not receive methotrexate The AG commented that the strategies were similar to those modelled by the manufacturers, except for the generic cDMARD sequence rather than named cDMARDs.

Table 20. The strategies evaluated in AG model

	1st tx	2nd tx	3rd tx	4th tx	5th tx	6th tx	7th tx
Biologic DMARDs in combination with methotrexate for a population with severe or moderate active rheumatoid arthritis previously treated with methotrexate							
Strategy 1	MTX	NBT					
Strategy 2	ABT iv+	RTX+	TCZ+	MTX	NBT		
Strategy 3	ABT sc+	RTX+	TCZ+	MTX	NBT		
Strategy 4	ADA+	RTX+	TCZ+	MTX	NBT		
Strategy 5	CTZ+	RTX+	TCZ+	MTX	NBT		
Strategy 6	ETN+	RTX+	TCZ+	MTX	NBT		
Strategy 7	GOL+	RTX+	TCZ+	MTX	NBT		
Strategy 8	IFX+	RTX+	TCZ+	MTX	NBT		
Strategy 9	TCZ+	RTX+	MTX	NBT			
Biologic DMARD monotherapy for a population with severe or moderate active rheumatoid arthritis previously treated with methotrexate							
Strategy 1	SSZ	NBT					
Strategy 2	ADA	ETN	TCZ	SSZ	NBT		
Strategy 3	ETN	ADA	TCZ	SSZ	NBT		
Strategy 4	TCZ	ADA	SSZ	NBT			
Biologic DMARDs in combination with methotrexate for a population with severe or moderate active rheumatoid arthritis not previously treated with methotrexate							
Strategy 1	MTX	Int CD+	MTX	NBT			
Strategy 2	MTX	Int CD+	ADA+	RTX+	TCZ+	MTX	NBT
Strategy 3	ADA+	RTX+	TCZ+	MTX	NBT		
Biologic DMARD monotherapy for a population with severe or moderate active rheumatoid arthritis not previously treated with methotrexate							
Strategy 1	MTX	NBT					
Strategy 2	MTX	ADA	ETN	TCZ	MTX	NBT	
Strategy 3	ADA	ETN	TCZ	MTX	NBT		

'+' with MTX; ABT iv - abatacept iv; ABT sc – abatacept sc; ADA – adalimumab; CTZ – certolizumab pegol; ETN – etanercept; Gol – golimumab; IFX – infliximab; NBT – non-biologic therapy; RTX – rituximab; TCZ - tocilizumab

Population characteristics

6.47 The AG used the BSRBR for patients who had previously taken methotrexate, which allowed for correlation to be maintained between age, gender, disease duration, DAS score, prior DMARD use, HAQ score, and weight. For patients who had not previously received methotrexate, the AG used the COMET trial as used in the Pfizer submission.

Cost of the interventions

6.48 The AG took into account all of the patient access schemes, and did not use a fixed weight for weight-based interventions. In the absence of robust data, the AG used the infusion cost of £154 and time of 1 hour from TA 247, but commented that it may be favourable to infliximab (with a recommended infusion time of 2 hours) and unfavourable to abatacept (with a recommended infusion time of 30 minutes). The AG used the average administration cost per subcutaneous injection of £3.05, but noted that TA247 did not comment on the assumption that 10% of subcutaneous injections would be performed by district nurses. The costs used by the AG for the interventions are listed in Table 21.

Table 21.The costs of the interventions calculated by the AG (from table 3 of the AR page 49)

	ABA iv	ABA sc	ADA	CTZ	ETA	GOL	IFX	TOC
Cost per year	[redacted]	[redacted]	£9224	£9363	£9431	£9187	£8222	[redacted]
Additional cost year 1*	[redacted]	[redacted]	-	-£2521	-	-	£1820	-
Administration cost per treatment	£154	£3.05	£3.05	£3.05	£3.05	£3.05	£154	£154

*Additional costs in year 1 includes costs of loading doses and the reduced costs associated with the free vials of certolizumab pegol provided in the PAS

All costs include PAS

Some of the costs have been updated following comments from consultation

Comparative treatment efficacy (Mixed Treatment Comparison)

6.49 The initial response to treatment was modelled using the EULAR response data from the AG network meta-analysis. Because a smaller number of trials included EULAR data compared to ACR response data and not all interventions could be included in the EULAR network, a separate analysis was also completed where ACR data were mapped to EULAR response using individual patient level data from the Veterans Affairs Rheumatoid Arthritis (VARA). The estimated response rates in the analyses based on

EULAR and the analyses also including the mapped ACR data can be compared in Figures 15 and 16.

Figure 15. Estimated EULAR response (main analysis)

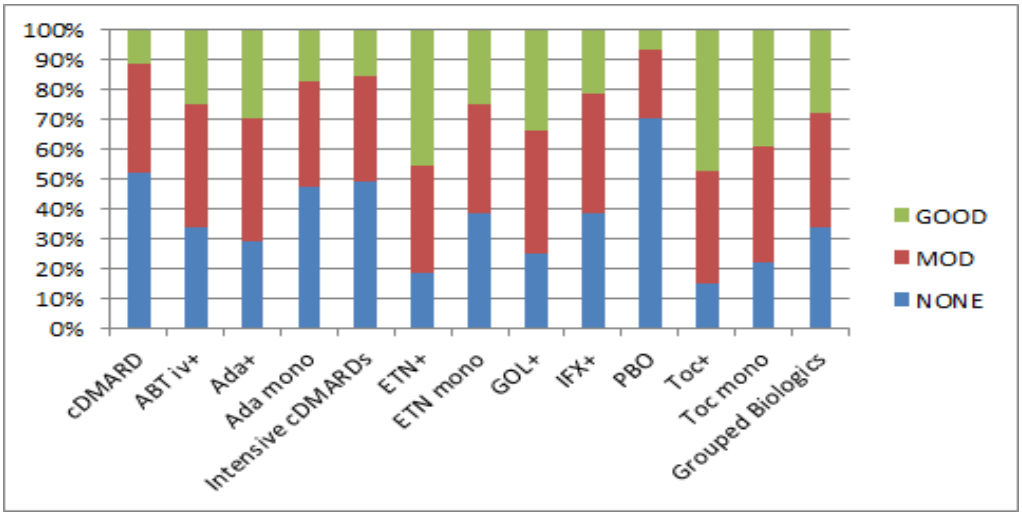
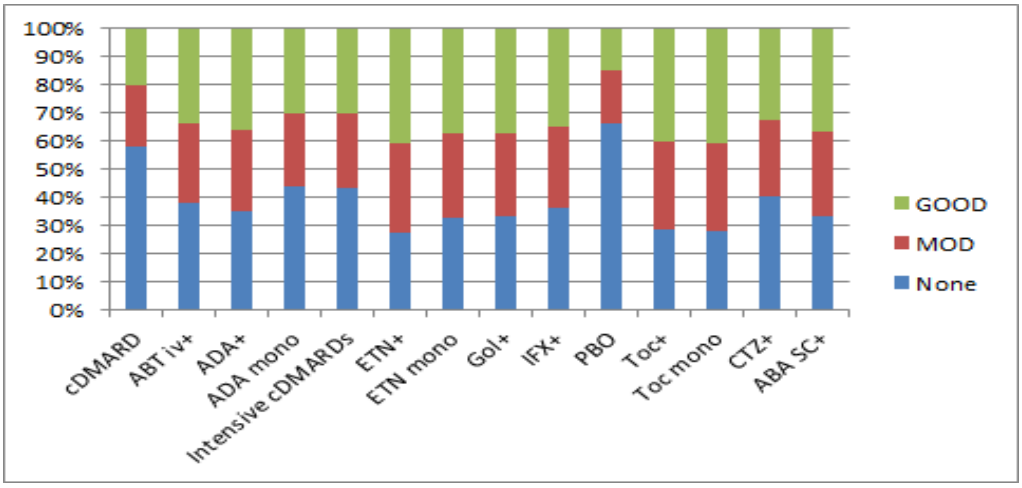


Figure 16. Estimated EULAR response including trials with ACR data mapped to EULAR response (main analysis)



HAQ change in relation to response levels

Biologic DMARDs

6.50 The AG estimated HAQ change following EULAR response based on data from the BSRBR cohort. The AG assumed that the relationship between EULAR response and HAQ improvement was independent of the biologic DMARD used. For a patient with the mean characteristics of the sample of the BSRBR, the model

used by the AG predicted a change of 0.29 in HAQ for a moderate EULAR response compared with 0.33 in the BSRBR data. The model predicted a change of 0.54 in HAQ for a good EULAR response, compared with a change of 0.55 in the BSRBR data.

cDMARDs

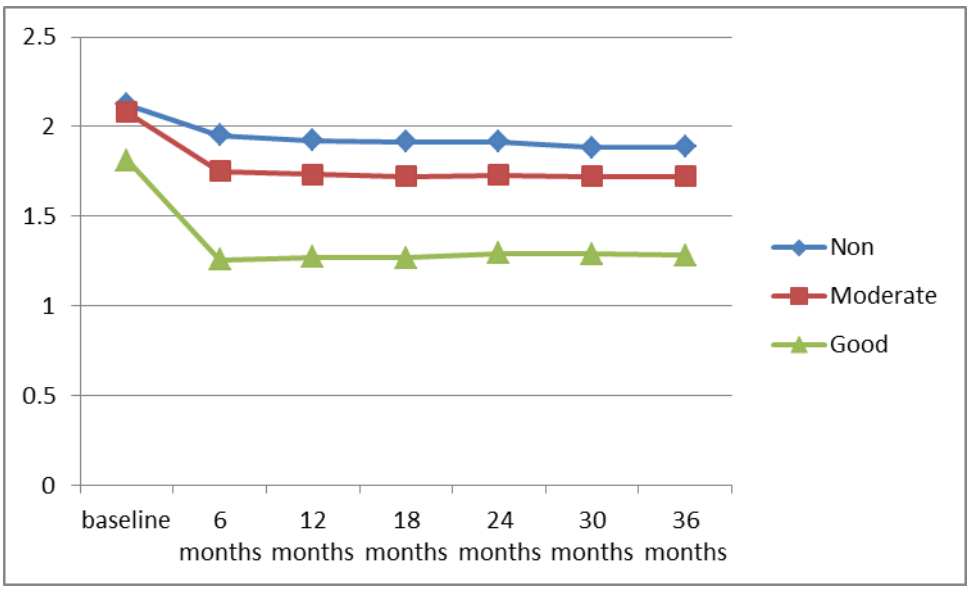
6.51 The AG assumed that the relationship between HAQ change and EULAR response was the same for cDMARDs as for biologic DMARDs in their base case analyses. In a scenario analysis the AG included data specifically for cDMARDs from the ERAS dataset. The mean HAQ change for no response was 0.05, 0.509 for a moderate response and 0.650 for a good response.

HAQ trajectory following initial response

Biologic DMARDS

6.52 The AG used 3 year data from the BSRBR to estimate the change in HAQ over time following the initial response. The HAQ change on a biologic DMARD was a function of the patient's baseline characteristics and 6 month EULAR response rate. The AG used data from 2417 patients 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 years' observation. Patients with disease that has a good response had a lower (that is better) baseline HAQ than those with disease that has a moderate or no response (see Figure 17).

Figure 17. Mean HAQ by EULAR response category for those receiving biologic DMARDs

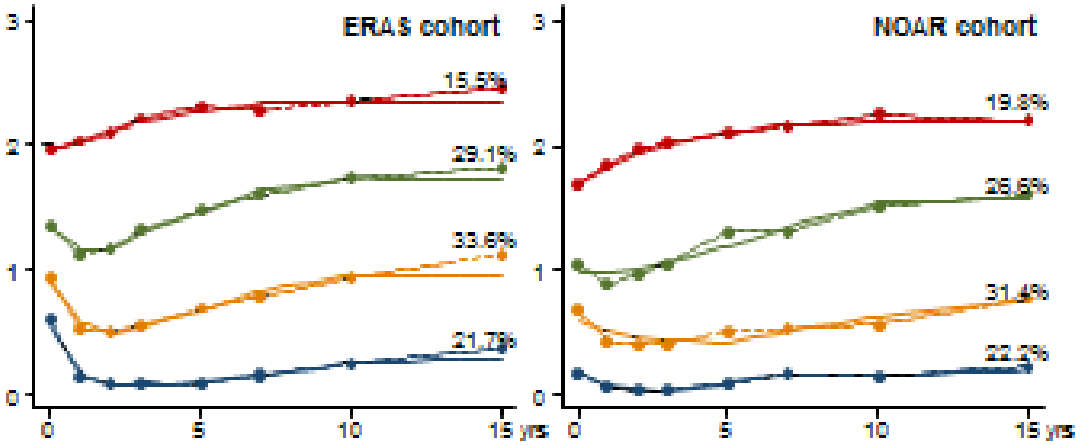


6.53 The AG assumed that a patient with disease that had no EULAR response stopped treatment after 6 months, in accordance with NICE guidance, therefore the changes in HAQ after the initial response were not modelled for this population. For good and moderate response the AG fitted an 'Autoregressive Latent Trajectory' model to estimate HAQ response at 6 months and longer term progression of HAQ in a single model. HAQ at baseline was treated as predetermined, with age, gender, disease duration (months), DAS score, and number of previous DMARDs as baseline covariates. The cost effectiveness model used estimates of the 6 month HAQ change for a patient with mean characteristics of the overall sample, a baseline HAQ of 2.03, with all error terms set to zero and conditional on EULAR response category. A moderate response was associated with a change in HAQ estimated to be 0.317 (standard error 0.048) and a good response was associated with a change in HAQ estimated to be 0.673 (standard error 0.112).

cDMARDs

6.54 The AG used Norton et al as a basis for estimating HAQ progression in patients receiving cDMARDs. Norton et al used data from the ERAS inception cohort study and identified 4 classes of patients, which were validated using the NOAR and ERAN datasets. The AG modified the Norton et al model so that patient variables were used as covariates within the statistical model as explanatory variables, and expected HAQ can be estimated at any point for a patient with given baseline characteristics. The AG incorporated age at disease onset, sex, deprivation level, disease duration, rheumatoid factor status at baseline, ACR criteria at baseline, DAS at baseline, failure of 2 DMARDs, and DAS at 6 months. Figure 18 illustrates the classes of patients identified by Norton with their respective HAQ trajectories (HAQ is marked on the vertical axis) over 15 years (years are shown on the horizontal axis).

Figure 18. The classes of patients on cDMARDs estimated by Norton et al



6.55 The Norton data suggested ‘J’ shaped HAQ progression curves for 3 groups of patients, with an initial rebound and then

worsening over time. The fourth group showed general worsening over time. In all groups the rate of worsening decreased over time. The AG commented that the 'J' shaped curve shown in Norton was likely to be a more appropriate reflection of a chronic disease than a simple linear annual progression as used in the manufacturers' submissions and previous NICE appraisals. The AG commented that this avoided the assumption that a large proportion of patients progress to a HAQ score of 3 before death which is not supported by observational data (Hernandez et al). The clinical advisers to the AG stated that observational studies of rheumatoid arthritis populations generally show a HAQ progression of less than 0.05 per year, but noted that these studies often cover all rheumatoid arthritis patients including those who would not have received biologic DMARDs. The linear assumption used in previous appraisals (see section 6.31) was included by the AG in a sensitivity analysis.

Time to discontinuation on treatment

6.56 The AG used the BSRBR database to estimate the time on treatment for the first biologic DMARD for patients with disease that had a good and moderate EULAR response. Age, gender, 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 biologic therapies were not used.

6.57 The AG stated that due to scarcity of data they assumed that the duration on treatment was unaffected by whether or not cDMARDs had previously been used and that the time on treatment for each EULAR response category for biologic DMARDs would be applicable to cDMARDs. The AG assumed that patients 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

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

Assumed NHS costs per HAQ band

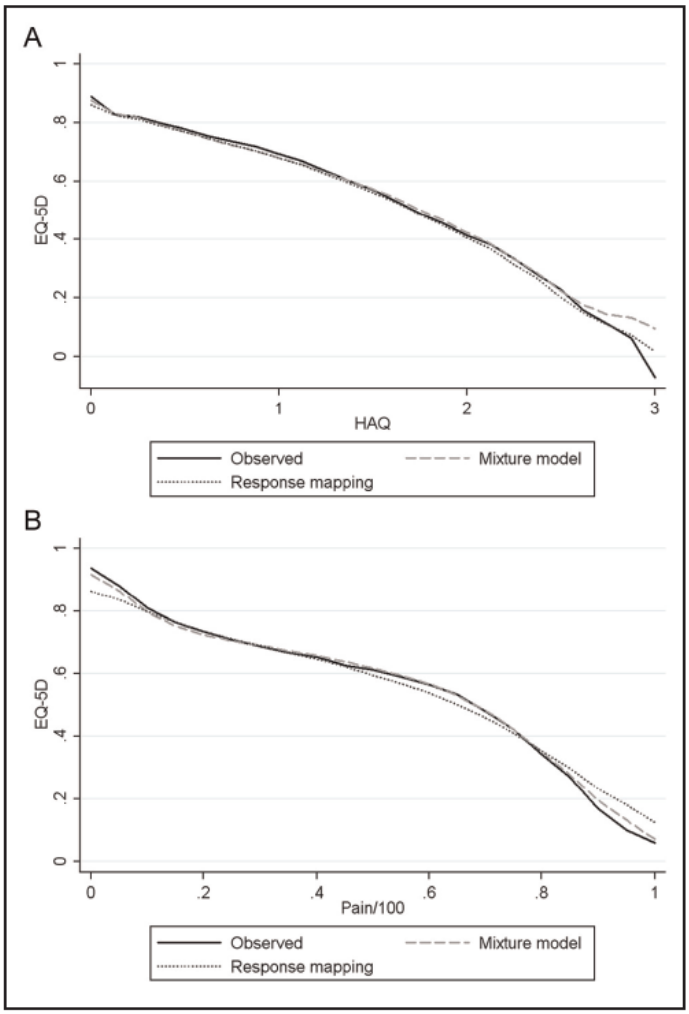
6.59 The AG used the hospital costs reported by AbbVie in their base case analyses. These were among the lowest presented and were relatively flat until the patient had a severe HAQ score (≥ 2.125). The data were taken from the NOAR database on inpatient days and joint replacements, multiplied by NHS reference costs (see section 6.33).

Utility related to HAQ

6.60 The AG considered that the estimate of EQ-5D was more accurate where it was based on pain and HAQ rather than HAQ alone. To include pain, the AG had to simulate the expected pain score associated with HAQ for each patient within the model. The AG 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 AG used data from ERAS to calculate the mean pain score and variance estimated for each valid HAQ score.

6.61 To calculate the EQ-5D from the HAQ score and simulated pain score the AG used a method based on mixture models from Hernandez Alava et al using data from 16,011 patients from the US National Data Bank for Rheumatic Diseases (see Figure 19).

Figure 19: The relationship between HAQ and utility assumed in the Assessment Group's model (taken from Hernandez et al 2013)



(A) Mean HAQ v. mean EQ-5D: observed v. predicted. (B) Mean pain v. mean EQ-5D: observed and predicted.

The model comprised four components, each of which includes HAQ and HAQ^2, pain, age and age^2 as explanatory variables. The AG noted that the model had a better fit than linear regression or response mapping approaches, did not generate non feasible values or suffer from systematic bias in the estimates.

The assumed costs and disutilities associated with adverse events

6.62 The AG assumed only serious infections would have significant costs and disutilities, and therefore limited the adverse events within the model to serious infections alone. A Cochrane review (Singh et al) indicated that serious infections were observed in 35

per 1000 patients (95% CI 27 to 46) for biologic DMARDs, and 26 per 1000 (95% CI not reported) for cDMARDs. The AG assumed the rate of infection was independent of biologic DMARD used. The AG 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 AG assumed that using biologic DMARDs would incur an additional £13.31 cost and QALY loss of 0.0001 per typical patient treated.

Mortality associated with rheumatoid arthritis

6.63 The AG found little data on the relationship between HAQ change and change in expected mortality, and assumed that only baseline HAQ score predicted mortality. As initial baseline HAQ increased so did the mortality hazard ratio, with the hazard ratio being independent of time (see Table 22).

Table 22. Hazard ratio for mortality associated with HAQ category

Initial HAQ category	Hazard Ratio (95% Confidence Interval)
0.000	1 (1 – 1) referent
0.125 – 0.375	1.4 (1.1 – 1.8)
0.500 – 0.875	1.5 (1.2 – 1.9)
1.000 – 1.375	1.8 (1.4 – 2.2)
1.500 – 1.875	2.7 (2.2 – 3.5)
2.000 – 2.375	4.0 (3.1 – 5.2)
2.500 – 3.000	5.5 (3.9 – 7.7)

AG model results

6.64 The AG analysed 24 combinations of factors. EULAR response in patients who had not previously received methotrexate was not analysed because no data were available (see Table 23).

Table 23. Combinations of factors analysed in the cost-effectiveness analyses

Population	Treatment provided …	Response Measure	HAQ trajectory on cDMARDs
severe active MTX-experienced	In combination with MTX	EULAR	Taken from the ERAS database
moderate active MTX-experienced	As monotherapy	ACR (mapped to EULAR)	Using previous NICE appraisal values
severe active MTX-naïve			

6.65 The AG also conducted sensitivity analyses assessing: the impact of including different RCTs in the network meta-analysis, using different mapping functions of HAQ to utility, using the discount rates in TA130 and increasing the impact of adverse events.

6.66 The AG commented that there was little difference between the cost effectiveness of different biologic DAMRDs, except for tocilizumab (which cannot be used after rituximab if it has been used as the first biologic DMARD). The AG also commented that the fully incremental ICERs for the methotrexate experienced populations may be misleading as the ICERs compared with cDMARDs alone are very similar, and dominated strategies may be only slightly more expensive and less effective than a comparator. For the population who has previously received methotrexate, the AG presented the median ICERs for biologic DMARD combination therapy (table 24) and monotherapy (table 25).

6.67 The key drivers of the ICERs are the source of the HAQ trajectory for cDMARDs (that is the linear assumption used in previous NICE appraisals and the manufacturer submissions (section 6.31) versus the non-linear curve used by the AG based on the ERAS

data (section 6.54). Using the discount rate applied in TA130 also reduces the ICER significantly. Other factors such as the trials included in the network meta-analysis and the assumed impact of adverse effects had less effect on the ICERs. The HAQ to utility mapping used by the AG reduced the ICERs compared to the equations used in the previous NICE appraisal TA195.

6.68 The overview presents the incremental analyses for the individual biologic DMARDs only for the key driver of the cost effectiveness (that is the HAQ trajectory assumed for cDMARDs). The overview presents incremental results for the AG main analysis of EULAR data and their larger network of evidence created by including trials that included a proportion of people who had previously received biologic DMARDs (plus AMBITION) and mapping ACR data to EULAR data (these analyses are highlighted in the tables 24 and 25 with a darker border).

Table 24.Summarised results: Median ICERs for all biologic DMARD strategies compared with the methotrexate alone strategy. Biologic DMARD combination therapy in patients previously treated with methotrexate

			Base Case +								
	Response Measure	Assumed HAQ Progression	Base case only	Including RCTs with prior biologic DMARDs use (without AMBITION)	Including RCTs with prior biologic DMARDs use (with AMBITION)	Including RCTS with inadequate MTX history (TEMPO and TEAR)	Alternative mapping of HAQ to utility (Malottki as used in TA195)	Alternative Discount rates (6% costs, 1.5% QALYs)	Impact of AEs assumed to be 100-fold higher	Alternative relationship between HAQ and pain (ERAS)	Probabilistic sensitivity analysis
Severe active MTX – experienced	EULAR	ERAS	£56,500	£56,000	£56,800	No data	£60,700	£41,200	£58,400	£97,200	£56,700
		Linear	£33,000	£33,600	£33,200	No data	£36,100	£23,400	£34,000	£63,800	£33,300
	ACR	ERAS	£52,800	£53,400	£55,100	£53,400	£58,900	£38,800	£54,800	£89,500	£53,200
		Linear	£32,100	£31,700	£31,700	£31,700	£34,300	£22,500	£33,100	£59,900	£31,400
Moderate active MTX-experienced	EULAR	ERAS	£61,700	£61,700	£65,000	No Data	£65,600	£45,000	£63,400	£68,300	£61,900
		Linear	£34,900	£33,800	£34,300	No Data	£35,400	£21,400	£35,900	£44,300	£33,900
	ACR	ERAS	£61,100	£57,900	£61,100	£74,700	£60,800	£42,300	£63,000	£67,500	£60,100
		Linear	£31,800	£31,100	£31,100	£33,400	£33,400	£22,600	£32,600	£42,700	£31,900

All numbers rounded to the nearest £100.

'EULAR' refers to the AG main analysis, 'ACR' refers to the wider network of evidence that also includes ACR outcomes mapped to EULAR response outcomes

'ERAS' refers to the AG assumption for HAQ trajectory on cDMARDs, 'Linear' refers to the assumption for HAQ trajectory used in previous appraisals and in the manufacturer models

Table 25. Summary of median ICERs for all biologic DMARDs compared with the methotrexate alone strategy. Biologic monotherapy in people previously treated with methotrexate

			Base Case +								
	Response Measure	Assumed HAQ Progression	Base case only	Including RCTs with prior biologic DMARDs use (without AMBITION)	Including RCTs with prior biologic DMARDs use (with AMBITION)	Including RCTS with inadequate MTX history (TEMPO and TEAR)	Alternative mapping of HAQ to utility (Malottki as used in TA195)	Alternative Discount rates (6% costs, 1.5% QALYs)	Impact of AEs assumed to be 100-fold higher	Alternative relationship between HAQ and pain (ERAS)	Probabilistic sensitivity analysis
Severe active MTX – experienced	EULAR	ERAS	£73,500	£76,600	£79,800	No data	£80,700	£54,200	£75,700	£125,700	£76,100
		Linear	£38,500	£38,300	£39,000	No data	£41,600	£27,300	£38,500	£74,800	£39,700
	ACR	ERAS	£65,600	£65,000	£76,700	£65,600	£70,300	£46,200	£67,400	£110,900	£65,300
		Linear	£36,400	£35,800	£35,200	£35,200	£38,300	£24,900	£36,400	£69,200	£35,500
Moderate active MTX-experienced	EULAR	ERAS	£75,700	£81,500	£80,000	No data	£75,000	£54,500	£77,800	£95,000	£76,400
		Linear	£36,900	£38,600	£35,600	No data	£38,200	£26,000	£37,800	£55,300	£37,700
	ACR	ERAS	£69,600	£69,700	£83,500	£70,000	£68,800	£50,000	£71,300	£80,300	£73,500
		Linear	£35,800	£36,700	£35,000	£35,700	£37,700	£24,600	£35,800	£50,100	£50,100

All numbers rounded to the nearest £100.

'EULAR' refers to the AG main analysis, 'ACR' refers to the wider network of evidence that also includes ACR outcomes mapped to EULAR response outcomes

'ERAS' refers to the AG assumption for HAQ trajectory on cDMARDs, 'Linear' refers to the assumption for HAQ trajectory used in previous appraisals and in the manufacturer models

Biologic DMARDs in combination with methotrexate in a population with severe active disease who had previously had methotrexate

6.69 The AG presented deterministic cost per QALYs for the combination therapy base case for people with severe active disease who had previously used methotrexate (Table 26 part A). This used EULAR response data and the estimate of the annual rate of HAQ progression from ERAS. The ICERs comparing biologic DMARDs in combination with methotrexate to methotrexate alone were between £54,727 and £58,217 per QALY gained. Probabilistic analyses gave similar ICERs between £54,781 and £58,202 per QALY gained. Using the linear HAQ progression for cDMARDs as used in the manufacturers' submissions and previous appraisals, the ICERs for biologic DMARDs in combination with methotrexate compared with methotrexate alone were between £31,381 and £34,004 per QALY gained (Table 26 part B). The probabilistic results were similar, with ICERs between £31,294 and £33,701 per QALY gained.

6.70 The AG commented that the ICERs derived from the ACR data mapped to EULAR were similar to those from the EULAR base cases, with ICERs of between £48,730 and £54,201 per QALY gained. Likewise, expanding the criteria for inclusion in the NMA to include trials that had some prior biologic use had only a modest impact on the ICERs (Table 26 part C). Using the linear HAQ progression for cDMARDs as used in the manufacturers' submissions and previous appraisals again reduced the ICERs (Table 26 part D).

Table 26 Deterministic results for biologic DMARDs in combination with methotrexate for a population with severe active disease previously treated with methotrexate

A. AG main analysis using EULAR data						B. Analysis using EULAR data and linear HAQ progression				
First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)		First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-		MTX	[redacted]	[redacted]	-	-
TCZ + MTX	[redacted]	[redacted]	£ 56,522	E Dominated		ABT + MTX	[redacted]	[redacted]	£ 31,381	£31,381
ABTiv + MTX	[redacted]	[redacted]	£ 54,727	£54,727		TCZ + MTX	[redacted]	[redacted]	£ 31,927	Dominated
IFX + MTX	[redacted]	[redacted]	£ 56,373	Dominated		IFX + MTX	[redacted]	[redacted]	£ 32,322	Dominated
ADA + MTX	[redacted]	[redacted]	£ 58,217	E Dominated		ADA + MTX	[redacted]	[redacted]	£ 34,004	E Dominated
GOL + MTX	[redacted]	[redacted]	£ 57,633	E Dominated		GOL + MTX	[redacted]	[redacted]	£ 33,695	E Dominated
ETN + MTX	[redacted]	[redacted]	£ 56,476	£71,530		ETN + MTX	[redacted]	[redacted]	£ 33,694	£ 60,756
C. Analysis using wider network of evidence						D. Analysis using wider network of evidence and linear HAQ progression				
First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)		First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-		MTX	[redacted]	[redacted]	-	-
TCZ +MTX	[redacted]	[redacted]	£54,206	E Dominated		TCZ +MTX	[redacted]	[redacted]	£ 30,967	E Dominated
ABT +MTX	[redacted]	[redacted]	£51,589	£51,589		ABT +MTX	[redacted]	[redacted]	£ 29,051	£ 29,051
IFX +MTX	[redacted]	[redacted]	£ 52,412	E Dominated		IFX +MTX	[redacted]	[redacted]	£ 29,857	E Dominated
ADA +MTX	[redacted]	[redacted]	£55,291	Dominated		ADA +MTX	[redacted]	[redacted]	£ 31,621	Dominated
ABTsc +MTX	[redacted]	[redacted]	55,342	E Dominated		ABTsc + MTX	[redacted]	[redacted]	£ 31,777	E Dominated
GOL +MTX	[redacted]	[redacted]	£54,918	E Dominated		GOL +MTX	[redacted]	[redacted]	£ 31,826	E Dominated
ETN +MTX	[redacted]	[redacted]	£ 56,107	E Dominated		ETN +MTX	[redacted]	[redacted]	£ 32,862	E Dominated
CTZ +MTX	[redacted]	[redacted]	£ 56,355	£ 92,435		CTZ +MTX	[redacted]	[redacted]	£ 33,114	£ 68,222

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab CPQ – cost per QALY gained; E– extendedly

Biologic DMARDs in combination with methotrexate in a population with moderate active disease who had previously had methotrexate

6.71 For the population with moderate disease activity who had previously had methotrexate, the AG presented deterministic cost per QALYs for the base case, using EULAR data, the ERAS cDMARD HAQ progression, in combination with methotrexate (Table 27 part A). The ICERs comparing biologic DMARDs in combination with methotrexate to methotrexate alone were between £58,742 and £63,645 per QALY gained. For the probabilistic base case analysis in this population, the ICERs were similar between £58,837 and £63,763 per QALY gained. Using the linear cDMARD HAQ progression rather than the HAQ progression from ERAS, the ICERs for biologic DMARDs in combination with methotrexate compared with methotrexate alone were between £33,424 and £36,400 per QALY gained (see Table 27 part B).

6.72 The ICERs derived from the wider network of evidence were similar to those from the EULAR base cases, with ICERs of between £54,197 and £63,310 per QALY gained (Table 27 part C). The ICERs for the moderate active population were somewhat higher than for the severe active population. Using the linear HAQ progression for cDMARDs as used in the manufacturers' submissions and previous appraisals again reduced the ICERs (Table 27 part D).

Table 27 Deterministic results for biologic DMARDs in combination with methotrexate for a population with moderate active disease previously treated with methotrexate

A. AG main analysis using EULAR data						B. Analysis using EULAR data and linear HAQ progression				
First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)		First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]				MTX	[redacted]	[redacted]		
TCZ +MTX	[redacted]	[redacted]	£ 58,742	E Dominated		TCZ+MTX	[redacted]	[redacted]	£ 33,807	E Dominated
ABT +MTX	[redacted]	[redacted]	£ 58,909	£58,909		IFX+MTX	[redacted]	[redacted]	£ 33,424	£ 33,424
IFX +MTX	[redacted]	[redacted]	£ 61,311	Dominated		ABT+MTX	[redacted]	[redacted]	£ 33,666	£ 49,138
ADA +MTX	[redacted]	[redacted]	£ 63,513	E Dominated		ADA+MTX	[redacted]	[redacted]	£ 36,226	E Dominated
GOL +MTX	[redacted]	[redacted]	£ 63,645	E Dominated		GOL+MTX	[redacted]	[redacted]	£ 36,039	E Dominated
ETN +MTX	[redacted]	[redacted]	£ 62,007	£ 91,315		ETN+MTX	[redacted]	[redacted]	£ 36,400	£ 69,450
C. Analysis using wider network of evidence						D. Analysis using wider network of evidence and linear HAQ progression				
First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)		First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX	[redacted]	[redacted]	-	-		cDMARD	[redacted]	[redacted]	-	-
TCZ+MTX	[redacted]	[redacted]	£ 60,748	E Dominated		TCZ+MTX	[redacted]	[redacted]	£ 31,813	E Dominated
ABT+MTX	[redacted]	[redacted]	£ 54,197	£ 54,197		ABT+MTX	[redacted]	[redacted]	£ 29,282	E Dominated
IFX+MTX	[redacted]	[redacted]	£ 55,722	£ 131,872		IFX+MTX	[redacted]	[redacted]	£ 29,141	£ 29,141
ADA+MTX	[redacted]	[redacted]	£ 61,591	Dominated		ADA+MTX	[redacted]	[redacted]	£ 31,042	Dominated
ABTS+MTX	[redacted]	[redacted]	£ 60,717	Dominated		ABTS+MTX	[redacted]	[redacted]	£ 31,076	Dominated
GOL+MTX	[redacted]	[redacted]	£ 61,440	Dominated		GOL+MTX	[redacted]	[redacted]	£ 31,150	E Dominated
ETN+MTX	[redacted]	[redacted]	£ 62,458	E Dominated		ETN+MTX	[redacted]	[redacted]	£ 32,139	E Dominated
CTZ+MTX	[redacted]	[redacted]	£ 63,310	£ 160,490		CTZ+MTX	[redacted]	[redacted]	£ 32,406	£ 68,881

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab CPQ – cost per QALY gained; E– extendedly

Biologic DMARD monotherapy for a population with severe or moderate active disease who had previously had methotrexate

6.73 The ICERs for biologic DMARD monotherapy were higher than for combination therapy with methotrexate. For patients with severe active disease receiving biologic DMARD monotherapy compared with sulfasalazine the ICERs were between £68,756 and £75,403 per QALY gained when the ERAS HAQ progression was used (Table 28 part A), and between £34,774 and £38,808 per QALY gained when the linear HAQ progression was used (Table 28 part B). The AG commented that the higher ICERs were primarily because after the failure of the first biologic DMARDs, rituximab could not be provided (that it, it is only licensed for use in combination with methotrexate, so cannot be used for those who cannot have methotrexate) and a more expensive biologic DMARD with similar efficacy had to be used. The ICERs were similar when the wider network of evidence was used with ACR data mapped to EULAR data (Table 28 parts C and D).

6.74 For patients with moderate active disease, the ICERs for patients receiving biologic DMARD monotherapy compared with sulfasalazine increased to between £72,081 and £76,354 per QALY gained when the ERAS HAQ progression was used (Table 28 part E), and to between £34,021 and £37,286 per QALY gained when the linear HAQ progression was used (Table 28 part F).

Table 28 Deterministic results for biologic DMARDs monotherapy for a population with severe or moderate active disease previously treated with methotrexate

A. AG main analysis using EULAR data - severe						B. Analysis using EULAR data and linear HAQ progression - severe				
First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)		First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]	-	-		SSZ	[redacted]	[redacted]	-	-
TCZ	[redacted]	[redacted]	£ 68,756	£ 68,756		TCZ	[redacted]	[redacted]	£ 34,774	£ 34,774
ETN	[redacted]	[redacted]	£ 73,532	£ 133,637		ETN	[redacted]	[redacted]	£ 38,501	£ 106,692
ADA	[redacted]	[redacted]	£ 75,403	Dominated		ADA	[redacted]	[redacted]	£ 38,808	Dominated
C. Analysis using wider network of evidence - severe						D. Analysis using wider network of evidence and linear HAQ progression - severe				
First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)		First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]				SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 72,186	£ 72,186		TCZ	[redacted]	[redacted]	£ 32,025	£ 32,025
ETN	[redacted]	[redacted]	£ 76,711	£125,145		ETN	[redacted]	[redacted]	£ 35,214	£ 77,823
ADA	[redacted]	[redacted]	£ 78,148	Dominated		ADA	[redacted]	[redacted]	£ 35,883	Dominated
E. AG main analysis using EULAR data - moderate						F. Analysis using EULAR data and linear HAQ progression - moderate				
First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)		First Intervention in the strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
SSZ	[redacted]	[redacted]				SSZ	[redacted]	[redacted]		
TCZ	[redacted]	[redacted]	£ 72,081	£ 72,081		TCZ	[redacted]	[redacted]	£ 34,021	£ 34,021
ADA	[redacted]	[redacted]	£ 76,354	E Dominated		ADA	[redacted]	[redacted]	£ 37,286	Ext Dominated
ETN	[redacted]	[redacted]	£ 75,721	£117,580		ETN	[redacted]	[redacted]	£ 36,863	£ 79,795

ABT iv – abatacept intravenous; ABT sc – abatacept subcutaneous; ADA – adalimumab; ETN – etanercept; GOL – golimumab; IFX – infliximab; MTX – methotrexate; TCZ – tocilizumab CPQ – cost per QALY gained; E– extendedly

Biologic DMARDs in combination with methotrexate for a population with severe active disease who had not previously had methotrexate[2]

6.75 The AG presented deterministic cost per QALYs for biologic DMARDs in combination with methotrexate for the severe active disease population who had not previously used methotrexate, using ACR data mapped to EULAR and the ERAS cDMARD HAQ progression (see Table 29). The AG assumed that adalimumab plus methotrexate would be representative of all the biologic DMARDs. The ICERs comparing biologic DMARD in combination with methotrexate to methotrexate followed by other non-biologic therapies were £63,251 per QALY gained for methotrexate followed by any biologic DMARD and £97,667 per QALY gained for adalimumab as the first treatment in the sequence. For the probabilistic base case analysis in this population, the ICERs comparing biologic DMARD in combination with methotrexate to methotrexate followed by other non-biologic therapies were £63,904 per QALY gained for methotrexate followed by any biologic DMARD and £98,814 per QALY gained for adalimumab plus methotrexate as a representative for the first treatment in the sequence.

Table 29 Deterministic base case results for biologic DMARDs in combination with methotrexate mapping EULAR data from ACR data, using the ERAS cDMARD progression in a population with severe active methotrexate naïve disease

Strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX → NBT	[redacted]	[redacted]		
MTX → biologic DMARD	[redacted]	[redacted]	£ 63,251	£ 63,251
ADA+MTX	[redacted]	[redacted]	£ 97,667	£ 419,244

CPQ – cost per QALY gained; → - followed by

[2] There was an error in the Assessment Report in sections 6.3.22.17 and 6.3.22.18 which were incorrectly labelled as being the results for monotherapy rather than combination therapy

6.76 Using the linear cDMARD HAQ progression rather than the ERAS non-linear HAQ progression, the ICERs comparing biologic DMARD in combination with methotrexate to methotrexate followed by other non-biologic therapies were £32,312 per QALY gained for methotrexate followed by any biologic DMARD and £43,620 per QALY gained for adalimumab plus methotrexate as the first treatment in the sequence, while the fully incremental analysis produced a cost per QALY gained of £102,679 for adalimumab plus methotrexate compared with methotrexate followed by any biologic DMARD (see Table 30). The probabilistic results were similar, with ICERs of £32,057 per QALY gained comparing methotrexate followed by any biologic DMARD to methotrexate followed by any non biologic therapy and £43,492 per QALY gained comparing adalimumab plus methotrexate to methotrexate followed by any non biologic therapy while the fully incremental analysis produced a cost per QALY gained of £104,052 for adalimumab plus methotrexate compared with methotrexate followed by any biologic DMARD.

Table 30. Deterministic base case results mapping EULAR data from ACR data – Linear cDMARD HAQ progression and a severe, methotrexate-naive, RA population treated in combination with methotrexate

Table 30. Deterministic base case results for biologic DMARDs in combination with methotrexate mapping EULAR data from ACR data, using the linear cDMARD HAQ progression in a population with severe active methotrexate naïve disease				
Strategy	Discounted Costs	Discounted QALYs	CPQ compared with MTX strategy	CPQ (fully incremental analyses)
MTX → NBT	[redacted]	[redacted]		
MTX → Bios	[redacted]	[redacted]	£ 32,312	£ 32,312
ADA+MTX	[redacted]	[redacted]	£ 43,620	£ 102,679

CPQ – cost per QALY gained; → - followed by

6.77 The AG did not present results for the severe, methotrexate-naïve population treated with monotherapy. The AG stated that the proportion of people who cannot receive methotrexate is small,

and that the ICERs for monotherapy in this population were unlikely to be substantially better than for treatment in combination with methotrexate.

6.78 The AG commented that the ICERs were particularly sensitive to the assumptions made about the HAQ progression. The ICERs produced if the assumptions applied in previous NICE appraisals were used were between £30,000 and £40,000 per QALY gained, while if the assumptions made based on the ERAS database were applied, the ICERs were over £50,000 per QALY gained for populations with moderate or severe active disease previously treated with methotrexate. The ICERs were lower for people with severe active disease than for people with moderate active disease, but the difference between the ICERs for these two groups was diminished if the linear HAQ progression assumption was used. The use of the discount rates applied in the appraisal of TA130 reduced the ICERs to between £21,000 and £23,000 per QALY gained if the linear assumption for cDMARD HAQ progression was applied and to between £38,800 and £45,000 per QALY gained if the ERAS dataset was used. The ICERs for patients with severe active who had not previously received methotrexate were high; over £400,000 per QALY gained for the base case and over £100,000 per QALY gained using the assumption of linear HAQ progression.

7 Equality issues

7.1 No equalities issues were identified at the scoping stage, except to note that rheumatoid arthritis is a leading cause of disability and more effective treatments for the condition would reduce discrimination and promote equity.

8 Innovation

8.1 In its submission, Pfizer stated that etanercept was innovative in its subcutaneous delivery method, and use in the population with moderate active disease.

8.2 In its submission, UCB stated that certolizumab pegol was innovative in that it is possible to predict the outcomes of treatment at 12 weeks, rather than at a 6 month decision point.

9 Authors

Grace Jennings
Technical Lead(s)

Zoe Garrett
Technical Adviser

Appendix A: Supporting evidence

Related NICE guidance

Published

- Rheumatoid arthritis: the management of rheumatoid arthritis in adults. NICE clinical guideline 79(2009).
- Abatacept for treating rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs (rapid review of technology appraisal guidance 234). NICE technology appraisal guidance TA280 (2013).
- Tocilizumab for the treatment of rheumatoid arthritis (rapid review of technology appraisal guidance 198). NICE technology appraisal guidance TA247(2012).
- Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs. NICE technology appraisal guidance 225(2011).
- Golimumab for the treatment of methotrexate-naive rheumatoid arthritis (terminated appraisal). NICE technology appraisal guidance 224(2011).
- Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. NICE technology appraisal guidance 195(2010)
- Certolizumab pegol for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 186(2010).
- Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 130 (2007).

NICE pathways

- There is a NICE pathway on rheumatoid arthritis, which is available from http://pathways.nice.org.uk/pathways/rheumatoid-arthritis.

Summary of NICE guidance

Section 1 of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 130 (2007).

1.1 The tumour necrosis factor alpha (TNF-α) inhibitors adalimumab, etanercept and infliximab are recommended as options for the treatment of adults who have both of the following characteristics.

- Active rheumatoid arthritis as measured by disease activity score (DAS28) greater than 5.1 confirmed on at least two occasions, 1 month apart.
- Have undergone trials of two disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.

1.2 TNF-α inhibitors should normally be used in combination with methotrexate. Where a patient is intolerant of methotrexate or where methotrexate treatment is considered to be inappropriate, adalimumab and etanercept may be given as monotherapy.

1.3 Treatment with TNF-α inhibitors should be continued only if there is an adequate response at 6 months following initiation of therapy. An adequate response is defined as an improvement in DAS28 of 1.2 points or more.

1.4 After initial response, treatment should be monitored no less frequently than 6-monthly intervals with assessment of DAS28. Treatment should be withdrawn if an adequate response (as defined in 1.3) is not maintained.

1.5 An alternative TNF-α inhibitor may be considered for patients in whom treatment is withdrawn due to an adverse event before the initial 6-month assessment of efficacy, provided the risks and benefits have been fully discussed with the patient and documented.

1.6 Escalation of dose of the TNF-α inhibitors above their licensed starting dose is not recommended.

1.7 Treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose). This may need to be varied in individual cases due to differences in the mode of administration and treatment schedules.

1.8 Use of the TNF-α inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended.

1.9 Initiation of TNF-α inhibitors and follow-up of treatment response and adverse events should be undertaken only by a specialist rheumatological team with experience in the use of these agents.

Section 1 of certolizumab pegol for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 186(2010).

1.1 Certolizumab pegol is recommended as an option for the treatment of people with rheumatoid arthritis only if:

- certolizumab pegol is used as described for other tumour necrosis factor (TNF) inhibitor treatments in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 130) **and**
- the manufacturer provides the first 12 weeks of certolizumab pegol (10 pre-loaded 200-mg syringes) free of charge to all patients starting treatment.

1.2 When using the DAS28 (as set out in NICE technology appraisal guidance 130), healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses to the DAS28 and make any adjustments they consider appropriate.

Section 1 of adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. NICE technology appraisal guidance 195 (2010).

1.1 Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or are intolerant of, other disease-modifying anti-rheumatic drugs (DMARDs), including at least one tumour necrosis factor (TNF) inhibitor. Treatment with rituximab should be given no more frequently than every 6 months.

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

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

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

1.5 Treatment with adalimumab, etanercept, infliximab and abatacept should be continued only if there is an adequate response (as defined in 1.2) 6

months after initiation of therapy. Treatment should be monitored, with assessment of DAS28, at least every 6 months and continued only if an adequate response is maintained.

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

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

Section 1 of golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs. NICE technology appraisal guidance 225(2011).

1.1 Golimumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to conventional disease-modifying anti-rheumatic drugs (DMARDs) only, including methotrexate, if:

- it is used as described for other tumour necrosis factor (TNF) inhibitor treatments in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (NICE technology appraisal guidance 130), **and**
- the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme.

1.2 Golimumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to other DMARDs, including a TNF inhibitor, if:

- it is used as described for other TNF inhibitor treatments in 'Adalimumab, etanercept, infliximab, rituximab and abatacept for the

treatment of rheumatoid arthritis after the failure of a TNF inhibitor' (NICE technology appraisal guidance 195), **and**

- the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme.

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

Section 1 of tocilizumab for the treatment of rheumatoid arthritis (rapid review of technology appraisal guidance 198). NICE technology appraisal guidance TA247(2012).

1.1 Tocilizumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults if:

- the disease has responded inadequately to disease-modifying anti-rheumatic drugs (DMARDs) **and** it is used as described for tumour necrosis factor (TNF) inhibitor treatments in Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (NICE technology appraisal guidance 130), specifically the recommendations on disease activity and choice of treatment **or**
- the disease has responded inadequately to DMARDs and a TNF inhibitor and the person cannot receive rituximab because of a contraindication to rituximab, or because rituximab is withdrawn because of an adverse event, **and** tocilizumab is used as described for TNF inhibitor treatments in Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (NICE technology appraisal guidance 195), specifically the recommendations on disease activity **or**
- the disease has responded inadequately to one or more TNF inhibitor treatments and to rituximab

- **and** the manufacturer provides tocilizumab with the discount agreed as part of the patient access scheme.

1.2 People currently receiving tocilizumab for the treatment of rheumatoid arthritis who do not meet the criteria in 1.1 should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

Section 1 of abatacept for treating rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs (rapid review of technology appraisal guidance 234). NICE technology appraisal guidance TA280 (2013).

1.1 Abatacept in combination with methotrexate is recommended as an option for treating rheumatoid arthritis in adults whose disease has responded inadequately to 2 conventional disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate, only if:

- it is used in accordance with the recommendations for other biological DMARDs in Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (NICE technology appraisal guidance 130) **and**
- the manufacturer provides abatacept with the discount agreed in the patient access scheme.

1.2 People currently receiving abatacept whose disease does not meet the criteria in section 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.