NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor (part review of NICE technology appraisal guidance 36, review of NICE technology appraisal guidance 126 and 141)

This document is a summary of the evidence and views submitted by consultees and the Assessment Group. It highlights key issues for discussion at the first Appraisal Committee meeting. NICE prepares the overview before it receives consultees' comments on the assessment report. The sources of evidence used in the preparation of this document are given in appendix A.

Background

The condition

Rheumatoid arthritis (RA) is a chronic, disabling, autoimmune condition characterised by inflammation of the synovial tissue of the peripheral joints. The synovial layer becomes enlarged because of an increase in the number of normal cells (hyperplasia), infiltration by white blood cells and formation of new blood vessels. This is accompanied by increased fluid in the joint cavity, which contains white blood cells and a high level of protein. Bony erosions of cartilage and bone occur where synovial tissue meets cartilage and bone. Erosions and loss of cartilage are rarely reversible, and such damage compromises the structure and function of the joints. This swelling and progressive joint destruction is often accompanied by stiffness and pain.

Inflammatory disease outside the joints can also pose a significant problem, with dryness of the eyes and mouth (Sjögren's syndrome) and nodules (particularly over extensor surfaces, such as the backs of elbows) affecting up to a third of people with RA. More severe inflammatory manifestations may lead to fibrosis in the lungs, inflammation affecting the lining of the heart and

lungs (pleural and pericardial effusions) or vasculitis (inflammation of the inner lining of the blood vessels). Heart conditions such as ischaemic heart disease and cardiac failure have been shown to be more common in people with RA. Osteoporosis is also more common because of reduced mobility, inflammation and/or the drugs used to treat RA (particularly steroids). Steroid use can also contribute to an increased risk of infection.

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

RA has a severe impact on quality of life. The release of large concentrations of proteins that drive inflammatory processes (such as tumour necrosis factor [TNF]) can result in profound fatigue, fever, sweats and weight loss. Pain is often considerable. Most people experience moderate disability within 2 years of diagnosis, and after 10 years, approximately 30% have severe disability. It is estimated that 40% of people with RA will stop working within 5 years of diagnosis. RA is three times more prevalent in women than in men. It can develop at any age, but usually starts between 40 and 60 years. RA affects 1% of the population, or approximately 400,000 people in England and Wales. Of these, approximately 15% have severe disease.

Current management

People with RA are usually treated in a hospital outpatient setting and then in primary care. There is no cure for RA, and treatment aims to improve quality of life and prevent or reduce joint damage. Treatment usually includes non-steroidal anti-inflammatory drugs (NSAIDs), which reduce pain, fever,

joint swelling and joint inflammation; disease modifying anti-rheumatic drugs (DMARDs), which slow the disease process and reduce joint damage; and corticosteroids, which control inflammation. DMARDs may be classified as conventional or biological. Biological DMARDs include the TNF inhibitors; adalimumab, etanercept and infliximab, as well as rituximab and abatacept.

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

NICE technology appraisal guidance 130 recommends adalimumab, etanercept and infliximab as options for the treatment of people with active RA who have a disease activity score (DAS28) greater than 5.1 and whose RA has failed to respond to at least two DMARDs, including methotrexate (unless contraindicated). TNF-α inhibitors should be given in combination with methotrexate; however, when methotrexate cannot be used because of intolerance or contraindications, adalimumab or etanercept can be given as monotherapy. Adalimumab, etanercept and infliximab should be withdrawn if response is not adequate within 6 months (as defined by an improvement in DAS28 score of more than 1.2 points). Response to treatment should be monitored at least every 6 months in people whose RA responds initially; treatment should be withdrawn if response is not maintained. An alternative TNF-α inhibitor may be considered when treatment is withdrawn because of intolerance before the initial 6-month assessment. NICE technology appraisal guidance 36 does not recommend the sequential use of TNF inhibitors; NICE technology appraisal guidance 130 does not include guidance on sequential use of TNF inhibitors.

NICE technology appraisal guidance 126 recommends rituximab plus methotrexate as an option for the treatment of people with severe active RA who have had an inadequate response to or intolerance of other DMARDs,

including treatment with at least one TNF inhibitor. Treatment with rituximab plus methotrexate should be continued only if there is an adequate response (defined as a DAS28 improvement of more than 1.2 points) after initiation of therapy. Repeat courses of rituximab should be provided no more often than every six months. NICE technology appraisal guidance 141 does not recommend the use of abatacept after the failure of a TNF inhibitor.

Several measures have been developed to assess response to treatment in RA. For example, the ACR response criteria (ACR20, 50 and 70) require a specified 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.

The technologies

Five interventions are considered in this appraisal (see table 1 for summarised information on each intervention).

Table 1 The technologies

Non-proprietary name	Adalimumab	Etanercept	Infliximab	Rituximab	Abatacept
Proprietary name	Humira	Enbrel	Remicade	MabThera	Orencia
Manufacturer	Abbott Laboratories	Wyeth Pharmaceuticals	Schering-Plough	Roche Products	Bristol-Myers Squibb Pharmaceuticals
Dose	40 mg subcutaneous injection, repeated every 2 weeks. Licensed in combination with methotrexate, except when methotrexate is not tolerated or considered inappropriate. In monotherapy, can be increased to 40 mg weekly.	25 mg subcutaneous injection, twice weekly. Alternatively, 50 mg administered once weekly. Licensed in combination with methotrexate, except when methotrexate is not tolerated or considered inappropriate.	3 mg/kg intravenous infusion over a 2-hour period followed by additional 3 mg/kg infusion 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If response inadequate after 12 weeks, may be increased by 1.5 mg/kg every 8 weeks, up to max. 7.5 mg/kg every 8 weeks. Alternatively, 3 mg/kg may be given every 4 weeks; discontinue if no response by 12 weeks of initial infusion or after dose adjustment. Licensed in combination with methotrexate.	1 g intravenous infusion, repeated 2 weeks after initial infusion. Initial infusion: 50 mg/hour for first 30 minutes; can be escalated in 50 mg/hour increments every 30 minutes to max. 400 mg/hour. Subsequent infusions: 100 mg/hour for first 30 minutes; can be escalated in 100 mg/hour increments every 30 minutes to max. 400 mg/hour. Subsequent courses at interval no less than 16 weeks. Licensed in combination with methotrexate.	Intravenous infusion, 30 minutes. Bodyweight less than 60 kg: 500 mg, repeated 2 and 4 weeks after initial infusion, then every 4 weeks thereafter; bodyweight 60–100 kg: 750 mg repeated 2 and 4 weeks after initial infusion, then every 4 weeks thereafter; bodyweight over 100 kg: 1 g repeated 2 and 4 weeks after initial infusion, then every 4 weeks thereafter. Licensed in combination with methotrexate.
Acquisition cost (excluding VAT; BNF edition 58)	Net price for a 40-mg prefilled syringe = £357.50	Net price for a 25-mg vial = £89.38	Net price for a 100-mg vial = £419.62	10 mg/ml, net price for a 10-ml vial = £174.63,	Net price for a 250-mg vial = £242.17

	50-ml vial = £873.15

TNF inhibitors

Adalimumab is a human-sequence antibody that binds specifically to TNF and neutralises its biological function by blocking its interaction with cell-surface TNF receptors. Adalimumab is indicated for the treatment of moderate to severe active RA in adults when the response to DMARDs, including methotrexate, has been inadequate. Adalimumab is also indicated for the treatment of severe, active and progressive RA in adults not previously treated with methotrexate. Adalimumab has been associated with infections, sometimes severe, including tuberculosis and hepatitis B reactivation. It is contraindicated in people with active tuberculosis or other severe infections, and in people with moderate to severe heart failure.

Etanercept is a recombinant human TNF-receptor fusion protein. It interferes with the inflammatory cascade by binding to TNF, thereby blocking its interaction with cell-surface TNF receptors. Etanercept is indicated for the treatment of moderate to severe active RA in adults when the response to DMARDs, including methotrexate (unless contraindicated), has been inadequate. Etanercept is also indicated for the treatment of severe, active and progressive RA in adults not previously treated with methotrexate. Etanercept has been associated with infections, sometimes severe, including tuberculosis and hepatitis B reactivation. It is contraindicated in people with sepsis or at risk of sepsis, and with active infections, including chronic or localised infections.

Infliximab is a chimeric monoclonal antibody that binds with high affinity to TNF, thereby neutralising its activity. Infliximab is licensed 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. Infliximab is also indicated for the treatment of severe,

active and progressive RA in adults not previously treated with methotrexate or other DMARDs. It has been associated with infections, sometimes severe, including tuberculosis and hepatitis B reactivation. It is contraindicated in people with tuberculosis or other severe infections, and in people with moderate to severe heart failure.

Other therapies

Rituximab is a genetically engineered chimeric monoclonal antibody that depletes the B-cell population by targeting cells bearing the CD20 surface marker. Rituximab is indicated for the treatment of adults with severe active RA who have had an inadequate response to or intolerance of other DMARDs, including one or more TNF inhibitor therapies. Repeat courses of treatment with rituximab should be given no more frequently than every 4 months. Rituximab has been associated with infusion reactions and infections, sometimes severe, including tuberculosis and hepatitis B reactivation. It is contraindicated in people with active severe infections, and severe heart failure or severe uncontrolled cardiac disease.

Abatacept is a selective T-cell co-stimulation modulator that blocks a key co-stimulatory signal required for T-cell activation. Abatacept is indicated for the treatment of moderate to severe active RA in adults who have had an insufficient response to or intolerance of other DMARDs including at least one TNF inhibitor. Abatacept has been associated with infections, sometimes severe, including sepsis and pneumonia. It is contraindicated in people with severe and uncontrolled infections, such as sepsis and opportunistic infections.

The evidence

Clinical effectiveness

Thirty-five studies were identified by the Assessment Group as meeting the criteria for inclusion in the systematic review. Five of these were randomised controlled trials (RCTs), one was a comparative study, one was a non-

randomised controlled study, and 28 were uncontrolled studies (including two long-term RCT extensions). The RCTs compared one of the technologies with placebo and/or with ongoing conventional DMARDs or biological DMARDs that have produced an inadequate response. These comparisons included:

- rituximab compared with placebo plus ongoing conventional DMARDs (REFLEX trial)
- abatacept compared with placebo plus ongoing conventional DMARDs (ATTAIN trial)
- abatacept added to ongoing etanercept compared with ongoing etanercept (Weinblatt 2007)
- abatacept added to ongoing biological or conventional DMARDs compared with ongoing biological or conventional DMARDs (ASSURE trial).
- infliximab compared with etanercept in people with an inadequate response to etanercept (OPPOSITE trial).

Three of the RCTs were subsequently excluded from the analysis by the Assessment Group because they either considered regimens outside of their marketing authorisation (Weinblatt 2007; ASSURE trial), or were not considered relevant (OPPOSITE trial).

Adalimumab

No RCTs were identified. Five uncontrolled studies with duration of follow-up ranging from 3 to 12 months met the criteria for inclusion. Apart from one multicentre study of 899 people (Bombardieri, 2007), sample sizes were small, ranging from 24 to 41. All people included in the studies had previous experience with at least one TNF inhibitor. Outcomes assessed varied among the studies, although four reported mean changes in DAS28. Mean changes in the HAQ score were reported in three studies. None of the studies assessed joint damage or quality of life. The results were not pooled because of substantial clinical and statistical heterogeneity. A summary of the key results is presented in table 2.

Table 2 Key results for adalimumab studies

Study	N	Follow-up (months)	ACR 20/50/70	Mean change DAS	Mean change HAQ
Bennett 2005	26	6	NR/NR/NR	-1.70	-0.31
Bombardieri 2007	899	3	60/33/13	-1.90	-0.48
Nikas 2006	24	12	75/50/33	NR	NR
Wick 2005	27	6	70/NR/NR	-1.30	NR
Van der Bijl 2008	41	3	46/27/12	-1.50	-0.21

ACR: American College of Rheumatology; DAS: disease activity score; HAQ: Health Assessment Questionnaire; NR: not reported.

Etanercept

No RCTs were identified. Seven uncontrolled studies with duration of follow-up ranging from 3 months to over 9 months met the criteria for inclusion. Sample sizes ranged from 25 to 201. All people included in the studies had previous experience with at least one TNF inhibitor. Outcomes assessed varied among the studies, although most reported ACR scores and mean changes in DAS28. Mean changes in HAQ score were reported in three studies. None of the studies assessed joint damage or quality of life. The results were not pooled because of substantial clinical and statistical heterogeneity between studies. A summary of the key results is presented in table 3.

Table 3 Key results for etanercept studies

Study	N	Follow-up (months)	ACR 20/50/70	Mean change DAS	Mean change HAQ
Bingham 2009	201	4	42/18/8	-1.60	-0.35
Buch 2005	25	3	72/64/20	NR	NR
Buch 2007	95	3	38/24/15	-1.47	NR
Cohen 2005	24	3	NR/NR/NR	-1.80	NR
Haraoui 2004	25	3	58/21/4	NR	-0.45
Iannone 2007	37	6	NR/NR/NR	-0.90*	0.00
Laas 2008	49	>9	NR/NR/NR	-0.47	NR

ACR: American College of Rheumatology; DAS: disease activity score; HAQ: Health Assessment Questionnaire; NR: not reported.

*DAS44 not DAS28.

Infliximab

Three uncontrolled studies were identified, each with a small sample size ranging from 20 to 24. The Assessment Group considered that the length of follow-up in the studies was unclear. All people included in the studies had tried one TNF inhibitor before; reasons for discontinuation included lack of efficacy. None of the studies reported ACR response criteria or quantitative results of changes in DAS28 and HAQ scores.

TNF inhibitors as a group

Some of the studies included in the assessment report looked at switching to an alternative TNF inhibitor, but they did not provide separate data for individual TNF inhibitors. One controlled study and 7 uncontrolled studies with duration of follow-up ranging from 3 months to 4 years were identified. ACR responses were reported in only one study. Two studies (Hjardem 2007; Blom 2009) reported outcomes by reason for withdrawing the first TNF inhibitor. The reason for withdrawing from the first TNF inhibitor was unclear in Solau-Gervais (2006). Only one study (using data from the British Society of Rheumatology Biologics Register [BSRBR]) reported a mean reduction in

HAQ score. No studies assessed joint damage or quality of life. A summary of the key results is presented in table 4.

Table 4 Key results for TNF inhibitors as a class studies

Study	N	Follow-up (months)	ACR 20/50/70	Mean change DAS	Mean change HAQ
Hyrich 2009	818	>6	NR	NR	-0.11
Gomez-Reino 2006	448	24	NR	NR	NR
Solau-Gervais 2006	70	>3	NR	NR	NR
Hjardem 2007	235	3	NR	-1.00	NR
Duftner 2008	109	Up to 48	NR	NR	NR
Karlsson 2008	337	3	49/26/7	NR	NR
Blom 2009	197	6	NR	-0.92	NR
Finckh 2009	163	11(median)	NR	-0.88	NR

ACR: American College of Rheumatology; DAS: disease activity score; HAQ: Health Assessment Questionnaire; NR: not reported.

Rituximab

One RCT (REFLEX, n=517) met the criteria for inclusion and was considered by the Assessment Group to be of good quality. REFLEX compared rituximab with placebo (with ongoing methotrexate in both groups) in people who have had an inadequate response to one or more TNF inhibitors. Outcomes assessed in REFLEX included ACR 20/50/70, HAQ, joint damage, quality of life, serious adverse events and serious infections. The study also reported the reasons for withdrawing TNF inhibitor treatment. The long term extension of the REFLEX RCT was also included, as were six uncontrolled studies. A pooled analysis combining data from the REFLEX RCT, its long-term extension, and other studies in the rituximab development programme was also identified. Duration of follow-up of the uncontrolled studies ranged from 6 months to 1 year and sample sizes ranged from 20 to 158. It is unclear how many patients were included in the pooled analysis. Outcomes assessed varied among the uncontrolled studies, with two (Keystone 2007; Finckh 2009) reporting mean changes in DAS28 and only one (Keystone 2007)

reporting changes in ACR score. None of the uncontrolled studies assessed joint damage or quality of life. The results generally support findings from the REFLEX trial. A summary of the key results is presented in table 5.

Table 5 Key results of rituximab studies

Study	N	Follow-up (months)	ACR 20/50/70	Mean change DAS	Mean change HAQ
REFLEX RCT					
Rituximab	308	6	51/27/12	-1.9	-0.40
Placebo	209	6	18/5/1	-0.4	-0.10
Uncontrolled studies					
Bokarewa 2007	48	12	NR	NR	NR
Jois 2007	20	6	NR	NR	NR
Keystone 2007	NR	6	65/33/12	NR	NR
Assous 2008	50	6	NR	NR	NR
Thurlings 2008	24	6	NR	NR	NR
Finckh 2009	155	11	NR	-1.61	NR
REFLEX extension					
Course 1*	480	NA	71/39/14	NR	NR
Course 2*	307	NA	73/43/21	NR	NR
Course 3*	235	NA	73/48/26	NR	NR
Pooled analysis					
Course 1*	500	NA	61/30/12	NR	-0.45
Course 2*	355	NA	70/41/19	NR	-0.48
Course 3*	264	NA	71/47/25	NR	-0.53
Course 4*	178	NA	64/42/21	NR	-0.50
Course 5*	84	NA	64/42/23	NR	-0.56

ACR: American College of Rheumatology; DAS: disease activity score; HAQ: Health Assessment Questionnaire; NR: not reported.

*Data for people receiving consecutive courses of rituximab treatment

Abatacept

One RCT (ATTAIN; n = 391), which the Assessment Group considered to be of good quality, and an extension of it (ATTAIN LTE; n = 317) were identified. ATTAIN compared abatacept with placebo (with ongoing DMARDs in both

groups) in people who have had an inadequate response to one or more TNF inhibitors. Outcomes assessed in the ATTAIN trial included ACR 20/50/70, DAS28, HAQ, quality of life, serious adverse events and serious infections (table 6). The trial also reported the reasons for withdrawing TNF inhibitor treatment. Further data from the RCT extension of the ATTAIN trial and a large prospective uncontrolled study (ARRIVE) generally supported findings from the ATTAIN trial.

Table 6 Key results of abatacept studies

Study	N	Follow-up (months)	ACR 20/50/70	Mean change DAS	Mean change HAQ
ATTAIN					
Abatacept	258	6	50/20/10	-1.98	-0.45
Placebo	133	6	20/4/2	-0.07	-0.11
ATTAIN LTE non-ITT analysis[1]					
Abatacept	192	12	65/32/18	-2.33	-0.52
Abatacept	151	24	75/46/23	-2.66	-0.62
Abatacept	132	36	82/51/23	-2.85	-0.65
Abatacept	113	48	76//46/19	-2.79	-0.58
Abatacept	79	60	74/51/23	-2.90	-0.56
ARRIVE	1046	6	NR	-2.00	NR

ACR: American College of Rheumatology; DAS: disease activity score; HAQ: Health Assessment Questionnaire; NR: not reported.

[1]ATTAIN LTE ITT analysis for ACR response on pages 126 to 129 of the Assessment Report. Patients switching from placebo to abatacept show similar results, pages 128 to 132 of Assessment Report.

Comparative effectiveness

No head-to-head trials directly comparing the five technologies, or comparing the technologies with other biological DMARDs or previously untried DMARDs were identified. One non-randomised controlled study (Finckh 2009) compared switching to rituximab with switching to an alternative TNF inhibitor. The published paper reports that the mean change in DAS28 score was significantly greater in the rituximab group (mean change -1.34; 95% CI: -1.54, -1.15) compared with the alternative TNF inhibitor group (mean change -0.93; 95% CI: -1.28, -0.59) (p=0.03) when the switch was because of ineffectiveness of the first TNF inhibitor.

The Assessment Group conducted an adjusted indirect comparison of rituximab and abatacept using data from placebo-controlled trials that included similar populations. The results, outlined in table 7, did not show a significant difference in their effectiveness (as defined by ACR response rate).

Table 7 Indirect comparison between rituximab and abatacept

Comparison	Response rate (CI)
ACR20	
Rituximab vs placebo	2.848 (2.076 to 3.907)
Abatacept vs placebo	2.554 (1.737 to 3.756)
Rituximab vs abatacept	1.115 (0.677 to 1.836)
ACR50	
Rituximab vs placebo	5.396 (2.866 to 10.158)
Abatacept vs placebo	5.403 (2.211 to 13.203)
Rituximab vs abatacept	0.999 (0.334 to 2.984)
ACR70	
Rituximab vs placebo	12.141 (2.956 to 49.859)
Abatacept vs placebo	6.754 (1.628 to 28.023)
Rituximab vs abatacept	1.798 (0.242 to 13.350)
Withdrawal, any reason	
Rituximab vs placebo	0.389 (0.294 to 0.515)
Abatacept vs placebo	0.531 (0.348 to 0.810)
Rituximab vs abatacept	0.733 (0.441 to 1.217)
ACR: American College of Rheumatology; CI: confidence interval.	

The Assessment Group did not report further analyses for comparative effectiveness.

Subgroup analyses

The Assessment Group considered a number of subgroups in their report: reason for stopping the first TNF inhibitor (intolerance, primary non-response, or secondary loss of response), auto-antibody status (rheumatoid factor or anti CCP positivity), number of TNF inhibitors previously tried, and prior TNF inhibitor tried. In addition, the Assessment Group, summarised data from the REFLEX trial provided commercial in confidence. The overview summarises data for the subgroups specified in the final scope for the appraisal.

Reason for withdrawal of first TNF inhibitor

The Assessment Group reported that no conclusions could be drawn on the extent to which the effectiveness of the technologies varies by reason for withdrawing from the first TNF inhibitor because of a lack of RCT evidence

The Assessment Group identified evidence from two uncontrolled studies of adalimumab (Bombardieri 2007, van der Bijl 2008) that showed statistically significant differences for ACR 20 and 50 response rates in favour of people who experienced a loss of response of their first TNF inhibitor in comparison with people who experienced a primary non-response. No other differences were statistically significant. Evidence from two uncontrolled studies of etanercept (Buch 2007, Bingham 2009) indicated that there was no significant difference in response between these subgroups. One study (Blom 2009) reported data for the TNF inhibitors as a class. This study reported an ITT analysis of EULAR response at 3 months which showed statistically significantly better response rates in people who switched due to primary non-response. Other differences were not statistically significant. Data for abatacept from the ATTAIN LTE reported that in a non-ITT analysis of the proportions of people experiencing a change in HAQ greater than 0.3 at 6 months, statistically significantly more did so where they had stopped their first TNF inhibitor due to loss of response. Other differences were not statistically significant. No data for infliximab and rituximab were identified.

Auto-antibody status

Evidence on auto-antibody status was only available for rituximab from the REFLEX trial. The trial reported no statistically significant differences for treatment effect by rheumatoid factor status. When participants were stratified according to both rheumatoid factor and anti-CCP status, data suggested a greater treatment response in people who were either rheumatoid factor or anti-CCP positive than in those who were both rheumatoid factor and anti-CCP negative. The Assessment Group notes that this analysis is post hoc and therefore should be treated with caution.

Cost effectiveness

Published literature

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

Manufacturer's submissions

All five manufacturers provided economic analyses to support their submissions. However, one model (etanercept, Wyeth Pharmaceuticals) was provided only as a narrative summary and not as a fully executable file. All submissions were based on cost–utility analyses run over a lifetime horizon and from the perspective of the healthcare provider. All but one submission (abatacept, Bristol-Myers Squibb) used conventional DMARDs as the base-case comparator. The abatacept submission compared abatacept with rituximab and with a 'basket' of TNF inhibitors. Table 71 (pages 190-193) of the assessment report summarises the five economic analyses provided.

Abbott Laboratories (adalimumab)

Abbott Laboratories developed a discrete-event simulation model and performed a cost–utility analysis of adalimumab compared with etanercept, infliximab, rituximab and abatacept, all of which were considered in combination with methotrexate. Each of the five strategies used the same treatment sequence: the comparator drug, followed by gold, then leflunomide,

then ciclosporin, then rescue therapy. Comparisons were also made with the following strategies:

- conventional DMARDs only (gold, then leflunomide, then ciclosporin, then rescue therapy)
- adalimumab followed by rituximab, then gold, then leflunomide, then ciclosporin, then rescue therapy.

The model simulates 100,000 people per treatment sequence, whose profiles are based on the baseline characteristics of people in the BSRBR, including a baseline HAQ score (after the failure of the first TNF inhibitor) of 2.1. The base-case model included a continuation rule using ACR50 response to determine whether a person continued therapy after an initial trial period.

Response to treatment was based on ACR response rates mapped to a change in HAQ score. ACR response rates (table 8) were derived from a mixed treatment comparison of 34 studies. Response rates were assumed to be equal across all TNF inhibitors. The change in HAQ score associated with each ACR response category was calculated from adalimumab clinical trial data (from people whose disease had responded inadequately to conventional DMARDs). The model assumed that the change in HAQ score for each ACR response was the same for biological DMARDs, but that this differed from that for conventional DMARDs; ACR20 response rate was associated with a change in HAQ score of -40.5% for biological DMARDs and -30.0% for conventional DMARDs. When people discontinued treatment, a full rebound effect was assumed (that is, the rebound following treatment discontinuation was assumed to be equal to the initial improvement).

Table 8 ACR Response Rates

	ACR 20	ACR 50	ACR 70
TNF inhibitors	64.26%	40.12%	20.54%
Rituximab	61.78%	38.41%	19.83%
Abatacept	54.69%	31.14%	14.83%
Conventional DMARDs	25.26%	10.40%	4.09%

In addition to the initial response to treatment, the model included underlying disease progression while on treatment. This was modelled in terms of HAQ score. HAQ score was assumed to worsen (that is, increase) at a constant annual rate, using the values described in NICE technology appraisal guidance 130 (that is, for people on treatment with: biologic DMARDs: 0.030; conventional DMARDs: 0.045; rescue therapy: 0.060). A quadratic mapping mechanism was used to convert HAQ scores to EQ-5D scores. This mechanism was estimated using EQ-5D data collected in tocilizumab (an alternative biological DMARD) trials. A linear mapping mechanism was explored in a sensitivity analysis.

Adverse events were included in the economic analysis, with higher rates for conventional DMARDs than for biological DMARDs. Mortality risks were derived by fitting a Gompertz function to the data from 2007 gender-specific UK life tables.

Costs included drug acquisition, administration, monitoring and hospitalisation (including joint replacement surgery). These costs were assumed to be equal for adalimumab and etanercept. As a result, adalimumab and etanercept were evaluated in the same treatment sequence and the results for these two drugs were considered similar throughout the submission. The cost of administering an intravenous drugs was estimated to be £462 for each infusion, based on the Healthcare Resource Group 2007/08 tariff. It was assumed that the administration of subcutaneous drugs would require 3 hours of nurse training incurring a one-off cost of £129. Retreatment with rituximab was assumed to occur every 9 months.

The base-case results show that compared with conventional DMARDs rituximab had the lowest incremental cost-effectiveness ratio (ICER) (£10,986 per QALY gained) while abatacept had the highest (£30,104 per QALY gained). The strategy of introducing rituximab after adalimumab or etanercept (that is, as a third-line biological DMARD) resulted in an ICER of £13,797 per QALY gained when compared with conventional DMARDs (table 9).

Table 9: Abbott Laboratories base case estimates

Technology	Total costs (£)	Total QALYs	ICER vs DMARDs (£)
DMARDs	26,866	1.69	-
Rituximab	41,966	3.06	10,986
Adalimumab or etanercept	50,289	3.16	15,962
Infliximab	58,107	3.14	21,529
Abatacept	61,054	2.83	30,104
Adalimumab or etanercept followed by rituximab	63,178	4.32	13,797

DMARD: disease modifying anti-rheumatic drug; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Univariate sensitivity analyses suggested that the model was most sensitive to the starting HAQ score, change in HAQ score while on treatment (that is, underlying disease progression), HAQ rebound, utility mapping of HAQ to EQ-5D and rituximab dosing schedule.

Wyeth Pharmaceuticals (etanercept)

Wyeth Pharmaceuticals presented the results of a Markov model with a 6-month cycle and carried out a cost–utility analysis of etanercept. The model that produced the results presented in the submission was not submitted. Abatacept was not included in the economic analyses.

The model compared three strategies:

- treatment with two, sequential TNF inhibitors
- treatment with a TNF inhibitor followed by conventional DMARDs
- treatment with a TNF inhibitor followed by rituximab.

For each strategy, people were assumed to have first received treatment with methotrexate, then sulfasalazine, then a ‘first TNF inhibitor’. It is unclear from the submission which TNF inhibitor was used; however, the Assessment Group noted that cost data suggest it was etanercept. After receiving one of the strategies listed above, people went on to receive a conventional DMARD

and then best supportive care. Again, it is unclear from the submission which TNF inhibitor was used as the '2nd TNF inhibitor'. The Assessment Group noted that cost data suggest an average of etanercept, adalimumab and infliximab in combination with methotrexate. Cost data also suggest that methotrexate was used as the 'DMARD' strategy, and that sulfasalazine was the DMARD used after the TNF inhibitor.

Baseline patient characteristics were reflective of patients in the TEMPO trial (an RCT of etanercept in people who had had an inadequate response to conventional DMARDs). Treatment effect for TNF inhibitors was based on change in HAQ score for patients treated with a second TNF inhibitor after primary non response, secondary loss of response and intolerance to their first TNF inhibitor. The data were taken from an adalimumab trial (Bombardieri, 2007). The values used were -0.44, -0.51 and -0.55 respectively. The estimated mean changes in HAQ score for those treated with rituximab (-0.40) was taken from the REFLEX trial; both were unadjusted estimates of absolute treatment effect observed in the trial. The effect of conventional DMARDs was assumed to be zero, based on data from the BSRBR registry showing that for people who stopped treatment with a TNF inhibitor the average HAQ score was unchanged after 1 year. A linear mapping mechanism was used to convert HAQ scores to EQ-5D scores during each model cycle.

The model included underlying disease progression while on treatment, which was modelled in terms of worsening HAQ score over time. HAQ score was assumed to remain the same while on biologic DMARDs. For those on conventional DMARDs, a change in HAQ score of 0.075 per six month cycle was assumed from the first six months up to 3 years, and then 0.10 per six month cycle from year three onwards.

Serious adverse events were included in the economic analysis, with higher rates for conventional DMARDs than for biological DMARDs. Baseline mortality rates were assumed to be 1.63 times the standard rate.

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

Base case results were presented for a range of changes in HAQ score for both TNF inhibitors and conventional DMARDs. The ICER for TNF inhibitors compared with conventional DMARDs was £15,294 per QALY gained, when switching as a result of primary non-response and £14,501 per QALY gained, when switching as a result of secondary loss of response. The ICER for TNF inhibitors compared with rituximab was £19, 077 per QALY gained and £16,225 per QALY gained when switching was for primary non response and secondary loss of response respectively. No probabilistic sensitivity analysis results were presented in the submission.

Schering-Plough (infliximab)

Schering-Plough developed a patient-level simulation model and performed a cost–utility analysis of infliximab. The model compared nine treatment sequences:

- adalimumab (or etanercept or infliximab or rituximab or abatacept), followed by a sequence of conventional DMARDs
- adalimumab (or etanercept or infliximab), followed by rituximab and then a sequence of conventional DMARDs
- a sequence of conventional DMARDs.

In the model people could receive a maximum of two biological DMARDs followed by a maximum of three conventional DMARDs, and were limited to a maximum of five treatments within each of the nine sequences. Baseline characteristics were based on people in the GO-AFTER trial (a trial of the TNF inhibitor golimumab in people who had had an inadequate response to a previous TNF inhibitor). European League Against Rheumatism (EULAR) response was used to determine continuation of treatment after an initial trial period.

The relative treatment effect of biological DMARDs was derived from a mixed treatment comparison of data from RCTs of biological DMARDs. It was assumed in the model that the relative treatment effect of TNF inhibitors would not be altered by previous TNF inhibitor treatment, but that the absolute treatment effect would be lower in those people who were TNF inhibitor naive. Having calculated the relative treatment effect in terms of ACR response, it was adjusted for disease duration and then mapped to calculate EULAR response rates using an algorithm derived from the GO-AFTER trial. This transformation allowed the relative treatment effect for biologic DMARDs from the mixed treatment comparison to be used with BSRBR EULAR data for conventional DMARDs to estimate the absolute treatment effect for biologic DMARDs in terms of EULAR response rates. The EULAR response categories were then mapped to gains in utility, which were estimated from algorithms derived from BSRBR data that mapped EULAR response categories to HAQ, and then to EQ-5D. HAQ score changes associated with each EULAR response category for biologics was different to those for conventional DMARDs.

Underlying disease progression while on treatment was modelled using change in HAQ score over time. It was assumed that there was no disease progression while people were being treated with biological DMARDs, while disease progression for people on conventional DMARDs was 0.042 per year. In addition it was assumed that people had the same radiological damage at the start of treatment with biological DMARDs as at the end. This assumption was made to reflect the lack of radiological progression associated with biological treatments. This was captured in the model by keeping age and disease duration constant while people were treated with biological DMARDs.

Adverse events were not included in the model. Standardised mortality ratios (from the World Health Organization Global Burden of Disease Programme) for people with RA were applied to 2008 UK life tables to estimate mortality.

Costs included drug acquisition and administration, monitoring and hospitalisation. It was assumed that in 63% of cases, there was no wastage of

unused infliximab as a result of vial sharing. The cost of administering infusional drugs was assumed to be £162.12, based on the cost given in the assessment report for NICE technology appraisal guidance 130 plus inflation. Two analyses were completed for rituximab: one assuming re-treatment every six months, and another assuming re-treatment every nine months.

The base-case results showed that when compared with a sequence of conventional DMARDs, rituximab had the lowest ICER for both 9-month (£17,422 per QALY gained) and 6-month doses (£27,161 per QALY gained). Among the TNF inhibitors, infliximab had the lowest ICER (£28,661 per QALY gained) (table 10).

Table 10: Schering-Plough base case estimates

Technology	Total costs (£)	Total QALYs	ICER vs DMARDs (£)
DMARDs	28,058	5.68	-
Rituximab	39,383	6.33	17,422
Infliximab	46,687	6.33	28,661
Etanercept	50,315	6.30	35,898
Adalimumab	51,250	6.34	35,138
Abatacept	56,263	6.31	44,769
DMARD: disease modifying anti-rheumatic drug; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.			

ICERs in the sensitivity analyses varied from £16,752 per QALY gained (rituximab compared with DMARDs, when a HAQ improvement of 0.01 per annum was assumed for all biological DMARDS) to £58,850 per QALY gained (infliximab then rituximab compared with rituximab, when the weight of the person was assumed to be 120 kg).

Roche Products (rituximab)

Roche Products developed a patient-level simulation model and performed a cost–utility analysis of rituximab compared with adalimumab, etanercept, infliximab and abatacept. Each of the five strategies used the same treatment sequence: the comparator drug, followed by leflunomide, gold and ciclosporin, then palliative care. A comparison of rituximab and conventional DMARDs

was also made. Response rates of leflunomide, gold and ciclosporin were assumed to be equivalent to methotrexate.

Baseline characteristics are reflective of people in the REFLEX trial. Response to treatment was defined in terms of ACR response rates, which were derived from two sources: a mixed treatment comparison of RCTs of TNF inhibitors in people who had had an inadequate response to conventional DMARDs; and an indirect comparison of the abatacept ATTAIN trial and rituximab REFLEX trial. The results of the mixed treatment comparison were then adjusted (reduced by 30%) to reflect a lower response to treatment observed in people who had had an inadequate response to a first TNF inhibitor (table 11). ACR response rates were then linked to change in HAQ based on an algorithm from data in the REFLEX trial. A rebound effect was assumed to occur immediately at the point of treatment withdrawal. A quadratic mapping mechanism derived from tocilizumab trial data was used to convert HAQ scores to EQ-5D scores. A linear mapping mechanism was explored in a scenario analysis.

Table 11 ACR Response Rates with TNF inhibitor adjustment

	ACR 20	ACR 50	ACR 70
Etanercept	45%	25%	10%
Infliximab	42%	23%	10%
Adalimumab	46%	31%	13%
Rituximab	46%	23%	14%
Abatacept	43%	22%	8%
Conventional DMARDs	15%	4%	1%

Disease progression was modelled using HAQ score. It was assumed that while a person was on a biological DMARD there was no change in HAQ score. For people on conventional DMARDs the change in HAQ score was 0.0225 per six month cycle, while for people receiving palliative care the value was 0.03 per six month cycle. Mortality risks were derived by adjusting data from 2008 UK life tables by the parameter (1.33) used in the Evidence Review Group report for NICE technology appraisal guidance 141.

Adverse events were not included in the economic analysis. The costs included drug acquisition and administration, monitoring and hospitalisation. The cost of administration for was assumed to be £162 per infusion and this included all premedication and monitoring costs. Subcutaneous drugs incurred monitoring and premedication costs of £1268 per year and administration costs (£136 for etanercept and £68 for adalimumab) reflecting that 10% of people will receive injections by a district nurse. Re-treatment with rituximab was assumed to occur every 8.7 months.

In the base case, TNF inhibitors (etanercept, infliximab and adalimumab) were dominated by rituximab. Adalimumab had more QALYs than rituximab, but also more costly than rituximab, resulting in an ICER of £310,771 per QALY gained. When compared with conventional DMARDs, rituximab was cost effective at £5311 per QALY gained (table 12).

Table 12: Roche base case estimates

Technology	Total costs £	Total QALYs	ICER vs rituximab (£)
DMARDs	46,671	3.456	5,311
Rituximab	52,356	4.527	-
Infliximab	62,846	4.457	rituximab dominates
Etanercept	65,603	4.510	rituximab dominates
Adalimumab	65,907	4.571	310,771*
Abatacept	68,437	4.466	rituximab dominates

DMARD: disease modifying anti-rheumatic drug; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

*ICER for adalimumab, rituximab less costly and less effective.

ICERs in the sensitivity analyses varied from £1909 per QALY gained (compared with conventional DMARDs when a 12-month time to retreatment was assumed for rituximab) to £326,397 per QALY gained (compared with adalimumab when a linear mapping mechanism was assumed for the HAQ to quality of life conversion). In most of the scenarios, rituximab dominated the other strategies.

Bristol-Myers Squibb (abatacept)

Bristol-Myers Squibb developed a patient-level simulation model and performed a cost–utility analysis of abatacept. The submission comprised two main comparisons:

- abatacept compared with rituximab, followed by infliximab, then conventional DMARDs, then palliative care
- abatacept compared with a 'basket' of TNF inhibitors, followed by another 'basket' of TNF inhibitors, then conventional DMARDs, then palliative care.

The submission argued that the TNF inhibitors could be treated as a class on the basis that no data were available on the differential efficacy of the individual treatments. The 'basket' was defined on the basis of market share, estimated by survey data. Efficacy, costs and other parameters related to that therapy were applied to the proportion of people receiving that therapy. Conventional DMARDs were not included as comparators because it was assumed that clinicians would be unlikely to revert to these therapies in this population. Baseline characteristics are reflective of people in the ATTAIN trial, although the weight distribution of people was based on data from the General Practice Research Database.

Response to treatment was defined in terms of change in HAQ score. Data for rituximab and abatacept were based on a mixed treatment comparison of the ATTAIN and REFLEX trials, which produced a mean change in HAQ score of 0.42 for those on abatacept, and 0.38 for those on rituximab. Data for TNF inhibitors were taken from an analysis completed by the Decision Support Unit for TA130 of data from the BSRBR register. The mean change in HAQ score was 0.21. When people discontinued treatment, it was assumed that the initial treatment effect was lost. A linear mapping mechanism was used to convert HAQ scores to HUI3 scores during each model cycle. Conversion to EQ-5D scores was explored in sensitivity analyses.

Underlying progression of disease while on treatment was modelled using HAQ score. The progression rate for abatacept was taken from the ATTAIN

trial and was an improvement in HAQ score of 0.0729 per year in analyses against rituximab, and 0.013 per year in analyses against TNF inhibitors. In the absence of any long-term HAQ progression data for TNF inhibitors and rituximab, an annual worsening of HAQ score of 0.012 was used, based on the rate used in NICE technology appraisal guidance 126.

Adverse events were included in the economic analysis for the first 6 months of treatment. Event rates for the TNF inhibitors were derived from the individual trials, rates for DMARDs from the published literature, and for abatacept and rituximab from the mixed treatment comparison. Mortality risks were derived by adjusting data from 2008 UK life tables by the parameter (1.33) used in the Evidence Review Group report for NICE technology appraisal guidance 141.

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

The base-case results showed that abatacept compared with rituximab (both followed by infliximab as a third biological DMARD) resulted in an ICER of £20,438 per QALY gained. Abatacept compared with the ‘basket’ of TNF inhibitors resulted in an ICER of £23,019 per QALY gained (table 13).

Table 13 Bristol-Myers Squibb base case estimates

Technology	Total costs (£)	Total QALYs	ICER vs abatacept (£)
TNF inhibitors	£53,234	3.66	£23,019
Abatacept	£64,122	4.13	-
Rituximab	£54,416	3.79	£20,438
Abatacept	£63,654	4.24	-

ICER: incremental cost-effectiveness ratio; TNF: tumour necrosis factor; QALY: quality-adjusted life year.

ICERs for abatacept in the sensitivity analyses varied from £14,145 per QALY gained (compared with rituximab, when a 1.5% discount rate was assumed for QALYs) to £40,534 per QALY gained compared with rituximab, when the abatacept HAQ progression rate was assumed to be a worsening of 0.012 per year (that is, the same rate as was assumed for the other biologics), rather than an improvement of -0.013 per year (as was assumed in the base case).

The Birmingham Rheumatoid Arthritis Model

The Assessment Group's independent economic analysis was carried out using the Birmingham Rheumatoid Arthritis Model (BRAM). The model is an individual patient sampling model that simulates a large population, and is an updated version of the one used for TA130. People are assumed to follow a sequence of treatments, each of which involves starting a treatment, spending some time on that treatment, stopping the treatment if it is toxic or ineffective, and starting the next treatment. The BRAM compares six treatment sequences, summarised in table 14.

Table 14 Treatment sequences compared in the BRAM

Strategy name	ADA	ETN	IFX	RTX	ABT	DMARDs
1st[t]	ADA	ETN	IFX	RTX	ABT	LEF
2nd	LEF	LEF	LEF	LEF	LEF	GST
3rd	GST	GST	GST	GST	GST	CyA
4th	CyA	CyA	CyA	CyA	CyA	AZA
5th	AZA	AZA	AZA	AZA	AZA	Pall
6th	Pall	Pall	Pall	Pall	Pall	

ABT: abatacept; ADA: adalimumab; AZA: azathioprine; BRAM: Birmingham Rheumatoid Arthritis Model; CyA: ciclosporin; DMARD: disease modifying anti-rheumatic drug; ETN: etanercept; GST: injectable gold; IFX: infliximab; LEF: leflunomide; Pall: palliative care; RTX: rituximab.
All biological DMARDs are assumed to be taken in combination with methotrexate.

When the model is run, initial characteristics for (virtual) patients are sampled from the starting distribution based on patient characteristics of the BSRBR. Each patient is then run independently through each of the four options and differences in costs and QALYs between options are recorded. This process is repeated for a sufficiently large number of patients to produce a statistically stable comparison between each pair of options.

The model allows for two stages of early quitting of treatment. The first step represents cessation of treatment after 6 weeks, which is assumed to be for toxicity. The second step represents cessation between 6 and 24 weeks after starting treatment, which could be for toxicity or inefficacy. No early quitting is allowed for rituximab, because it is necessary to model the full costs of each cycle of treatment. For long term survival on treatment, Weibull curves were fitted to available data.

HAQ improvement varies between individual patients in the model, with changes in HAQ scores calculated using a multiplier. The multipliers are sampled from beta distributions, each derived from the literature (adalimumab: Bombardieri 2009; etanercept: Bingham 2009; infliximab: assumed same as etanercept; rituximab: REFLEX trial; abatacept: ATTAIN trial).

People's HAQ scores are assumed to improve (decrease) when they start a treatment and this improvement is lost when they stop a treatment, regardless of the reason for doing so. While receiving treatment, a person's condition is assumed to decline slowly over time. This is modelled by occasional increases in HAQ score of 0.125; the mean time between these increases varies by treatment. In the base-case analysis, HAQ is assumed to remain constant while a person is on treatment with a biological DMARD. Mean rates of HAQ increase on conventional DMARDs and on palliative care are modelled as mean times to increase of 2.7 and 2 years respectively. A

quadratic equation was used to convert HAQ scores to EQ-5D scores. The equation used gives negative values for high HAQ scores; changes to the model to allow for such scores to be adjusted to zero were used in scenario analyses.

Costs included drug acquisition and administration plus monitoring. The administration cost for infusional drugs was assumed to be £141.83, based on the cost given in the assessment report for NICE technology appraisal guidance 130 plus inflation. Costs for hospitalisation and joint replacement were estimated using a cost per unit HAQ score. Retreatment with rituximab is assumed to occur every 8.7 months.

Base-case results show similar ICERs for the TNF inhibitors, with lower ICERs for rituximab and higher ICERs for abatacept. Compared with conventional DMARDs alone, the ICER for rituximab is lower than the ICERs for other biological DMARDs. Rituximab dominates the TNF inhibitors (that is, it has a lower cost and more QALYs) (table 15). The ICER for abatacept compared with rituximab is over £100,000 per QALY gained.

Table 15 BRAM base case estimates

Technology	Total costs (£)	Total QALYs	ICER vs DMARDs (£)
DMARDs	48,800	2.14	-
Rituximab	69,100	3.10	21,200
Infliximab	72,800	2.81	36,200
Adalimumab	74,500	2.89	34,300
Etanercept	74,800	2.81	38,800
Abatacept	92,800	3.28	38,600

DMARD: disease modifying anti-rheumatic drug; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

A number of different scenario analyses were performed (pages 219-221 of the Assessment Report). These included varying the time on TNF inhibitors and on biological DMARDs, varying the rituximab treatment interval, varying the change in HAQ score while on biological DMARDs, varying quality of life scores, and varying the equation used to convert HAQ to quality of life. No subgroup analyses were performed.

The scenario analyses indicate that the results are subject to considerable uncertainty. The Assessment Group noted that important drivers of that uncertainty include:

- the assumptions about HAQ change on biological DMARDs
- the equation converting HAQ to health-related quality of life – in particular whether negative quality of life scores can be allowed
- the assumed time between treatments for comparisons involving rituximab
- the inclusion of adverse event costs for biological DMARDs made little difference to the results.

Issues for consideration

Clinical effectiveness evidence

There are limited clinical effectiveness data available on the sequential use of TNF inhibitors, the data available for the TNF inhibitors are mainly from uncontrolled studies, and from small patient populations. Limited data are available considering the effectiveness of conventional DMARDs used after the failure of TNF inhibitors.

- Does the Committee consider that the clinical effectiveness of the technologies in comparison with conventional DMARDs or other biological DMARDs has been demonstrated?

- Can the TNF inhibitors be considered as a group with the same or similar clinical effectiveness?

Effectiveness estimates in the economic models

Different methods are used to incorporate clinical effectiveness data into the economic models. Methods include the use of mixed treatment comparisons, indirect comparisons and the use of data from single trial arms. The estimates of effectiveness of conventional DMARDs are derived from a range of

sources, including registry data, placebo-controlled clinical trials, and from trials of early RA (with adjustment in efficacy).

- Given the available clinical effectiveness data, what does the Committee consider to be the most appropriate method of incorporating this into the economic models?

- What does the Committee consider to be an appropriate estimate and source of data for the effectiveness of conventional DMARDs?

Treatment sequences

The submitted economic models include a range of treatment sequences and comparisons. What is the most appropriate treatment sequence and comparator at this point in the care pathway?

Response criteria and defining the effect of treatment

Current guidance in TA130 defines response to treatment as improvement in the DAS28 score by >1.2. Not all economic models have included a response criterion, while others based on available clinical trial data, have used either ACR or have mapped ACR to EULAR response to define response to treatment and continuation of treatment.

In addition the models use a variety of outcomes data for example some models base the initial treatment response on HAQ score change (either absolute change or a multiplier), others include ACR response mapped to change in HAQ score, while another includes ACR response, mapped to EULAR response mapped to HAQ score. The BSR report in their submission that HAQ score does not adequately capture the clinical response following treatment with a TNF inhibitor in those with significant disability because of the irreversible joint damage associated with RA.

- What is the most appropriate outcome for use in the economic modelling?
- Is it appropriate to include a response criterion?

Assumptions about underlying disease progression while on treatment

The economic models incorporate a variety of assumptions and estimates about the rate of underlying disease progression (measured in the economic models as changes in HAQ score over time) while on biological DMARDs, conventional DMARDs and palliation.

- What does the Committee consider to be the most appropriate estimates?
- Does the Committee consider that it is appropriate to assume that biologic DMARDs delay disease progression more so than conventional DMARDs?
- Is it appropriate to assume disease progression worsens, remains constant or improves while on treatment with biological DMARDs?
- Does the Committee consider that the evidence supports an assumption that there may be differences in the rate of underlying disease progression between the different biological DMARDs?

Assumptions about administration

What does the Committee consider to be the most appropriate estimates and sources for the cost of administration of the biological DMARDs?

- Is it appropriate to use different estimates of cost for the administration of different intravenous biological DMARDs?
- Is it appropriate to assume wastage of infliximab or infliximab vial optimisation?
- Is it appropriate to assume that the cost of administering intravenous biological DMARDs also incorporates the costs of pre-medication and monitoring, including those of any concurrent conventional DMARDs?

Subgroup analyses

Limited evidence has been identified on differential clinical effectiveness of a second TNF inhibitor based on the reason for withdrawing the first. Any evidence suggesting statistically significant differences come from uncontrolled studies.

- Does the Committee consider the evidence shows differences in clinical and cost effectiveness based on reason for withdrawing the first TNF inhibitor?

A subgroup analysis suggests that there may be a greater treatment response in people who are either rheumatoid factor or anti-CCP positive than in those who were both rheumatoid factor and anti-CCP negative.

- Does the Committee consider the evidence shows differences in clinical and cost effectiveness based on auto-antibody status?

Rituximab retreatment schedules

The time between rituximab retreatment is an important driver of the results of the economic modelling. Current NICE guidance TA126 on rituximab allows retreatment no more than six monthly. In some of the economic models the dosing frequency has been modelled as every 8.7 months, while others use a 6-month dosing schedule.

- What is the most appropriate dosing interval for rituximab?

Infliximab dose escalation

The marketing authorisation for infliximab allows dose escalation or increased frequency of dosing if there is an inadequate response to treatment or a reduction in treatment effect. Infliximab dose escalation is not recommended by NICE in TA130. The Bristol-Myers Squibb model allows dose escalation which increases the cost of the 'basket' of TNF inhibitors.

- Does the Committee consider dose escalation of infliximab appropriate?

Equality and diversity

No equality and diversity issues were identified in the scoping of this appraisal.

Ongoing research

There are several phase IV trials of TNF inhibitors in RA that are ongoing or about to start. These include:

Rituximab trials	
REFLEX (WA17042) Open Label Extension WA17531	Patients with active, seropositive and seronegative RA responding inadequately to TNF inhibitors (TNF-IR)
MIRROR (WA17044)	Patients with active, seropositive and seronegative RA responding inadequately to MTX (MTX-IR and TNF-IR)
SUNRISE (U3384g)	Patients with active, seropositive and seronegative RA responding inadequately to TNF inhibitors (TNF-IR)
DANCER (WA17043) Week 104 CSR And Open Label Extension WA16855	Patients with active, seropositive and seronegative RA responding inadequately to MTX (MTX-IR and TNF-IR)
WA16291 and Open Label Extension WA16855	Patients with active seropositive RA responding inadequately to MTX (MTX-IR and TNF-IR)
Abatacept trials	
ATTAIN LTE	Patients with active rheumatoid arthritis who inadequately responded to anti-TNF therapy.
Infliximab trials	
RESTART (C0168Z05)	Patients with active rheumatoid arthritis who inadequately responded to etanercept or adalimumab.

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Appendix A: Sources of evidence considered in the preparation of the overview

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

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

B Submissions or statements were received from the following organisations:

Manufacturers/sponsors

Roche Products
Schering-Plough
Bristol-Myers Squibb Pharmaceuticals
Wyeth Pharmaceuticals
Abbott Laboratories

Professional/specialist, patient/carer and other groups:

Arthritis and Musculoskeletal Alliance
British Health Professionals in Rheumatology
British Society for Rheumatology
National Rheumatoid Arthritis Society
Royal College of Nursing
Royal College of Physicians

C Additional references used:

Technology Appraisal No.130, October 2007, Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. Superseded technology appraisal No. 36. Expected review date September 2010.