NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to provide:

- clarification on the literature searches undertaken
- a reason why a treatment sequence was not used that included a second biologic agent or rituximab
- clarification on whether the inclusion of trials on rituximab and tocilizumab would help to complete the network meta-analysis
- clarification on the relationship between an increase in the dosage of infliximab and efficacy in the model, and whether weight-based dosing is assumed for infliximab
- clarification on differences in the distribution for 'time on treatment' for patients whose disease responds to treatment, Health Assessment Questionnaire (HAQ) changes from baseline and serious adverse events
- clarification on differences between abatacept and infliximab observed within the ATTEST trial
- clarification on the manufacturer's mixed treatment comparison
- the cost-effectiveness results presented incrementally
- a rationale for assuming that serious events are not associated with cost implications
- clarification on the modelling within the economic model.

Licensed indication

Abatacept in combination with methotrexate (Orencia, Bristol-Myers Squibb and Otsuka Pharmaceuticals) is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults whose disease responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate or a TNF-α inhibitor.

This single technology appraisal relates only to treatment following inadequate response to one or more non-biological (conventional) DMARDs including methotrexate.

Key issues for consideration

Clinical effectiveness

- Is there sufficient evidence that abatacept plus methotrexate is clinically effective compared with conventional DMARDs plus methotrexate or biologics (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab) plus methotrexate?
- The manufacturer's submission focuses on a population of people for whom subcutaneous injections are not suitable. Is it appropriate to focus on this population? Is the manufacturer's explanation of those to be included in this population justifiable? What drives the decision about whether subcutaneous or intravenous agents are given in clinical practice?
- The population in the included trials had received on average fewer than two DMARDs before treatment with abatacept. Was this population representative of patients in the UK whose rheumatoid arthritis had failed to respond to conventional DMARDs?
- The manufacturer considered a change in HAQ score of at least 0.3 from baseline as a criterion for a response (and therefore for continuing treatment). Given that the reduction in HAQ score with methotrexate alone

was estimated to be 0.27, is a 0.3 change in HAQ score clinically meaningful?

- The manufacturer assumed that while receiving and responding to a biologic DMARD the HAQ score would remain constant, and when stopping treatment it would return to the initial HAQ score (that is, the HAQ score would show no deterioration). Are these assumptions appropriate?

Cost effectiveness

- In the manufacturer's economic model one biologic DMARD was given and, if discontinued, a sequence of treatment with conventional DMARDs began. Does the design of the economic model reflect UK clinical practice? What are the implications for the cost effectiveness of abatacept?
- No vial sharing (for any treatments) was assumed in the manufacturer's base-case analyses. The manufacturer's sensitivity analysis, which incorporated vial sharing, resulted in a substantial increase in the incremental cost-effectiveness ratio (ICER). Is it appropriate to assume no vial sharing?
- No dose escalation (with abatacept) was assumed in the manufacturer's base-case analyses. The manufacturer's sensitivity analysis, which incorporated dose escalation with abatacept, resulted in a substantial increase in the ICER. Is it appropriate to assume no dose escalation for abatacept?
- Is it appropriate to assume an administration time of 30 minutes for abatacept and 2−3 hours for infliximab?
- The manufacturer used change in HAQ score, rather than Disease Activity Score (DAS), to determine a number of factors throughout the model, such as utility, cost and treatment continuation. What are the implications of this in the economic modelling?
- Is it appropriate to assume that a serious adverse event is only experienced within the initial 6 months of treatment?

1 Decision problem

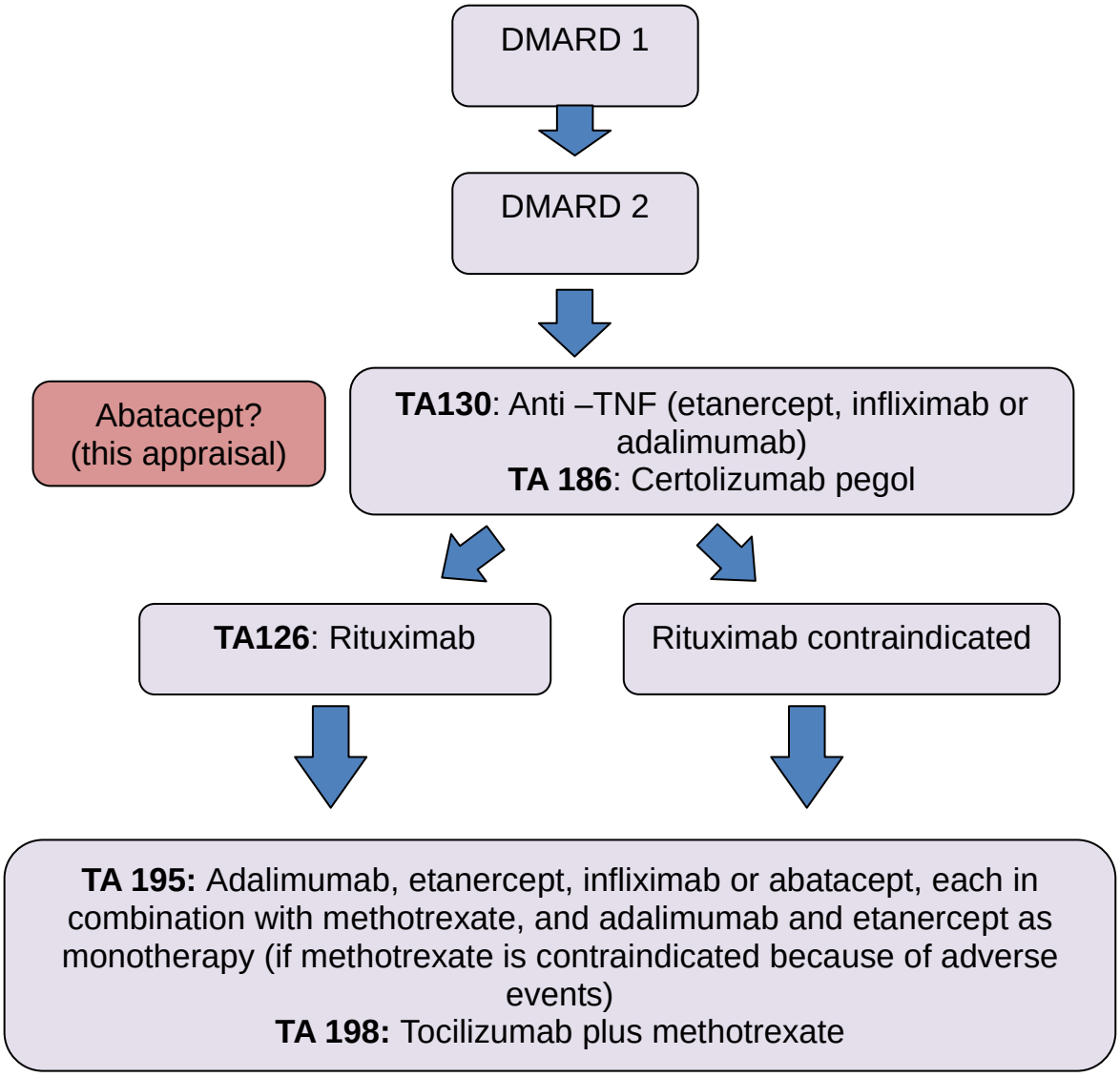
1.1 Decision problem approach in the manufacturer's submission

Population	Adults whose rheumatoid arthritis has had an inadequate response to one or more conventional DMARDs including methotrexate
Intervention	Abatacept 500, 750, or 1000 mg/day, in combination with methotrexate
Comparators	• Conventional DMARDs • Infliximab
Outcomes	• Disease activity • Physical function • Joint damage • Pain • Mortality • Fatigue • Extra-articular manifestations of disease • Adverse effects of treatment • Health-related quality of life (HRQoL).
Economic evaluation	The cost effectiveness of abatacept is expressed in terms of incremental cost per quality-adjusted life year (QALY). There is a lifetime time horizon for estimating clinical and cost effectiveness. Costs are considered from the perspective of the NHS and of personal and social services.
Other considerations	No subgroup analyses were conducted.

The decision problem for this appraisal concerns the use of abatacept in adults whose rheumatoid arthritis has responded inadequately to previous therapy with one or more DMARDs including methotrexate. The marketing authorisation also includes the use of abatacept in adults whose rheumatoid arthritis has responded inadequately to a TNF-α inhibitor. The latter indication

is covered 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). Figure 1 illustrates relevant published NICE technology appraisal guidance.

Figure 1: Relevant NICE guidance



Abatacept in combination with methotrexate is recommended in ‘Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of

rheumatoid arthritis after the failure of a TNF inhibitor' (NICE technology guidance 195), as a treatment option for adults with severe active rheumatoid arthritis who have had an inadequate response to, or are intolerant 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. Furthermore, treatment with 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.

1.2 Evidence Review Group comments

1.2.1 Population

The ERG stated that the focus of the manufacturer's submission focused on the population of people for whom self-administration of subcutaneously injected biological agents is inappropriate. The manufacturer considered that there are approximately 10% of people eligible for a biologic DMARD who would not be able to receive DMARDs subcutaneously because of an inability to self-administer the injections (for example, because they have a needle phobia or difficulty handling needles). The ERG noted that, in practice, assistance in administering subcutaneously injected DMARDs may be provided at home. Therefore, the population for whom these DMARDs are inappropriate may be smaller than that stated by the manufacturer. In addition, the ERG noted that the clinical evidence submitted by the manufacturer did not exclude people for whom self-administration of subcutaneously injected biological agents was not appropriate.

The ERG stated that the populations included in the randomised controlled trials (RCTs) used in the manufacturer's submission differed from the patient population which the ERG's clinical advisers would consider eligible for

treatment with abatacept. The ERG noted that the populations in the trials had a shorter duration of rheumatoid arthritis and had previously received an average of fewer than two DMARDs. The ERG noted that this contrasts with current standard UK clinical practice, where three or four DMARDs are typically used before initiating biological therapy. The ERG stated that this is likely to lead to more favourable results of treatment with abatacept in the clinical trials compared with treatment with abatacept in UK clinical practice.

1.2.2 Intervention

Abatacept is a selective modulator of the T lymphocyte activation pathway. It is administered as an intravenous infusion in combination with methotrexate. Methotrexate is an antimetabolite, which competitively inhibits the enzyme dihydrofolate reductase; it is administered orally as a tablet.

1.2.3 Comparators

The manufacturer's submission focuses on conventional DMARDs and infliximab as comparators. The rationale given by the manufacturer for choosing infliximab for this comparison is that the use of abatacept in clinical practice would be limited to people with rheumatoid arthritis for whom subcutaneous treatments are inappropriate.

1.2.4 Outcomes

The ERG noted that the outcomes included in the manufacturer's submission are broadly similar to those listed in the scope. However, the ERG stated that no data were available on extra-articular manifestations of disease and that there were limited data on outcomes that could be important to patients (for example, pain, fatigue, HRQoL).

The ERG noted that with the exception of joint damage, the outcomes included in the submission are generally subjective. The blinding of patients, care providers and outcomes assessors to treatment allocation is therefore crucial.

1.2.5 Economic evaluation

The manufacturer provided a cost-utility analysis to estimate the cost effectiveness of abatacept compared with conventional DMARDs and biologic DMARDs for the treatment of rheumatoid arthritis after the failure of conventional DMARDs. The ERG considered that the design of the model was complex and had numerous errors. Further details can be found in section 3.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer's submission presented clinical effectiveness data from four RCTs. All the RCTs were multicentre studies, double-blind and placebo-controlled. Three trials were of 1 years duration (Kremer Phase 2b, AIM and ATTEST studies), and one trial was of 4 months' duration (IM101-119). In all trials abatacept was infused intravenously over a 30-minute period on days 1, 15 and 29 or 30, and 28 days or monthly thereafter. All groups also received a once-weekly dose of methotrexate.

The Kremer Phase 2b RCT enrolled 339 adults aged between 17 and 83 years with rheumatoid arthritis (diagnosed using the American College of Rheumatology criteria) whose disease had had an inadequate response to methotrexate for at least 6 months. Adults were randomly assigned to one of three study arms: abatacept 2 mg/kg or 10 mg/kg or matching placebo. Because the licensed dose of abatacept is 10 mg/kg, the submission did not focus on the lower dose of 2 mg/kg of abatacept and no results for this arm will be presented in this document.

The Abatacept in Inadequate Responders to Methotrexate (AIM) study was a phase III RCT that enrolled 652 adults with rheumatoid arthritis (diagnosed using the American College of Rheumatology criteria) whose disease had had

an inadequate response to methotrexate for at least 3 months. Adults were randomly assigned to one of two study arms: 10 mg/kg of abatacept or matching placebo.

The Abatacept or Infliximab versus Placebo, a Trial for Tolerability, Efficiency and Safety in Treating Rheumatoid Arthritis (ATTEST) study, was a phase III RCT that enrolled 431 adults with rheumatoid arthritis (diagnosed using the American College of Rheumatology criteria) whose disease had had an inadequate response to methotrexate for at least 3 months. Adults were randomly assigned to one of three study arms: 10 mg/kg of abatacept or 3 mg/kg of infliximab intravenously infused over a 2-hour period on days 1, 15, 43 and 85 and then every 56 days, or matching placebo.

Study IM101-119 was a phase III RCT that enrolled 50 adults with rheumatoid arthritis (diagnosed using DAS28). Adults were randomly assigned to one of two study arms: 10 mg/kg of abatacept or matching placebo.

The common primary endpoint in the Kremer Phase 2b and AIM studies was the ACR 20 response rate to treatment at 6 months as defined by the American College of Rheumatology (ACR). An ACR 20/50/70 response is defined as a 20%/50%/70% improvement in tender and swollen joint counts and the same level of improvement in three of the following variables: patient and physician global assessments, pain, patient assessment of functional ability (HAQ) and acute phase reactants. ACR 50 and ACR 70 responses at 6 months and 1 year were included as secondary outcome measures in the Kremer Phase 2b, AIM and ATTEST studies. The AIM study also listed change from baseline in radiographic progression of joint erosions and improvement of ≥ 0.3 in Health Assessment Questionnaire Disability Index (HAQ-DI) as primary outcome measures. The primary endpoint in the ATTEST study was the reduction in DAS28. The primary outcome measure in study IM101-119 was the change in wrist synovitis score at 4 months.

Secondary outcomes in the studies include: physical function measured using either the HAQ-DI or the Modified Health Assessment Questionnaire (MHAQ), HRQoL as measured by SF-26 scores, global assessment scales and numbers of adverse events.

The manufacturer's submission also presented four non-RCT studies, of which three were long-term extensions of the Kremer Phase 2b, AIM and ATTEST studies, and one was an integrated analysis of safety data from a number of studies, including the Kremer Phase 2b, AIM, ATTEST studies.

Study populations

Baseline patient and disease characteristics were generally similar across the treatment arms in the included RCTS. However, the IM101-119 differed from the AIM, ATTEST and Kremer Phase 2b studies in that the mean time since first diagnosis was around 2.25 years in the IM101-119 study compared with the three other studies. Similarly, the mean numbers of swollen and tender joints per treatment group were 8−11 and approximately 13 in the IM101-119 study, whereas in the three other studies participants had a mean of 20−22 swollen joints and 28−32 tender joints at randomisation. See pages 81−4 and 123 of the manufacturer's submission, and pages 55−7 of the ERG report for further details.

Results from the studies

Data on DAS28 scores at 6 months and 1 year were available for the AIM, ATTEST and Kremer Phase 2b studies (see table 1).

Table 1 Relative risk (95% CI) related to DAS28 score at 6 months and 1 year

	AIM	Kremer Phase 2b	ATTEST		
	Abatacept 10 mg/kg + MTX versus placebo	Abatacept 10 mg/kg + MTX versus placebo	Abatacept 10 mg/kg + MTX versus placebo	Infliximab 3 mg/kg + MTX versus placebo	Abatacept 10 mg/kg versus infliximab
6 months					
Low disease activity (DAS28 ≤ 3.2)	5.73 (2.70, 12.14)	2.07 (1.35, 3.18)	1.92 (1.01, 3.64)	2.38 (1.28, 4.41)	0.81 (0.53, 1.22)
Remission (DAS28 <2.6)	17.12 (2.36, 123.94)	2.82 (1.49, 5.36)	3.85 (1.16, 12.8)	4.36 (1.33, 14.2)	0.88 (0.48, 1.62)
1 year					
Low disease activity (DAS28 ≤ 3.2)	7.18 (3.41, 15.12)	2.27 (1.54, 3.34)	–	–	1.51 (1.05, 2.18)
Remission (DAS28 <2.6)	7.93 (2.93, 21.43)	3.45 (1.91, 6.23)			1.47 (0.86, 2.52)
CI, confidence interval; DAS, Disease Activity Score; MTX, methotrexate;					

In the three studies, relative to placebo, abatacept was associated with significantly higher likelihoods of having low disease activity (a positive value indicates higher likelihood of low disease activity) and of achieving remission (higher value indicates higher likelihood of achieving remission) at 6 months, as was infliximab in the ATTEST study. At 12 months, in the Kremer phase 2b and AIM studies, relative to placebo, abatacept was still associated with statistically significant greater likelihoods of low disease activity or remission. In the ATTEST study, no comparison with placebo was available at 12 months, and the study was not powered to compare abatacept with infliximab.

Physical function, using measures from the HAQ, were presented in the AIM, ATTEST and Kremer Phase 2b studies. The threshold for defining a clinically

meaningful improvement was set at 0.22 in the Kremer Phase 2b study and at 0.3 in the AIM and ATTEST studies.

Table 2 Results related to HAQ-DI score at 6 months and 1 year

	AIM	Kremer Phase 2b	ATTEST		
	Abatacept 10 mg/kg + MTX	**Abatacept 10 mg/kg + MTX**	**Abatacept 10 mg/kg + MTX**	**Infliximab 3 mg/kg + MTX**	**Abatacept 10 mg/kg versus infliximab**
6 months					
HAQ-DI score mean CFB (mean difference versus placebo) (95% CI)	-0.19 (-0.29, -0.10) p < 0.001	-0.28 (-0.44, -0.12) p < 0.05	-0.38 (-0.53, -0.23) p < 0.001	-0.30 (-0.45, -0.15) p < 0.001	–
Clinically meaningful HAQ-DI response (>0.3) (RR versus placebo) (95% CI)	1.34 (1.14, 1.58)	1.73 (1.29, 2.33)	1.50 (1.16, 1.94)	1.44 (1.11, 1.86)	1.05 (0.88, 1.25)
1 year					
HAQ-DI score mean CFB (mean difference versus placebo) (95% CI)	-0.29 (-0.38, -0.19) p < 0.001	-0.36 (-0.52, -0.21) P < 0.001	–	–	-0.08 (-0.22, 0.06)
Clinically meaningful HAQ-DI response (>0.3) (RR versus placebo) (95% CI)	1.61 (1.35, 1.94)	1.79 (1.27, 2.52)			-0.09 (0.90, 1.33)
CFB, change from baseline; CI, confidence interval; HAQ-DI, Health Assessment Questionnaire Disability Index , MTX, methotrexate; RR, relative risk					

All three studies reported at 6 months that abatacept was associated with a statistically significant greater reduction in mean HAQ score from baseline relative to placebo (a reduction in mean HAQ score indicates an improvement). Significant differences relative to placebo were also seen at 1 year in the Kremer Phase 2b and AIM studies. The ATTEST study reported at 6 months that infliximab was associated with a statistically significantly greater reduction in mean HAQ score from baseline relative to placebo. No significant differences were reported between abatacept and infliximab at 1 year

In both the Kremer Phase 2b and AIM studies, the likelihood of achieving a clinically meaningful improvement in physical function was significantly higher in the abatacept group compared with the placebo group at 6 months and 1 year (a positive value indicates an improvement). The ATTEST study reported significantly more patients in the abatacept and infliximab groups, compared with the placebo group, achieving a clinically meaningful improvement in physical function at 6 months or 1 year. No significant difference between the abatacept group and the infliximab group was achieved at 6 months or 1 year.

The outcome of ACR responses at 6 months and 1 year were reported in all three trials. At both 6 months and 1 year, abatacept 10 mg/kg and infliximab were associated with a significantly higher likelihood of achieving an ACR 20, ACR 50 or ACR 70 response compared with placebo. There were no reported statistically significant differences between the abatacept and infliximab groups in ACR 20, ACR 50 or ACR 70, at 6 months or 1 year. See pages 100-134 of the manufacturer's submission for further details of ACR responses and of all other secondary outcomes.

Health related quality of life

Data on HRQoL measured using the SF-36 at 6 months and 1 year were collected in the AIM, ATTEST and Kremer Phase 2b studies. In the Kremer Phase 2b and AIM studies, abatacept was associated with statistically significant improvements from baseline relative to placebo in the physical and mental components of the SF-36 at 6 months. The ATTEST study reported significant improvements in the physical and mental components of the SF-36 in both the abatacept and infliximab groups compared with the placebo group. At 6 months and 1 year, abatacept was associated with greater improvements from baseline compared with infliximab in both components. Statistical significance was achieved in the physical component of SF-36 at 1 year. See pages 114−7 of the manufacturer's submission for further details.

Adverse events

Data on adverse events were reported in the ATTEST, Kremer Phase 2b, AIM and IM101-119 studies. In three studies, abatacept compared with placebo at 6 months or 1 year was not associated with a significantly higher rate of serious adverse events. The ATTEST study reported that abatacept compared with infliximab at 1 year was associated with lower serious adverse events (9.6% versus 18.2%), lower discontinuation rates because of adverse events (3.2% versus 7.3%) or serious adverse events (2.6% versus 3.6%), and lower rate of serious infections (1.9% versus 8.5%) and acute infusion events (7.1% versus 24.8%). Longer term data incorporated into the safety analyses of abatacept indicated that the incidence of serious adverse events did not increase over time.

See pages 125−6 and 196−211 of the manufacturer's submission for further details and results.

Manufacturer's pairwise meta-analyses

The manufacturer carried out a series of pairwise meta-analyses using data from the Kremer phase 2b, AIM and ATTEST studies to compare the efficacy

of abatacept plus methotrexate with placebo plus methotrexate. The outcomes included in the analyses were change from baseline in HAQ score, change in baseline in DAS28, DAS28 improvement and ACR response rate.

The manufacturer's fixed effects meta-analyses reported a mean reduction (improvement) from baseline in HAQ score for the group receiving abatacept plus methotrexate compared with the group receiving placebo plus methotrexate at 24 or 26 weeks (-0.2524, 95% confidence interval [CI]: -0.3253 to -0.1794) and 52 weeks (-0.3105, 95% CI: -0.3934 to -0.2275). A mean reduction (improvement) from baseline in DAS28 score was reported in the group receiving abatacept plus methotrexate compared with the group receiving placebo plus methotrexate at 24 or 28 weeks (-1.123, 95% CI -1.3275 to -0.9186). See pages 137−145 of the manufacturer's submission for further details and results.

Manufacturer's network meta-analyses

The manufacturer also carried out a mixed treatment comparison to evaluate the efficacy of abatacept plus methotrexate compared with five biologic DMARDs (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) plus methotrexate, and placebo. The comparisons were indirect comparisons via placebo, with the exception of abatacept versus infliximab, which was a direct comparison. Eleven RCTs were used to inform the mixed treatment comparison. Three of the RCTs were of abatacept, of which one (ATTEST) compared abatacept with infliximab and two compared abatacept with placebo (AIM and Kremer Phase 2b); two were of adalimumab; two were of certolizumab pegol; two were of etanercept; one was of golimumab and one compared infliximab with placebo. The mixed treatment comparison focused on the change from baseline in the HAQ score at 24/26 weeks.

Table 3 Differences in HAQ-DI change from baseline at 24 or 26 weeks compared with abatacept plus methotrexate

Treatment effect relative to abatacept + MTX	Difference between HAQ changes	2.5% CrL	97.5% CrL
Placebo + MTX	-0.30	-0.42	-0.16
Adalimumab + MTX	0.03	-0.17	0.26
Certolizumab pegol + MTX	0.09	-0.11	0.29
Etanercept + MTX	-0.02	-0.25	0.22
Golimumab + MTX	0.04	-0.23	0.32
Infliximab + MTX	-0.11	-0.30	0.10

CrL, credibility limit

The mixed treatment comparison indicated that abatacept plus methotrexate was more efficacious than placebo plus methotrexate (negative value indicates benefit with abatacept), and was expected to display efficacy comparable with that of most other biologic DMARDs, with differences ranging from -0.11 compared with infliximab to 0.09 compared with certolizumab pegol. The absolute change from baseline for biological agents in combination with methotrexate ranged from -0.46 (infliximab) to 0.65 (certolizumab pegol). See pages 146−175 of the manufacturer's submission for further details and results.

2.2 Evidence Review Group comments

The ERG reviewed the literature search strategy included in the manufacturer's submission. The ERG noted that the manufacturer's evidence base for the assessment of clinical effectiveness may not be complete: because the Medline search strategy failed to identify at least one relevant publication, the literature search failed to search some relevant databases and the searches were restricted to English publications. The ERG noted that

although it was unlikely that any major European or North American trials were not identified, two relevant studies (one Korean and one Japanese trial) were not included in the manufacturer's submission.

The ERG stated that the presentation of results from the included studies displayed a number of inconsistencies and omissions, such as failing to present all the relevant data, which were available in the public domain. Where data presented in the manufacturer's submission differed from published data, explanations were generally not provided.

The ERG noted that the populations in the included studies had a shorter duration of rheumatoid arthritis, and had previously taken fewer conventional DMARDs than is current standard UK clinical practice before the initiation of biological therapy. Therefore, although the submitted evidence largely reflects the decision problem defined in the final scope, the difference between the populations is such that less benefit may be gained from abatacept in UK clinical practice compared with the study populations.

It was noted that the studies that were identified and included in the review of clinical effectiveness measured outcomes that were appropriate and clinically relevant, including the outcomes listed in the final scope. Moreover, the studies were considered to be of reasonable methodological quality, although they incorporated some risk of bias because of differential discontinuation rates in placebo in people randomised to placebo and active treatment, and the methods used to deal with incomplete data and non-adherence to study therapy.

ERG meta-analyses

The ERG undertook meta-analyses to compare the efficacy of abatacept plus methotrexate with placebo plus methotrexate. The analyses indicated that, at 6 months and 1 year, abatacept compared with placebo was associated with significantly increased likelihoods of an improved DAS28 score and of

achieving DAS28-defined low disease activity and remission. The analyses also indicated that at 6 months and 1 year, compared with placebo, abatacept was associated with a significantly increased likelihood of achieving a meaningful HAQ response. See pages 62, 65 and 68 of the ERG report for further details and results.

2.3 Statements from professional/patient groups and nominated experts

The patient experts and clinical specialists stated that there is good-quality evidence to suggest that abatacept is effective with relatively low toxicity. There is limited use of abatacept in current clinical practice, but there is some anecdotal evidence that also suggests abatacept is well tolerated and effective. All the patient experts and clinical specialists stated that it was important to provide people with rheumatoid arthritis with as many treatment options as possible, particularly as the mean age for diagnosis of rheumatoid arthritis is relatively low. Because abatacept has a different mechanism of action from other biologic DMARDs, it may be particularly effective for some people; however, there is no evidence to suggest which people may benefit the most from abatacept compared with other biologic DMARDs.

It was noted that, compared with infliximab, abatacept has a shorter infusion times (30 minutes compared with 2 hours for infliximab) and that no pre-medication is required with abatacept (unlike with infliximab). Some clinical specialists noted that should abatacept be recommended then additional resources for extra infusions may be required; however, it may be possible that the infusions could eventually be given at home rather than at specialist centres.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer conducted a systematic review of economic evaluations of abatacept in combination with methotrexate given to people whose moderate to severe active rheumatoid arthritis had had an inadequate response, or intolerance to, methotrexate. Fourteen economic evaluations met the inclusion criteria for the systematic review; however, none was considered to address the decision problem of this appraisal.

The manufacturer developed a de novo economic model (summarised in pages 228–96 of the manufacturer's submission), which is a patient-level simulation. When entering the model an individual patient is assigned baseline characteristics (that is, age, gender, weight and HAQ score). Each patient is allocated to one of three treatment arms: abatacept plus methotrexate, biologic DMARD plus methotrexate (that is, adalimumab, certolizumab pegol, etanercept, golimumab or infliximab), or conventional DMARD. The manufacturer simulated 8000 patients and considered that this provided stable results from the model. The model used a lifetime horizon.

The economic model has three distinct phases:

- An initial 6-month phase (trial period): patients are allocated to treatment (as described above and on page 247 of the manufacturer's submission), and remain on this unless they experience a lack of response (defined as an HAQ change from baseline of less than 0.3), serious adverse events, or death.

- Patients who remain on their allocated treatment enter the long-term maintenance phase. In this phase patients remain on their allocated treatment while their rheumatoid arthritis is responding to treatment (defined as an HAQ change from baseline of greater than 0.3). Patients

leave this phase if there is a lack of clinically relevant HAQ response (that is, if the treatment becomes ineffective), or death.

- Patients who discontinue their allocated treatment (either in the initial phase or the long-term phase) enter the next phase of a sequence of conventional DMARDs. Regardless of their initial treatment arm, patients receive the following sequence of conventional DMARDs: leflunomide, gold, azathioprine, ciclosporin, penicillamine, palliative care. Treatments are given while there is an HAQ response and no serious adverse events. The sequence is followed until the patient dies, which can happen at any time in the model. The risk of death for modelled patients depends on age, sex and HAQ score.

The patients simulated in the model were assumed to have a mean age of 51.5 years with a standard deviation of 12.90; 77.8% of people were assumed to be female. The mean baseline HAQ was assumed to have a mean of 1.71 with a standard deviation of 0.70.

Serious adverse events were assumed to occur in the first 6 months of taking each treatment. The rate at which serious adverse events occurred for each treatment was taken from a mixed treatment comparison (page 253 of the manufacturer's submission) and the rates for abatacept, etanercept and infliximab are summarised in the ERG report (table 32, page 99). If a serious adverse event was experienced then treatment was discontinued and the HAQ score remained at the value which the patient began treatment. No costs or utility decrements associated with adverse events were incorporated into the model.

During the initial 6-month treatment phase, treatment was continued if there was a reduction in HAQ score from baseline of at least 0.3. The manufacturer stated that this figure was derived from the endpoints of the AIM and ATTEST trials. The estimated improvements in HAQ were taken from the indirect

comparison (reported in the clinical effectiveness section and in table B39 on page 170 of the manufacturer's submission). It was assumed that all changes in HAQ would occur gradually with a linear change in HAQ over 3 months until the score was achieved. If patients did not experience an HAQ reduction of 0.3, treatment was discontinued and the HAQ score was assumed to return immediately to the one that the patient had when treatment began.

For patients continuing into the treatment maintenance phase, time to discontinuation was assumed to be equal for all biologic DMARDs (that is, a patient would discontinue abatacept treatment at the same time as a patient would discontinue etanercept treatment). The time to discontinuation on biologic DMARDs was sampled from a Weibull distribution with a mean value of 8.82 years and median value of 4.21 years (see page 252 of the manufacturer's submission).

It was assumed that while people received biologic DMARDs their HAQ score would remain constant. It was also assumed that while people received conventional DMARDs their HAQ score would increase by 0.045 each year, and while receiving palliative care their HAQ score would increase by 0.06 each year. Three months before the end of each long-term maintenance phase, it was assumed that there would be an HAQ reduction for each patient. It was assumed that the HAQ scores of people receiving biologic DMARDs would be the same at the end of treatment as at the start of treatment; and that the HAQ scores of people receiving conventional DMARDs and palliative care would be higher at the end of treatment than at the start of treatment because of the annual increase in HAQ score (see figure 5 on page 103 of the ERG report for a schematic).

Death was assumed to be influenced by HAQ score and could occur at any phase of the model. The mortality hazard ratio increased by 1.33 (95% CI: 1.10 to1.61) for each unit increase in HAQ score.

The costs in the model were taken from UK sources and publications identified in the systematic review and were based on values from 2009. Costs associated with biologic DMARDs were taken from the British national formulary 60. Costs of conventional DMARDs and palliative care were incorporated into costs associated with disease and were not costed individually. Dosing of the biologic DMARDs was defined in accordance with each individual summary of product characteristics. Abatacept infusions were given on days 1, 15 and 29 and thereafter every 4 weeks. They were weight-based: patients weighing less than 60 kg received two vials (£484.34), patients weighing between 60 kg and 100 kg received three vials (£726.51) and patients weighing over 100 kg received four vials (£968.68). Vial sharing in the base case was not assumed. It was assumed that infliximab and etanercept could be dose escalated: 29% of patients receiving infliximab increased their dose to 5 mg/kg at 1 year and 1% of patients receiving etanercept increased their dose to 37.5 mg at 1 year. No dose escalation with abatacept was assumed. The costs and dosing regimens of the other biologic DMARDs are detailed in table B75 on pages 254–5 of the manufacturer's submission.

Administration costs for the biologics administered with intravenous infusions were taken from 'Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor' (NICE technology guidance 195) and the costs for subcutaneous injections from the Personal Social Services Research Unit (PSSRU). Details of the unit cost, dose description and route, and cost of administration are provided in table 4 below.

Table 4 Unit and administration costs

Treatment	Unit cost (2010) (£)	Dose description (SmPc)	Route	Cost per administration (2010) (£)
Abatacept	242 (250 mg)	500−1000 mg (10 mg/kg) weeks 0,2,4, thereafter every 4 weeks	IV (30 min)	158
Rituximab	175 (100 mg)	1000 mg weeks 0 and 2, thereafter not more frequent than every 6 months	–	–
Etanercept	89 (25 mg)	25 mg twice weekly	sc	30
Adalimumab	358 (40 mg)	40 mg every other week	sc	30
Infliximab	420 (100 mg)	3 mg/kg weeks 0, 2 and 6, thereafter every 8 weeks	IV (2−3 hour)	310
Tocilizumab	102 (80 mg)	8 mg/kg but no lower than 480 mg every 4 weeks	–	–
Certolizumab pegol	358 (200 mg)	400 mg weeks 0, 2 and 4 followed by 200 mg every 2 weeks	sc	30
Golimumab	775 (50 mg)	50 mg every 4 weeks	sc	30
sc, subcutaneous				

Costs associated with rheumatoid arthritis were incorporated into the model by relating a cost to an HAQ score interval (see table 75 on page 255 of the manufacturer's submission). The costs associated with rheumatoid arthritis included costs for hospitalisation, surgical interventions, ambulatory and community care, monitoring, conventional DMARDs and palliative care.

The utility of each individual in the model was assumed to be related to the HAQ score. In the base case, utility was inversely related to the HAQ score using a quadratic approach. Three alternative approaches to deriving utilities from HAQ scores were tested in the sensitivity analyses.

Pairwise and fully incremental results were presented by the manufacturer. Deterministic base-case results are presented in the manufacturer's submission as an all-treatment comparison in table B87 and as comparisons of abatacept, infliximab and conventional DMARDs in table B88. The manufacturer stated that the probabilistic results were similar (see tables B89 and B90 of the manufacturer's submission).

Table 5 PSA results base case

Treatment	Cost	QALY	ICER versus cDMARD	ICER (incremental analysis)
cDMARD	£76,276	4.88	Ref	–
Certolizumab pegol	£103,976	6.16	£21,592	£21,592
Etanercept	£107,653	6.12	£25,361	Dominated
Infliximab	£109,419	5.96	£30,693	Dominated
Adalimumab	£111,922	6.29	£25,359	£64,732
Abatacept	£114,548	6.16	£29,916	Dominated
Golimumab	£115,372	6.25	£28,592	Dominated
*cDMARD, conventional DMARD; *PSA, probabilistic sensitivity analyses.				

Table 6 PSA results base case

Treatment	Cost	QALY	ICER versus cDMARD	ICER (incremental analysis)
cDMARD	£76,276	4.88	Ref	–
Infliximab	£109,419	5.96	£30,693	Extendedly dominated
Abatacept	£114,548	6.16	£29,916	£29,916
cDMARD, conventional DMARD				

When all treatments were compared (that is, for people who could receive subcutaneous interventions), then the manufacturer stated that abatacept was dominated by adalimumab and certolizumab pegol (that is, abatacept was less effective but more costly than adalimumab and certolizumab pegol) (see table 5).

When abatacept, infliximab and conventional DMARDs were compared (that is, for people who could not receive subcutaneous interventions), then infliximab was extendedly dominated (that is, a combination of the other treatments would provide the same health gain at a reduced cost) (see table 6). There were 6.16 QALYs gained with abatacept plus methotrexate compared with 4.88 QALYs gained with conventional DMARDs. Total costs were £114,548 with abatacept plus methotrexate and £76,276 with conventional DMARDs. The ICER was £29,916 per QALY gained for abatacept plus methotrexate compared with conventional DMARDs.

A range of one-way sensitivity analyses was conducted by the manufacturer and reported in tables B91 and B92 in the manufacturer's submission (pages 288-89 of the manufacturer's submission). The results of the sensitivity analyses suggest that reducing the time horizon to 5 years has a large effect on the ICER. Alternative utility mapping and changing the decrease in HAQ required for a person to be classed as a responder have small effects on the ICER.

3.2 Evidence Review Group comments

The ERG considered that the economic model submitted by the manufacturer was relatively complex in its programming and noted a number of concerns. The ERG categorised these concerns as follows: the conceptual model; the population of the model; the internal validity of the model and the probabilistic sensitivity analyses (see pages 111–19 of the ERG report for full details of all the concerns).

With regards to the conceptual model, the ERG considered that the design did not reflect current standard UK practice because it did not allow the use of multiple biologic DMARDs (that is, in the model only one biologic DMARD was given and, if discontinued, the sequence of conventional DMARDs started). The ERG considered that a comparison of abatacept with sequences that could involve multiple biologic DMARDs would be unfavourable to abatacept. Additionally, the ERG noted that sequences containing both infliximab and abatacept had not been included in the manufacturer's submission, and the ERG considered that a multiple infusion strategy could be more cost effective than a single infusion.

The ERG noted that dose escalation with infliximab and etanercept but not abatacept had been included in the base-case analyses. The ERG stated that it was not clear whether, in clinical practice, dose escalation with abatacept may also occur and that this could have been modelled in the manufacturer's submission. The ERG noted the manufacturer's sensitivity analysis where dose escalation was removed from the model and this increased the ICERs for abatacept.

In the base-case analyses, no vial sharing was assumed. The ERG stated that it may be possible that in larger units vial sharing may be possible and that incorporating vial sharing into the model may reflect clinical practice. The ERG noted the manufacturer's sensitivity analysis that incorporated vial sharing and that the ICERs for abatacept increased substantially. The ERG highlighted that no sensitivity analysis incorporating assumptions of vial sharing and no dose escalation had been conducted by the manufacturer.

The HAQ score has been used to determine a number of factors throughout the model, such as utility, costs and treatment continuation. The ERG noted that DAS28 is routinely used in clinical practice and may have been a more useful tool. However, it acknowledged that the mapping of utility values according to HAQ score was used in 'Adalimumab, etanercept, infliximab,

rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor' (NICE technology guidance 195). The ERG noted that a sufficient response for continuing treatment was a change in HAQ score of at least 0.3 from baseline. The ERG highlighted that although this was based on the endpoints of the key trials, an improvement of 0.3 in HAQ score may not be clinically meaningful, and also that the estimated reduction in HAQ score with methotrexate alone was similar at 0.27. The ERG further noted that if a patient's rheumatoid arthritis is considered not to respond to treatment, then it is assumed that the HAQ score will revert back to the score when the treatment was started; this does not account for any worsening of HAQ while on treatment.

The ERG noted concerns regarding the probabilistic sensitivity analysis: specifically that the changes in HAQ score for each treatment had not been included in the analyses (that is, these values were not changed throughout the probabilistic analysis: they were fixed at the midpoint value). The ERG stated that the results from the probabilistic sensitivity analysis conducted by the manufacturer are therefore incorrect and that the confidence interval around the mean probabilistic ICER will be increased.

The rates of serious adverse events were taken from a fixed effect meta-analysis; however, the ERG considered that a random effects method could be more appropriate. Also, no costs or utility decrements were incorporated into the model when people experienced serious adverse events; the ERG considered that because of the lower rate of serious adverse events with abatacept, including these could reduce the ICERs. In addition, adverse events that were not considered to be serious were not incorporated into the model; it was unclear to the ERG what impact this might have on the ICERs. No utility decrements associated with infusions were included in the model and the ERG considered that because infliximab is given less often than abatacept this could potentially increase the ICERs.

The ERG considered that the approximation of costs associated with rheumatoid arthritis with HAQ score was appropriate. However, it considered that the manufacturer may have double counted the cost of joint replacement because costs for this were also included in the costs associated with rheumatoid arthritis. Also, the ERG was concerned that the costs associated with rheumatoid arthritis may also include productivity costs, and as such they would be outside the NICE reference case. The ERG considered that more appropriate costs would be £1120 per HAQ unit, which included costs for joint replacement and hospitalisation.

The ERG highlighted a number of technical concerns about the methodology of the network meta-analysis and calculations used to derive the estimates of effectiveness (and thus influencing how long each treatment is given for). In particular, the ERG had concerns about how missing values had been imputed and how the placebo response across the trials had been used within the analysis. However, the ERG stated that correcting for the concerns gave similar results to those presented in the manufacturer submission's and that this was unlikely to have a large impact on the ICERs.

Additional work undertaken by the ERG

The ERG therefore undertook exploratory sensitivity analyses to investigate the impact of some of the key concerns on the cost-effectiveness estimates of abatacept. The focus of the exploratory analyses was on the comparison of abatacept, infliximab and conventional DMARDs (that is, in a population for whom subcutaneous injections are inappropriate). The ERG re-ran the economic model as submitted by the manufacturer and noted some slight discrepancies in the reported results. The ERG then conducted a number of exploratory sensitivity analyses, as detailed below in table 47 of the ERG report. The ERG noted that the key parameters affecting the ICER was whether vial sharing or dose escalation was assumed.

The ERG then conducted five analyses to incorporate various changes to the parameters that had been identified as important concerns. The analyses were presented as follows:

- ERG 'objective analysis': Arithmetic errors corrected; £1120 costs with rheumatoid arthritis; time of discontinuation for infliximab and abatacept independently sampled; standard deviation of response to treatment set to 0.3; rate of serious adverse events set equal for abatacept and infliximab; dose escalation for infliximab not assumed.
- ERG 'optimistic analysis': ERG objective analysis but with the rate of serious adverse events taken from the manufacturer's submission; HAQ increase required to be a responder increased to 0.5; dose escalation assumed for infliximab but not abatacept.
- ERG 'favourable analysis': ERG objective analysis but with the rate of serious adverse events taken from the manufacturer's submission; HAQ increase required to be a responder increased to 0.5.
- ERG 'pessimistic analysis': ERG objective analysis but vial sharing for infliximab assumed and the utility estimation reported from Bansback et al. used.
- ERG 'hybrid analysis': ERG optimistic and pessimistic scenarios weighted in the ratio of 37:63, and with vial sharing in 63% of cases (taken from NICE technology appraisal 195)

The results for the ERG analyses are contained in table 7.

Table 7 ERG deterministic analyses

Analysis	Treatment	Cost	QALY	ICER versus cDMARD	ICER (inc. analysis)
ERG objective	cDMARD	£35,545	4.48	–	–
	Infliximab	£66,404	5.50	£30,340	£30,340
	Abatacept	£76,737	5.76	£32,255	£39,748
ERG optimistic	cDMARD	£35,657	4.47	–	–
	Infliximab	£66,738	5.51	£30,332	Extendedly Dominated
	Abatacept	£71,499	5.76	£29,661	£29,661
ERG favourable	cDMARD	£35,628	4.48	–	–
	Infliximab	£63,604	5.49	£27,615	£27,615
	Abatacept	£73,441	5.76	£29,552	£36,916
ERG pessimistic	cDMARD	£35,503	4.48	–	–
	Infliximab	£61,066	5.37	£28,611	£28,611
	Abatacept	£76,525	5.62	£36,045	£63,208
ERG hybrid	cDMARD	£35,556	4.48	–	–
	Infliximab	£63,016	5.42	£29,294	£29,294
	Abatacept	£75,322	5.67	£33,519	£49,427
cDMARD, conventional DMARD					

The ERG also conducted probabilistic sensitivity analyses for each of the scenarios. These corrected for the fact that the HAQ score and the rate of serious adverse events were not included in the original probabilistic sensitivity analysis conducted by the manufacturer. The probabilistic results are in table 49 of the ERG report; the ERG noted that the deterministic and probabilistic ICERs were similar.

3.3 Further considerations following premeeting briefing teleconference

The following issues were discussed at the premeeting briefing teleconference:

- It was stated by the clinical lead that DAS28 is routinely used in UK clinical practice when deciding stop and start rules for patients; however, it was not used by the manufacturer in the economic model. It was considered that this was because the mapping of utility values according to HAQ score was used in a recent review of interventions for rheumatoid arthritis conducted by NICE ('Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor' [NICE technology guidance 195]).

- It was noted by the cost-effectiveness lead that the results of the ATTEST study, which included a comparison of abatacept with infliximab, are different from the results presented by the manufacturer in the mixed treatment comparison. It was further noted that the ATTEST study was not powered to detect statistical differences between abatacept and infliximab.

- The clinical lead stated that vial sharing of infliximab is used in UK clinical practice and is permissible according to its marketing authorisation.

- It was noted that NICE is currently appraising golimumab for the treatment of rheumatoid arthritis after failure of previous DMARDs, and that the expected date of issue is June 2011.

- It was noted that the manufacturer's economic model assumes that dose escalation would occur for infliximab and etanercept but not for

abatacept. Dose escalation of infliximab was considered in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 130) and the Appraisal Committee considered that it should not be recommended.

4 Equalities issues

No issues were identified during the scoping of this appraisal.

The manufacturer's submission stated that abatacept is suitable for people who might otherwise fall outside or through the current net of treatment, specifically those who require or reasonably request intravenous infusion, including:

- people who cannot or will not self-administer subcutaneously
- people who require regular monitoring, including those with comorbidities such as advanced heart disease, malignancies, or active infection,
- people who would particularly benefit from regular attendance at a site where staff are available during the administration of treatment.

The manufacturer's submission also noted that treatment of rheumatoid arthritis with anti-TNF agents is associated with an increased risk of reactivation of latent tuberculosis, whereas treatment with abatacept may have a lower propensity to reactivate latent tuberculosis. It also noted that there is a raised prevalence of tuberculosis among ethnic subgroups, and that a person from an ethnic minority group may therefore not receive the full benefit of current treatment options. The manufacturer stated that because abatacept is associated with a reduced risk of reactivation of latent tuberculosis, it may reduce inequity in access to treatment for that subgroup of people.

The ERG noted that people eligible for treatment with biological agents, but for whom subcutaneous self-injection of biological agents would be inappropriate, would currently receive treatment with either rituximab or rituximab delivered intravenously, or with subcutaneous biological agents administered by a healthcare professional. See pages 27−28 and 43−58 of the manufacturer's submission for further details.

5 Authors

Scott Goulden (Technical lead) and Rebecca Trowman (Technical Adviser), with input from the Lead Team (Terry Lewis, Dr Sanjeev Patel and Professor Stephen Palmer).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by School of Health and Related Research (ScHARR), University of Sheffield:

- Lloyd Jones M, Stevenson M, Stevens J, et al. Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs: A Single Technology Appraisal, February, 2011.

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Bristol-Myers Squibb and Otsuka Pharmaceuticals

II Professional/specialist, patient/carer and other groups:

- British Health Professionals in Rheumatology
- British Society for Rheumatology
- National Rheumatoid Arthritis Society
- Primary Care Rheumatology Society
- Royal College of Nursing
- Royal College of Physicians endorsing British Society for Rheumatology
- Royal College of Pathologists

C Additional references used:

a. Bansback, N., Brennan, A., and Ghatnekar, O. Cost (2005) Effectiveness of adalimumab in the treatment of patients with moderate to severe rheumatoid arthritis in Sweden. Annals of the Rheumatic Diseases; 64 995-1002.